Medicinal Marijuana

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INTRODUCTION

LEARNING OUTCOMES

After completing this course, the learner will be able to:

1. Distinguish medicinal marijuana (Cannabis sativa) from recreational marijuana and the use of hemp.
2. Discuss pharmaceutical drug development from the marijuana plant and its potential applications in dental treatment.
3. Summarize the science concerning the best clinical research evidence for use of marijuana in the treatment of oral disease.
4. Identify the current status of legalization of marijuana for medicinal and recreational use and its impact on healthcare systems.
5. Review oral health care considerations specifically affecting patients who currently use marijuana.

COURSE INTRODUCTION

Throughout history, plants have occupied central roles in health beliefs and practices, healthcare systems, sociopolitical controversy, and healthcare reform. In the 19th century, lobelia (*Lobelia inflata*), a plant indigenous to the North American continent and used medicinally for centuries by indigenous peoples, gained attention. The plant was used both to aid respiration and to induce vomiting for various health and spiritual concerns (Moerman, 1998). Lobelia became the focus of health care during a period of extensive healthcare reform (Berman & Flannery, 2001). There was debate about the safety of lobelia just as there is today with other controversial plants, such as ephedra (*Ephedra sinensis*), tobacco (*Nicotiana tabacum*), and marijuana (*Cannabis spp.*). Medicinal use of plants continues to be one of the cornerstones of healthcare cultures and systems

around the world. Because of their accessibility, cultural history, and relatively safe record of traditional use, medicinal plants remain at the center of health care as traditional medicine (World Health Organization, 2013). Over the years, leading plant scientists such as Farnsworth and Soejarto (1991) reported the existence of more than 250,000 higher species of chemically distinct plants on Earth, of which between 35,000 and 70,000 have been used medicinally over the centuries. It is estimated that only a fraction of all flower-bearing plants have been examined and only a small subset have had their chemical constituents identified or had their healing properties researched in double-blind, placebo-controlled trials. The potential of the plant world for producing cures for disease and relief from everyday discomfort is recognized by botanists, ethnobotanists, and pharmacognosists (people who pursue drug discovery from plants). The public continues to be a driving force in medicinal plant use. People follow their time-honored plant-oriented healing traditions in self-care practices. They also urge the scientific community to develop new drugs and applications.

All healthcare paradigms – self-care, traditional medicine, and biomedical – are interested in the medicinal use of marijuana, but this course will specifically focus on the dental realm. This plant, which has been employed for centuries in self-care and traditional medicine, is now the focus of much interest in terms of biomedical development for use in alleviating diseases and in chronic pain management. Yet, as will be discussed in this course, marijuana is federally classified as an illegal drug.

This course is an introduction to the genus *Cannabis* (and species such as *sativa* and *indica*). It presents a synopsis of the plant's history and the scientific information currently available to guide public and professional exploration, from self-care to biomedicine and clinical trials.

A review of the literature produces thousands of reports, theoretical and population research papers, and books, on medicinal marijuana. Few clinical trials exist, however, that might begin to answer some of the questions from the public and health professionals about the physical and psychological effects of the plant and its constituents. This course offers a synopsis of traditional and biomedical data about the plant and the issues related to public and professional use in an attempt to answer some of the most common questions that oral healthcare professionals (OHCPs) may have when counseling those currently using, or who are deciding whether to use marijuana. Marijuana, for both medicinal and recreational use, is a highly controversial and disputed subject. It is important to note that it is not the purpose of this course to sway opinion for or against

marijuana but to inform based on current medical evidence.

Although healthcare professionals and leadership, including those at the National Institutes of Health (National Academies of Science, Engineering, and Medicine, 2017) and the World Health Organization (2013), call for medical marijuana research, federal prohibition of marijuana use in the United States creates a challenge for scientific analysis of this illicit drug. However, public attraction to marijuana for medical and recreational use drives medical science to explore emerging evidence of the role of the endocannabinoid system in health and disease. Establishment of a body of clinical-trial research on marijuana to complement current evidence is necessary to inform the public and establish best-practice guidelines for healthcare professionals. However, as will be demonstrated in this course, even if federal laws were to loosen or be abolished, the feasibility of developing and administering robust clinical trials would be met with considerable hurdles. This course includes references to the most current research evidence available, drawing, when possible, on clinical trial research.

There is much to learn about medicinal marijuana from evidence other than clinical trials. This course includes historical data and evidence from in vitro studies, literature reviews, meta-analyses, surveys, and community health studies that have contributed in a meaningful way to current scientific understanding of the health outcomes witnessed in the public sphere, where marijuana use is proliferating.

This course adopts the common name “marijuana” to refer to the species *Cannabis sativa* and *C. indica,* as well as hybrids of the two. The science of botanical nomenclature requires that a genus and species name be italicized and that the genus be capitalized. Much of the medical and scientific literature refers to marijuana as “cannabis” not *Cannabis spp.,* and state registries use the term “marijuana,” not Cannabis. Marijuana is the term commonly employed by the public. Although supporters of marijuana use and legalization are concerned about the social stigma surrounding the use of the word “marijuana,” there is no intention to further stigmatize the plant in this course. The common name for the plant was chosen for the title of this course because it is likely to be more recognizable by OHCPs seeking continuing education courses that include the information provided here. For consistency, ease, and clarity, the term “marijuana” will be used. Botanical names may also be employed to add specificity to the information presented.

Designed for dentists, dental hygienists, and dental assistants, this intermediate-level course will review the pharmacology and current state of medicinal marijuana as it relates to oral health

care. The information presented in this course should be considered essential knowledge for all OHCPs, both seasoned and newly credentialed.

Disclaimer: Throughout history, plants have been at the center of many controversies about health care. Marijuana (*Cannabis spp.*) is one of those plants. Medicinal marijuana is a highly controversial topic in the United States today. The act of authoring this course should not be misconstrued as agreement with or opposition to the use of marijuana, recreationally or medicinally, or alignment with the movement to legalize marijuana.

MEDICINAL MARIJUANA

BOTANICAL BACKGROUND, CULTURAL HISTORY, AND MISUSE OF MARIJUANA (*CANNABIS SPP.*)

A person who walks across a lawn, cultivates a garden, or forages in forests and water is engaging with the plant world of trees, flowers, grasses, fungi, fruits, food, and medicinal plants. Although marijuana (*Cannabis spp.*) is but one of thousands of types of plants, it is a common topic of private and public conversations in the early 21st century. Furthermore, marijuana is perhaps one of the most praised and condemned plants in history. This module explores the medicinal qualities of marijuana and its constituents, as well as the cultural history that continues to grow with the plant and its role in forming U.S. drug enforcement policy. This module also introduces some of the suggested reasons for the resurgence of interest in marijuana among Americans seeking healing, relief, and hope and the reversal from many in the public from demanding prohibition to lobbying for legalization (McKenna, 1992, and Barber 2018). Oral healthcare professionals (OHCPs) who are engaged in shared decision making with people in their care can employ the context provided by cultural history, including botanical science and clinical trial data.

Marijuana's history in treating various conditions is long and successful. It is not the newest drug on the market, though new drugs have been manufactured from its constituents. Marijuana contains chemical compounds and nutrients that can affect changes in people's physical, emotional, mental, and spiritual health and well-being. Whole marijuana leaf or seed is what people commonly use, although more pharmaceutically-elegant formulations are becoming available on the American pharmacopeia for medical use (Mathias, 2018). Marijuana has retained its culture of traditional use referred to by scientists as "crude" medicine when a plant is used in a

form close to its natural state. Some might think of the term “crude medicine” as suggesting that the medicine is simple, but medicinal plants, including marijuana, are rarely simple. When studied more closely, they reveal themselves to be replete with hundreds of chemical constituents, in this case cannabinoids, many of which can induce powerful biochemical changes. Although this module does include specific botanical and pharmaceutical data, and known mechanisms of action of marijuana, evidence derived from historical human use provides OHCPs with insight into treating patients either considering the use of marijuana, or already using it.

BOTANICAL BACKGROUND

Marijuana (*Cannabis spp.*) is a strong plant with stems that grow easily from 3 to 20 feet in nearly every climatic condition. The leaves are palmate (they look like the palm of a human hand), each with five to seven lanceolate (long and pointed) leaflets. The plant is native to Northern India and Southern Siberia and is a member of the small Cannabaceae family of plants. One other medicinal plant in the Cannabaceae family is hops (*Humulus lupulus*), a plant employed in the brewing of beer. Carl Linnaeus, the 18th century Swedish botanist and physician who created a system for naming plants (The Linnean Society, 2018), named marijuana *Cannabis sativa* in 1753. Marijuana that is cultivated in a dry, hot climate, produces resin in greater quantities, along with fiber that is poor for commercial purposes. In countries with milder, humid weather, the hemp fiber is stronger and more durable and less resin is produced (Abel, 1980). Because of the historical emphasis on hemp cultivation for quality fiber, the intoxicating effects of marijuana were largely unknown in America until the 19th century. Today, however, the leaves, seeds, flowers, and stems, along with the resin that oozes from the stems and leaves of the plant, are used medicinally, recreationally, and in ritual. (See Table 1.) When marijuana is harvested for fiber or its leaf, it is cut close to the ground with a special sickle. Harvesting resin is more painstaking. The resin is known as “hashish.” *Cannabis indica* is the species typically grown for its higher resin content for the hashish market. A late 19th-century analysis described the leaves as containing chlorophyll, a volatile oil, gummy extractive, a bitter body, albumen, lignin, sugar, and salts such as potassium nitrate, silica, and phosphates (Felter & Lloyd, 1898/1983). Approximately 60 cannabinoids have been identified in marijuana, but delta-9-tetrahydrocannabinol, or “THC,” is the main

psychoactive component.

Smoking marijuana has a paradoxical effect on mood: It can be stimulating or sedating. This type of effect is not typical of central nervous system stimulants or depressants, but it is more consistent with the effects of psychedelic drugs such as lysergic acid diethylamide (LSD; Block, Erwin, Farinpour, & Braverman, 1998). Marijuana plants are dioecious, which means that there are distinctly male and female plants. Growers focus on the identification, care, and propagation of female plants because females produce more resin and flower later (Abel, 1980). "Not only do males not produce a usable drug, but if pollen from male plants reaches females, the females will begin to 'set' seed and will cease their production of resin" (McKenna, 1992, p. 154). The intoxicating resin is secreted by glandular hairs located around the flowers.

Is There a Difference Between Marijuana and Hemp?

Marijuana is the most used common name for Cannabis sativa in the West; however, there are numerous others. As Terence McKenna (1992, p. 150) comments, "The thousands of names by which cannabis is known in hundreds of languages are testament to its cultural history and ubiquity." There is a significant difference, however, between plants known by the common names "marijuana" and "hemp." Although they are both *Cannabis sativa,* hemp is a different strain of marijuana that is low in THC. Marijuana (and hemp) seeds contain no THC, and can thus be sold in the market as food; but during processing it is possible for trace amounts of THC from the leaf to stick to the outer husk of the seed in an amount that is measurable upon analysis. Hemp products on the market cannot have THC. Hemp seed, which is used in producing soap, lamp oil, and paint as well as food products such as oil and butter, is 31% protein after the husk is removed. It is rich in vitamins, minerals, and nutrients, such as linoleic acid (an essential fatty acid) and tocopherols (vitamin E), and the concentration of unsaturated fatty acids can exceed 90%, higher than most vegetable oils on the market, particularly the Yunma No. 1 and Bama Huoma varieties (Chen et al., 2010). Hemp seed oil is high in flavonoids, such as flavanones, flavanols, and isoflavones, which are known antioxidants (Smeriglio et al., 2016).

A common recipe for the use of hemp seed is hemp porridge. The hemp plant is best known, however, for its use in fiber production, primarily of cordage for weaving and rope making. Hemp fiber, along with mulberry tree bark pulverized into pulp, was also the basis for the invention of paper traditionally ascribed to a Chinese court official, Ts'ai Lun, in AD 105. However, fragments

of paper containing hemp fiber have been found in Chinese graves dating back to the first century BC (Abel, 1980).

CULTURAL HISTORY OF MARIJUANA USE

Marijuana has a rich history that spans the gamut from high social acclaim as a plant of great spiritual power to intense suspicion. The plant has been associated with ritual, religious, social, and medical customs in India for thousands of years. Marijuana is referred to as one of the five sacred plants suggested for freedom from anxiety in the *Atharva Veda* (circa 1400 BC), an ancient Indian text on healing (Abel, 1980). In Tibetan tantric tradition, marijuana is burned to drive out evil forces. Gautama Buddha is said to have subsisted on one hemp seed each day for 6 years preceding his enlightenment. Alternatively, the term "assassin" used in the English language is thought to have been derived from the word *hashishin,* which was applied to a murderous sect, which in its religious rites, used hashish for intoxication (Felter & Lloyd, 1898/1983). One of the few surviving books of the *Zend-Avesta,* ancient holy book of the Zoroastrians, *Vendidad,* translated as the "Law Against Demons," calls *bhanga* a "good narcotic" that may allow some of the highest mysteries to be revealed. Chinese priest-doctors used marijuana stalks engraved with snake-like figures in their demon-ridding rites (Abel, 1980). There also is reference to marijuana in the *Talmud,* a holy book in Jewish culture. Marijuana is referred to in Mexico as "*mota.*" The Mexican phrase "*esta ya le dio las tres,*" or "you take three times (puffs)" of marijuana, refers to *mota* as the "opium of the poor" used as a hangover-free intoxicant, a "social lubricant and an antidote to drudgery and fatigue" (Lee, 2012, p. 39).

Marijuana leaf, or resin from the leaf and stem (hashish), is typically smoked. The resin and seed of the plant can also be eaten. Eating hashish was the preferred method of ingestion for centuries. Smoking of Cannabis was introduced to Europe only after Columbus returned with tobacco from his second trip to the New World (McKenna, 1992). Traditionally, the effects of smoking are thought to be more immediate. A variety of apparatuses and techniques are available for smoking marijuana. The favorite device for smoking marijuana in India is a *chelum,* a wooden, ceramic, or soapstone tube that is packed with herb. The Scythians, a nomadic Central Asian people, are credited with bringing marijuana to Eastern Europe around 700 BC (McKenna, 1992)

and discovering that inhalation was the most effective way to appreciate the effects of the plant. Centuries later, Dr. William B. O'Shaughnessy, scientist and physician, is said to have introduced marijuana to England in 1842 in his *Bengal Dispensatory and Pharmacopoeia* (Block et al., 1998).

Marijuana seed has been used in traditional Chinese medicine. The ancient emperor Shen Nung (circa 2700 BC), patron of agriculture, is credited with the discovery of marijuana as a medicine. Marijuana seed, or "*huo ma ren,*" is classified as "moist laxative" in the Chinese Materia Medica (Bensky & Gamble, 1993). It is also used in patterns of yin (heat) deficiency with constipation, such as may occur in older adults after illness with fever and in women postpartum. Poultices of the pounded seed are used on wounds to clear the heat in the wound and promote healing. The ground seed is also known to be effective in lowering blood pressure in animals and humans (Bensky & Gamble, 1993). It is typically used with other herbs in formulation. The Chinese have historically used marijuana with wine to create an anesthetic called *ma-yo* when performing difficult surgical operations. According to Abel (1980), "The Chinese were well aware of marijuana's unusual properties … many did not approve. Due to the growing spirit of Taoism which began to permeate China around 600 BC, marijuana intoxication was viewed with special disdain" (p. 13). By the first century of the Common Era, the Taoists had relented and, going along with their interest in magic and "seeing spirits," people were once again adding marijuana seeds to their incense burners.

The Ohio State Medical Society conducted the first official U.S. government study of marijuana in 1860. They catalogued conditions that doctors had successfully treated with marijuana, from "bronchitis and rheumatism, to venereal disease and post-partum depression. The use of marijuana as an analgesic was so common that medical textbooks and journals identified several types of pain for which it should be administered" (Lee, 2012, p. 26). In Great Britain, "Sir William Osler, often called the founder of modern medicine, endorsed marijuana as the best treatment for migraine headaches" and Sir John Russell Reynolds, the personal physician to Britain's Queen Victoria, prescribed hemp to the queen to relieve her menstrual cramps, calling it "one of the most valuable medicines we possess" (Lee, 2012, p. 26). Marijuana was used for such conditions as

> *Delirium tremens, neuralgia, gout, rheumatism, infantile convulsions, low mental conditions, insanity, etc., and in inflammatory conditions in cases where opium disagrees and is often preferable to opium. Acute mania and dementia, epilepsy … are among the*

> *nervous disorders in which it exerts a positively beneficial and soothing action … The drug is a useful hypnotic for the insane. As a remedy for pain, it ranks among the first; the more spasmodic the pain the better it acts.* (Felter & Lloyd, 1898/1983, p. 425)

An alcohol tincture of marijuana leaf in sweetened water has been used medicinally to increase the strength of uterine contractions without adverse effects, as well as for menorrhagia and chronic cystitis. Herbalists use marijuana tincture in combination with lady's mantle (*Alchemilla vulgaris*) and witch hazel (*Hamamelis virginiana*) to slow postpartum hemorrhage caused by uterine atrophy (Weed, 1986). "Impotence is said to have been cured by it. Cannabis has some reputation as a remedy for chronic alcoholism, and for the cure of the opium habit" (Felter & Lloyd, 1898/1983, p. 426). The Iroquois have used marijuana as a psychological aid for people who are recovering from illness but somehow do not think that they are getting well (Moerman, 1998).

In Ayurveda, a traditional medicine of India, marijuana is referred to as *vijaya, siddhapatri, ganjika, bhanga,* and *hursini* (Nadkarni, 1976). Bhang was a symbol of hospitality and given to guests. Sushruta, a renowned physician of ancient India, recommended marijuana to relieve congestion and regulate body fluids, and as a sleep and digestive aid, analgesic, and aphrodisiac. At the start of the 18th century, Gobind Singh, the Tenth Guru of the Sikh religion, gave bhang to soldiers facing dangerous missions (Abel, 1980). In Ayurveda, marijuana has been used in treating numerous infectious diseases (Touw, 1981). Some Indians regard marijuana as "*sattvik nasha*" or "peaceful intoxication." To make *thandi,* an intoxicating drink whose effect lasts 3 hours without hangover, marijuana powder is mixed with equal parts black pepper, dried rose petals, poppy seeds, almonds, cardamom, cucumber and melon seeds, sugar, milk, and water (Nadkarni, 1976).

SUBSTANCE MISUSE AND MARIJUANA

The marijuana "high," or intoxication, is described in different ways. Some people report feeling inebriated, while others are simply relaxed. Some people use plants such as marijuana in the pursuit of religious, spiritual, or ecstatic experience. Humans tend to be fascinated with altered states of consciousness, be it through prayer, meditation, music and the arts, drugs, or plants.

Traditional shamans regard plants as more than sources of foods and drugs, seeing them as sentient life forms that are interdependent and communicate with each other and humans. Tompkins and Bird (1973), in their classic book *The Secret Life of Plants*, conducted clinical research on the spiritual as well as physical and emotional relationships between plants and people. McKenna (1992, p. xvii) states that,

> *Analysis of the existential incompleteness within us that drives us to form relationships of dependency and addiction with plants as drugs will show that at the dawn of history, we lost something precious, the absence of which has made us ill with narcissism. Only a recovery of the relationship that we evolved with nature through use of psychoactive plants before the fall into history can offer us hope of a humane and open-ended future.*

Nineteenth-century Americans and Europeans preferred to ingest marijuana baked into pastry or as a tincture in tea or wine, until people began to realize that they could achieve a milder, quicker, and more manageable high by inhaling marijuana fumes. Smoking hashish was considered at the end of the 19th century to be "stylish and elegant" (Lee, 2012, p. 37).

Unfortunately, adolescents and young children are now smoking marijuana in steadily increasing numbers to get high too. The NIDA (2017b) public education materials list the following signs and symptoms of marijuana use in youth:

- chronic cough;
- unusually giggly and/or uncoordinated;
- very red, bloodshot eyes or use eyedrops often;
- hard time remembering things that just happened;
- has drugs or drug paraphernalia – drug-related items including pipes and rolling papers – possibly claiming they belong to a friend if confronted;
- has strange-smelling clothes or bedroom;
- uses incense and other deodorizers;
- wears clothing or jewelry or has posters that promote drug use; and
- has unexplained lack of money or extra cash on hand.

RECREATIONAL VERSUS MEDICINAL USE OF MARIJUANA

Even people who have no knowledge of the newest drug on the market for pain or disease likely grew up with knowledge about marijuana, just as they may have known about tobacco (*Nicotiana tabacum*) and the alcoholic beverages that are made from numerous plants. People who are using marijuana have a story to tell their nurse, pharmacist, or behavioral health practitioner. The first step in the care of the person using marijuana is to gather that story, which is the natural history of his or her use. Because marijuana has a large variety of applications, this section provides the first information a healthcare professional needs when caring for the user: knowledge about the plant and its traditional use.

Marijuana has four basic uses, as food, fiber, recreation, and medicine. It can also be used in excess, resulting in substance abuse. However, the boundaries between the various uses can be blurred. It is not always easy, for example, to distinguish recreational and medicinal use of whole marijuana leaf or seed. The difference may be determined best by the intention and practice of the user. Terence McKenna (1992, p. 163) suggested that the employment of the term "recreational" when applied to substance use "trivializes the cognitive impact of the substance used," and that "low doses of most drugs that affect the central nervous system are felt by the organism as artificial stimulation or energy, which can be directed outward in the form of physical activity in order both to express the energy and to quench it." However, "recreational use" is still a term used globally to describe the purpose of becoming intoxicated (using marijuana to "get high") for personal amusement rather than for a health concern. People often choose to self-prescribe marijuana for recreational use. But people also consciously self-care or self-medicate with marijuana. There is an entire subculture today that promotes daily self-medication with marijuana (usually through smoking), just as there was a hashish-eating culture before the 19th century.

Some people perceive marijuana as a contributor to human society's evolution to greater peace and tolerance. Two of the authors who have been recognized as providing some of the best insights into marijuana's history of use are ethnobotanist Terence McKenna and author Martin Lee, 1994 winner of the Pope Foundation Award for Investigative Journalism. McKenna, renowned for his work on plant hallucinogens, writes of marijuana in his book *Food of the Gods*

(1992) that, although people tend to focus on episodes of intoxication when talking about plants/drugs like marijuana, individuals regularly use plants like marijuana – as well as other less intoxicating plants such as coffee (*Coffea arabica*) and tea (*Camellia sinensis*) that best ensure a response such as energy stimulation, relaxation, or mood elevation. When OHCPs ask about their self-medication patterns of use with tobacco, alcohol, and caffeine, people may reveal a regular history of use. McKenna writes that, "Plant use is an example of a complex language of chemical and social interactions. Yet most of us are unaware of the effects of plants on ourselves and our reality, partly because we have forgotten that plants have always mediated the human cultural relationship to the world at large" (McKenna, 1992). Marijuana use can thus be seen as yet another mediator of that relationship. Marijuana users have not forgotten the time-honored relationship with medicinal plants; they actively and consciously engage in it. Some even capitalize on it.

Healthcare professionals, who prescribe drugs or herbs in their practices, may advise and prescribe marijuana for medicinal purposes in states where it is legal to do so and warranted in care. Martin Lee, in his 2012 book Smoke Signals, writes that in the 19th century it was common physician practice to prescribe marijuana. The toxicology of a plant, as well as its history of safe use in a particular manner, is a consideration in risk-benefit shared decision making. Toxicology is determined not only by the constituents in a plant but also by the responses of the humans who use the plant. Healthcare professionals are challenged to understand the health behaviors of people engaged in plant use, especially when the healthcare professional has not experienced use of the plant. Because marijuana is currently an illegal substance under federal law, many healthcare professionals may not have firsthand experience with the effects of marijuana. Psychoactive plants such as marijuana, along with the user's quest for an altered state of consciousness and possible involvement in a lifestyle that includes daily use, pose unique challenges to healthcare professionals.

Some marijuana users extend their partnership with marijuana well beyond nutritional, recreational, and medicinal use. Marijuana can be a substance of misuse, becoming habitual and detrimental to life, leaving the user unable to stop using even when it is identified as causing problems. Research suggests that between 9% and 30% of marijuana users may develop some degree of marijuana use disorder (NIDA, 2017c). People who begin using marijuana before the age of 18 are 4 to 7 times more likely than those who start using marijuana as adults to develop a marijuana use disorder (NIDA, 2017c). There are no reports in the United States of anyone dying

from marijuana use alone (NIDA, 2017c); however, people do report disturbing effects, such as anxiety and paranoia. There is an increase in the reports of such adverse effects to emergency departments, thought to be related to the rise in marijuana food manufacture and the cultivation of plants with higher THC levels (NIDA, 2017c).

According to the United Nations Office on Drugs and Crime (UNODC), as of 2015 there were some 183 million users of marijuana, roughly 3.8% of the global population, making marijuana the most widely used illicit drug in the world (UNODC, 2017a, 2017b). In the Western Hemisphere, marijuana use is on the rise. Estimates for the Americas show an increase from 37.6 million people (or 6.5% of the population aged 15 to 64 years) who used marijuana in 2005 to 49.2 million (or 7.5% of the population aged 15 to 64 years) in 2015 (UNODC, 2017a, 2017b).

Persons who stop using marijuana after a long period of use can have withdrawal symptoms like those of nicotine withdrawal: irritability, sleep problems, anxiety, decreased appetite, and craving – which can be the impetus for relapse. Withdrawal symptoms, however, are generally mild and peak a few days after use has stopped. They gradually disappear within about 2 weeks (NIDA, 2017c). Currently no medications have been approved by the FDA for treating marijuana use disorder or addiction, although promising research is under way to find medications to treat withdrawal symptoms such as sleep disturbances and to ease cravings and other effects of marijuana (NIDA, 2017a, 2017c).

IS MARIJUANA A GATEWAY DRUG?

Understanding the gateway process involves sequence (use of a gateway drug leading to use of hard drugs), association (increased likelihood of hard drug use in those who use marijuana), and, controversially, causation. Researchers have demonstrated that marijuana use occurs prior to use of harder drugs such as cocaine and heroin and that, relative to nonusers, marijuana users are considerably more likely to subsequently report use of hard drugs. However, the evidence for causation, or that marijuana use exerts a causal influence on the likelihood of using other illicit drugs, has been less clear (Agrawal & Lynsky, 2013).

Animal studies have shown that exposure to addictive substances like THC can change how the brain responds to other drugs, particularly as regards response-reward mechanisms that

can signal addiction behaviors. This finding suggests that marijuana may potentially be a gateway drug for some users; however, it is important to note that factors other than these biological mechanisms, such as a person's social environment, are also critical in determining a person's further risk for drug use.

Trends in people's use of marijuana leading to further drug use can also be explained by marijuana often being one of the more accessible substances, along with alcohol and tobacco (NIDA, 2017b).

According to Miech, Patrick, O'Malley, and Johnston (2017), since 2013, attending college has become a substantially stronger risk factor for marijuana use. Before 2013, adolescents in college who had never used marijuana by the 12th grade were 17% to 22% more likely to use marijuana in the past 12 months than were their age peers who were not in college. This higher relative risk steadily increased and more than doubled in the following years to 31% in 2013, 41% in 2014, and 51% in 2015 (Miech, et al., 2017). Academic leaders are beginning to consider interventions for marijuana use as they have for binge drinking and other lifestyle choices and behaviors that can affect education, socialization, and health.

There are some in the criminal justice field, for example, who now argue that the gateway drug theory is an, "unjustified oversimplification of the dynamics of drug use reflecting the interests of certain stakeholder rather than wise social policy" (Kleinig, 2015, p. 971). The drugs are a branch pattern of the issues of the tree and its roots. A lack of or poor parenting, living in the wrong neighborhood, the need to belong, lack of self-esteem, or whatever it is that makes a self-destructive dependence attractive is the actual "gateway."

IS MARIJUANA SAFE?

Figure 1 depicts typical dose-response curves for medications, illustrating the distance between the effective-dose curve and the lethal-dose curve as being the margin of safety (Golan, 2016). On the x-axis you can see an increasing amount of medication being tested and on the y-axis you can see the response to the medication in the study population from no responders to a 100% response rate. Another name for the margin of safety is the therapeutic index. The therapeutic index can be calculated by dividing the lethal dose in 50% of the population studied (LD_{50}), by the effective dose in 50% of the population studied (ED_{50}). The therapeutic index for

aspirin is 23:1 whereas the therapeutic index for morphine is 50:1. In other words, morphine may be considered a safer drug than aspirin from a toxicity standpoint because more of the drug is required to be lethal. In the case of marijuana, the therapeutic index is closer to 20,000-40,000:1 (Schaffer Library on Drug Policy, 2018). Evidence from early animal studies and human case reports indicate that the ratio of lethal dose to effective dose is quite large and this ratio is much more favorable than that of many other common psychoactive drugs including alcohol and barbiturates (Phillips, Turk & Forney, 1971, and Brill et al, 1970).

More recently, the American Medical Association confirmed that it is theoretically possible to die from a marijuana overdose, however, a person would need to smoke 1500 pounds within 15 minutes (Annas, 1997). Given this significant margin of safety, the authors concluded that federal authorities should rescind the prohibition of the medical use of marijuana for seriously ill patients and allow physicians to decide which patients to treat. The government should change marijuana's status from that of a Schedule I drug (substances, or chemicals defined as drugs with no currently accepted medical use and a high potential for abuse) to that of a Schedule II drug (substances, or chemicals defined as drugs with a high potential for abuse, with use potentially leading to severe psychological or physical dependence) and regulate it accordingly.

An important risk associated with any plant medicine use is adulteration. The American Botanical Council hosts the Botanical Adulterants Program, in which various industry partners "adopt" an herb that is then watched for quality and purity in the marketplace, along with accidental and intentional adulteration. It has been claimed that marijuana cultivars are greatly increasing in THC potency (McLaren, Swift, Dillon & Allsop, 2008) and that scientific testing of marijuana is needed to monitor potency, contamination, and adulteration to address any potential or actual public health risks. There are also concerns about engineered marijuana-based products. One example is "Spice," also called "K2," "herbal incense," or "fake weed." This product consists of shredded, dried plant material sprayed with chemicals designed to act on the same brain cell receptors as THC. The chemicals are often much more powerful and unpredictable. Some of these products are labeled "not for human consumption," and many are now illegal (NIDA, 2016). But new chemical compounds are constantly being manufactured. The effects, like the ingredients, often vary, and users may present to an emergency room with rapid heart rate, vomiting, and negative mental responses, including hallucinations, after using these substances (NIDA, 2016).

According to a 1999 report by the Institute of Medicine (IOM; now the Health and

Medicine Division of the National Academies), marijuana's adverse effects are "within the range of effects tolerated for other medications." This is not to say that marijuana is completely without adverse effects, especially when consumed in uncontrolled circumstances. There are chronic effects related to THC and chronic smoking. Marijuana smoking, as with all smoking, may be associated with increased risk of cancer and lung damage (IOM, 1999). The primary adverse effect of acute marijuana use is identified as diminished psychomotor ability. People should be advised not to operate heavy equipment or vehicles when under the influence of marijuana, THC, or any cannabinoid drug. Some people also experience dysphoria (a feeling of unease, discomfort, and generalized dissatisfaction). According to the IOM report (1999), older people with no previous experience with taking marijuana often experience psychological effects that are disturbing to them, such as disorientation after being treated with THC. These effects appear to be felt more with oral THC than smoked marijuana. In 2001, researchers who interviewed 3,882 survivors of myocardial infarction (MI) found that the risk for developing MI was 4.8 times higher than average within the hour immediately after marijuana use (Mittleman, Lewis, Maclure, Sherwood, & Muller, 2001). After MI, mortality is significantly higher in marijuana users than in the general population (Thomas, Kloner, & Rezkalla, 2014). On the other hand, a recent study of 5,113 adult participants' coronary artery risk found no association with the incidence of cardiovascular disease from cumulative lifetime or recent use of marijuana (Reis et al., 2017).

A study of women who smoked marijuana at least once a month during pregnancy found impaired placental development, as indicated through analysis of human tissue obtained at about 7 weeks of gestation. It also found that CB1 and CB2 were decreased in the placenta of marijuana smokers as compared to pregnant nonsmokers (Chang et al., 2017). Marijuana use during pregnancy has been associated with low birth weight and increased risk of both brain and behavioral problems in babies (NIDA, 2017a). Some THC can get into breast milk if a mother is using marijuana regularly (NIDA, 2017a).

As each state re-examines the legal status of marijuana, healthcare professionals may be compelled to re-examine marijuana and their own roles in supporting use in self-care and professional health care. This re-examination does not necessarily mean that healthcare providers will change their opinions. However, reflection is a natural response to mounting public inquiry of health professionals as marijuana use grows exponentially. Contemporary beliefs about marijuana run the gamut from prohibition to social promotion. Some consider marijuana, when

compared with alcohol, to be "benign." Others are concerned that marijuana may serve as a "gateway" drug. Still others ask why people seek the escape of a "high" in the first place. The existential issues of substance use and misuse are just as important with marijuana as with any other drug. Although concerns over marijuana's use, misuse, and global market may have been to a certain degree eclipsed by the current focus on the "opioid crisis," its impact continues to be reported by the U.S. National Institute on Drug Abuse and the UNODC that concludes the following:

> *Research has shown that, notwithstanding the usefulness of some cannabinoids in the management of specific medical conditions, their use, particularly in the botanical form of herbal cannabis with unknown content and dosage, can be detrimental to health. To protect human health, it is therefore necessary that the principles of safety, quality and efficacy and the rigorous scientific testing and regulatory systems that apply to established medicines be applied also to cannabis-based medicines.* (UNODC, 2017b, p. 29)

IS MARIJUANA EFFECTIVE?

Based on the UNODC opinion above and other regulatory bodies such as the Institute of Medicine (IOM) and the National Institute of Health (NIH), a new open-door initiative for scientific research on the medical potential of marijuana (cannabinoids) was started back in 2002 at the University of California San Diego campus and the launch of twenty-five studies through their Cannabis Research Center. The National Institute on Drug Abuse (NIDA) website states that, currently, the quality of health research on marijuana and its components varies widely, and the whole plant is, "significantly more potent now and we now know a lot more about the potential harmful effects of marijuana on the developing brain" (NIDA, 2016). The challenge that continues to face healthcare providers, however, is that we can never condone the smoked formulation of any medication given the significant respiratory pathology patients develop. Through the act of pyrolysis followed by inhalation, the search is on for more pharmaceutically elegant formulations of marijuana in order to apply our principles of safety, quality and efficacy and the rigorous scientific testing and regulatory systems that apply to established medicines.

Although some may view the subject of marijuana as, "increasingly difficult to talk about

in part because of the mixed messages being sent by the passage of medical marijuana laws and legalization of marijuana in some states" (NIDA, 2017c), health professionals can choose to become informed so that they can play a discerning role in the current dialogue about what is best for the people in their communities. In support of that role, this module presents cultural and historical context for the use of marijuana over the centuries with the evidence from the best clinical research available, including data from botanical science and clinical trials. It is the botanical background that may explain what might have attracted people to marijuana for thousands of years.

The high derived from inhaled marijuana occurs when cannabinoids in the leaf are released into the lungs, where they may in turn pass into the bloodstream. The amount of THC and other cannabinoids consumed determines the potency effects, ranging from sedating to psychoactive. The effects of smoking are rapid, whereas the effects from eating marijuana or hashish can be delayed by at least 30 to 60 minutes (Table 2). When marijuana is inhaled, either as combusted or vaporized plant matter, THC reaches peak concentration in 2 to 5 minutes, followed by a rapid drop-off. Inhaled cannabinoids reach their peak concentration in 5 to 10 minutes, declining rapidly for a period of 30 minutes (Fasinu et al., 2016). The action of THC in inhaled oils, as one might find in electronic cigarettes, is not yet known (Abrams, 2016). Orally ingested marijuana has a lower and variable bioavailability. It may take hours for THC to reach peak plasma concentrations, which then remain elevated with a terminal half-life of 25 to 30 hours (Abrams, 2016). When THC is ingested, it is initially metabolized in the liver to a psychoactive substance called 11-hydroxy-THC, explaining why people eating marijuana-baked products or capsules may report a more significant psychoactive effect compared with those who inhale it (Abrams, 2016).

Original research leading to successful isolation of THC, led to the discovery and cloning of cannabinoid receptors in 1990 (CB1 receptors). THC acts on CB1 receptors which also receive chemicals involved in normal brain function and development, and which share a common signalling pathway with opioids, promoting each others' reinforcing properties. CB1 receptors are located at presynaptic junctions where they are involved in the regulation of ion channels and modulation of the release of dopaminergic, γ-aminobutyric acid (GABA), glutamatergic, serotoninergic, adrenergic, and cholinergic neurotransmitters (Howlett, 1995).

Working backwards, if the human brain has specific cannabinoid receptors, it is unlikely that from an evolutionary standpoint humans would have developed these in response to chemicals

found in plants. More likely, humans would only have evolved CB1 receptors in response to the existence of an endogenous ligand for the CB1 receptor. This research ultimately led to the discovery of arachidonic acid ethanolamide, or anandamide: naturally occurring human cannabinoid chemicals. For differentiation, the term phytocannabinoid refers to constituents that occur naturally in the marijuana plant, as opposed to endocannabinoids, which occur naturally in lipid-derived neurotransmitters found in the human body. In 1993, a second type of cannabinoid receptor was discovered and cloned and while CB1 receptors are located predominantly in the central nervous system, these other receptors are expressed in peripheral tissues and are known as CB2 receptors.

According to NIDA (2017c), science suggests that "marijuana overactivates parts of the brain that contain the highest numbers of CB1 receptors causing the 'high' that people feel." (NIDA 2017c) People feel other effects from marijuana, such as changes in mood, impaired movement, altered sense of time, sensory alterations, difficulty thinking and problem solving, and impaired memory (NIDA, 2017c). Chronic users of marijuana can generally distinguish between the highs produced by smoking *Cannabis sativa* versus the effects of *C. indica*. The *C. sativa* high is characterized as uplifting and energetic, felt in the head and described as spacey or hallucinogenic. *C. sativa* gives a feeling of optimism and well-being, along with pain relief, and it is used for daytime smoking. *Cannabis indica* provides an effect described as a "body high" that promotes relaxation, stress relief, and an overall sense of calm. *Cannabis indicas* are supposedly effective for insomnia and are therefore used in the late evening (Hazekamp & Fishedick, 2012). In higher doses of *C. sativa* or *C. indica*, people can also experience hallucinations, delusions, and psychosis (NIDA, 2017c). Conversely, it is the stimulation of CB2 receptors in the periphery which may contribute to other medicinal effects such as the less addictive, anti-inflammatory potential of cannabinoids (Thomas et al, 2007).

THE ENDOCANNABINOID SYSTEM AND DRUG DEVELOPMENT

The study of drug development from a single plant such as marijuana, with its extensive cultural history, takes time, resources, and innovation. Because the marijuana drug market still includes massive amounts of whole-plant material, the trajectory for drug development involves

people and professionals from many different societal and scientific paths. Agricultural scientists working where marijuana may be grown legally can develop plant cultivars, but vendors looking for plants with higher delta-9-tetrahydrocannabinol (THC) levels are working in the field as well. High-THC-level marijuana is what is being sold on the recreational market. Currently, more than 700 cultivars have been identified for *Cannabis sativa* and *C. indica* (Hazekamp & Fishedick, 2012).

Another group exists with expertise in pharmacognosy, pharmaceutical and natural product development. They study plants and their constituents to discover mechanisms of action for observed effects in humans that might be replicated in synthetic drug development. One of the primary foci of this work with marijuana has been to elucidate how to achieve therapeutic benefits from the plant without its psychoactive effects. Plant science has determined that there are two major neuroactive phytocannabinoids (plant constituents) responsible for some of the actions in the *Cannabis* plant, cannabidiol (CBD) and THC (NIDA, 2017c). Much pharmaceutical drug development has been focused on separating and studying these two constituents from marijuana. The psychoactive effect attributed to THC is the primary concern of people involved in crude plant development for recreational use. Marijuana contains more than 500 identified phytochemical constituents, of which at least 104 are cannabinoids (Fasinu, Phillips, ElSohly, & Walker, 2016). Marijuana's "phytocannabinoid" compounds have potential central nervous system action, with heterogeneous psychoactive effects and neuropharmacological actions. Research on the endocannabinoid system (ECS) is an emerging field attempting to answer public demand for greater scientific understanding of the marijuana plant at the center of the ongoing sociopolitical controversy over self-medication with marijuana. Healthcare professionals, parental advocates, and end users pose the questions that drive demand for drug development (Kendall & Alexander, 2017).

The data most often utilized for forensic, legislative, and medicinal purposes are examination for the presence of THC and tests that distinguish hemp (fiber) from marijuana (medicinal). However, the most widely studied and preferred medicinal constituent is CBD. Where THC exerts its pharmacologic effects by mimicking the body's own cannabinoid neurotransmitters and binds to the two G-protein-coupled cell membrane receptors CB1 and CB2, CBD has little binding affinity for either of the two cannabinoid receptors. Instead, CBD binds to fatty acid binding proteins (FABPs), which is thought to explain why it lacks psychoactive activity. These

receptor are involved in the sensation of pain, cold, and sensitivity to heat (Bisogno et al., 2001). More recently cannibidiol is seeing utility as a treatment of epilepsy, particularly in young patients (Klotz et al, 2018). So, while THC is responsible for the euphoric and psychotomimetic effects of marijuana, CBD demonstrates other medicinal effects including analgesic, anti-inflammatory, and anxiolytic activity without the psychoactive effects of THC (Fasinu et al., 2016 and Ligresti, De Petrocellis, & Di Marzo, 2016).

To date, the U.S. Food and Drug Administration (FDA) has only approved two oral cannabinoid medications for cancer-related, chemotherapy-induced nausea and vomiting: dronabinol (Marinol©) and the synthetic cannabinoid nabilone (Cesamet©) (Marinol, 2017 and Cesamet, 2013). While one meta-analyses of controlled trials have found these drugs to be helpful when compared with placebo, unfortunately neither of these medications represents a first line therapy and they each have variable success, primarily because they have a single active ingredient (NCI, 2017).

Dronabinol is pure THC in an oil-filled, soft gelatin capsule. Nabilone is a synthetic analogue of THC. Designs for synthetic drugs are often derived from the chemical structures of original plants or constituents. Nabilone comes as a capsule and as a solution (liquid) to take by mouth. Dronabinol capsules and solution are used to treat nausea and vomiting caused by chemotherapy and are usually taken 1 to 3 hours before chemotherapy and then every 2 to 4 hours after chemotherapy, for a total of four to six doses a day. The first dose of the solution is usually taken on an empty stomach at least 30 minutes before eating, but the following doses can be taken with or without food. When dronabinol capsules and solution are used to increase appetite, they are usually taken twice a day, about an hour before lunch and supper. The person swallows the dronabinol solution with a full glass of water (6 to 8 ounces). Dronabinol may be habit forming. People on dronabinol should not eat grapefruit or drink grapefruit juice due to a potentially serious drug-plant interaction (Prescribers Digital Reference [PDR], 2018). Dronabinol oil capsules are also contraindicated in those with sesame-oil sensitivities (PDR, 2018).

Medical science is beginning to recognize that it is the interplay of different cannabinoids in combination (and in different ratios) which may be the key to more effective pharmaceutical products in the future. Determination of the best plant sources of medicinal-grade marijuana typically involves analysis of 28 compounds, using a system such as principle component analysis. Different cultivars and marijuana extracts have variable amounts of THC depending upon the plant

variety used in the preparation. Higher THC-to-CBD ratios are associated with more prominent psychoactivity (euphoric, relaxant, and anxiogenic effects), whereas low ratios of THC-to-CBD are more sedating (Fasinu et al., 2016). *Cannabis indica* has a higher CBD-to-THC ratio. Standardization of constituents in medicinal plants – including marijuana – that are so easily subject to environmental changes is challenging for manufacturers and researchers alike.

Dosing with a marijuana constituent such as THC or CBD, or for that matter with an FDA-approved drug such as dronabinol or nabilone, really challenges the user and healthcare professionals who care for them to be mindful of the person's unique response to the herb or drug. There may be research studies, publications, and clinical guidelines that provide standardized dosing information, however, the psychoactive nature of THC still requires that it be considered for titration based on a user's response. The ambiguity inherent in plant medicine practice generally is evidenced when partnering with marijuana. That ambiguity resolves over time as users and healthcare professionals become more knowledgeable concerning the qualities and actions of the plant as medicine upon various individuals.

In Canada and 28 other countries, Sativex© was the first pharmaceutical grade marijuana-based prescription medication to come to market, and it is currently being considered for release in the United States (Sativex, 2015, and Kendall & Alexander, 2017). Sativex© is a dimer of delta-9-tetrahydrocannabinol and cannabidiol and is indicated for use in adult patients with multiple sclerosis neuropathic pain or for cancer pain. Patients self-administer this buccal spray as a cannabinoid analgesic. In the United States, Epidiolex© (cannabidiol) has "cleared the last hurdle after the Drug Enforcement Administration labeled the drug as having a low abuse potential." (Epidiolex, 2018) The company now plans to bring this treatment for childhood epilepsy to the U.S. market by the end of 2018 (Mathias, 2018).

The endocannabinoid system (ECS) is affected by stress, food intake, and behavioral change. Endocannabinoids act like dopamine in that they bind to specific receptor proteins located on the surface of some cells. A presynaptic dopamine neuron can produce endocannabinoid molecules that bind to cannabinoid receptors on adjacent GABA neurons, thereby reducing the amount of GABA being released (Fasinu et al., 2016). Inhibiting GABA neurons boosts the dopamine signal. The ECS functionally impacts synaptic communication with direct modulatory effects on pain perception, eating, anxiety, learning, memory, and growth and development in the central nervous system, as well as motor control, immune competency, tumor cell proliferation,

and inflammation. The endocannabinoids may also "exert effects via non-CB receptors through certain serotonin or vanilloid receptor subtypes" (Fasinu et al., 2016, p. 784). Cannabinoids and their receptors are involved in basic physiology and pathophysiology, including roles in gene expression and possibly in mediating complex disease processes such as schizophrenia, cancer, neurodegeneration, and chronic pain. In addition to the brain, the ECS is found in many parts of the body. For example, the activation of cannabinoid receptors by endocannabinoids on epidermal cells regulates normal function of the skin as a barrier. Engaged CB1 and CB2 receptors can modify the proliferation, differentiation, and apoptosis of epidermal cells. Endocannabinoids also suppress inflammation in the epidermis.

Russo and others are exploring the hypothesis of "endocannabinoid deficiency" and its relationship to people's positive responses to diseases when dosed with marijuana's phytocannabinoids. First posed in 2001, this hypothesis was based on genetic overlap and comorbidity, patterns of symptomatology that could be mediated by the ECS, and the finding that exogenous cannabinoid treatment frequently provided symptomatic benefit. However, objective support and formal clinical trial data have been lacking. Currently, however, "statistically significant differences in cerebrospinal fluid anandamide levels have been documented in migraineurs," and imaging studies have demonstrated ECS deficiency in posttraumatic stress disorder (Russo, 2016, p. 155). Additional studies have provided a firmer foundation for the notion of ECS deficiency, and clinical data shows evidence of decreased pain, improved sleep, and other benefits to cannabinoid treatment and adjunctive lifestyle approaches affecting the ECS (Russo, 2016).

COMMON MEDICINAL USES AND EVIDENCE OF EFFECTIVENESS FOR MARIJUANA

Epilepsy

Approximately 3.4 million people in the United States have epilepsy (Epilepsy Foundation, 2014), and nearly 30% of those people are unresponsive to standard medications (Detyniecki & Hirsch, 2015). Symptomatic treatment of epilepsy is the most common strategy; however, antiepileptic drugs often have troubling side effects and fail in the treatment of temporal lobe

epilepsy (Soltesz et al., 2015). It is understandable that parents of children who must wear crash helmets because of seizures uncontrolled by current pharmaceutical treatments would consider reaching for marijuana or a marijuana-based drug for their children. It may seem a rational choice when weighing the extensive body of historical (Felter & Lloyd, 1898/1983) and anecdotal clinical evidence for successful treatment with marijuana against the risk that a child faces every time he or she suffers a seizure. To date, there is a lack of quality clinical research evidence with sufficient sample sizes to support or negate marijuana's traditional use in the treatment of seizures in people of any age. However, evidence is increasing that physiological states such as stress and pathophysiological conditions such as epilepsy modify the endocannabinoid signaling system (ECS).

In epilepsy, cannabinoid type 1 (CB1) receptors are markedly downregulated throughout the hippocampus in the acute phase shortly after the initiating insult, but they are upregulated in the chronic phase of the disorder (Soltesz et al., 2015). "The concurrent upregulation of CB1 receptors on GABAergic terminals and downregulation of CB1 receptors on glutaminergic axons that takes place in epilepsy may mechanistically contribute to seizures" (Soltesz et al., 2015, p. 272), but the importance of these biological processes is not well understood.

Studies have shown that the ECS plays an important role in modulating seizure activity, and deficiency or defect in the ECS is being studied as the possible cause for seizure. For example, one study published in the New England Journal of Medicine (Friedman & Devinsky, 2016) found lower levels of anandamide in cerebrospinal fluid in people with epilepsy than in healthy people serving as study controls. It is well documented that cannabinoids can provoke seizures, depending on the dosage, the content and ratio of the cannabidiol (CBD) and THC, and the underlying conditions in the patient. However, anti-seizure medications that are already on the market are known also to provoke seizures in some patients and to be associated with clinically significant drug-drug interactions (Friedman & Devinsky, 2016). Current evidence also suggests that, although THC has anticonvulsive effects, at higher doses it can be proconvulsive (Detyniecki & Hirsch, 2015). However, phase III randomized controlled trials with oral CBD (Epidiolex) support efficacy and adequate safety profiles for children with Dravet syndrome (fever-induced epilepsy) and Lennox-Gastaut syndrome (childhood epilepsy) at doses of 10 and 20 mg/kg/day (O'Connell, Gloss, & Devinsky, 2017).

In 2014, the Cochrane Collaboration (Gloss & Vickrey, 2014) published its review on

cannabinoid use in epilepsy. The stated goal of the review was to evaluate the literature for human studies that explored the effect of CBD on seizure freedom for 12 months, or three times the longest usual seizure-free interval. The researchers rejected many of the studies they reviewed because they were not clinical trials. Four pioneering studies from 1980 to 1990 met all the inclusion criteria except the primary outcome. They were reviewed because they included adverse events, one of the secondary outcomes; however, the studies included inadequate numbers of participants for the drawing of conclusions. In one study, 15 patients with temporal lobe epilepsy, who experienced at least one generalized seizure weekly, received 200 mg to 300 mg of CBD daily or placebo for as long as 4.5 months. Investigators did observe that participants tolerated the CBD without toxicity. In the second study reviewed, 12 participants with uncontrolled seizures were treated with three capsules of sunflower oil (as placebo) or sunflower oil and 100 mg of CBD (300 mg daily) for the first week, followed by two capsules (200 mg daily) for 3 more weeks. There were no differences in seizure frequency between the two groups, although no details were given. The only side effect was mild drowsiness. In the third study, nine participants were randomized to groups receiving either 200 mg of CBD or placebo. Participants continued to take their regular medication plus CBD or placebo for 3 months. Two of four participants treated with CBD were seizure-free for the 3 months of treatment, and none of the five in the placebo group experienced improvement. No adverse effects were reported. In the fourth trial, 12 participants were treated with a single-blind placebo for 6 months, then a double-blind dose of 300 mg of CBD or placebo in a crossover trial lasting an additional 12 months. Ten patients in the trial did not experience changes in the frequency or character of seizures, but reported no adverse effects. The small sample size (48 total participants) and low quality of the study designs left the authors unable to draw conclusions from the review.

An Israeli multicenter trial was conducted with 74 children (aged 1 to 18 years) with refractory epilepsy (resistant to more than seven drugs) who were treated with marijuana oil for at least 3 months and an average of 6 months. Patients were treated with sublingual marijuana oil extract of one of two strains: “Cheese pie” and “Avidekel,” both containing a CBD/THC ratio of 20:1, dissolved in olive oil, given three times daily. Daily dose ranged from 2 to 27 mg/kg/ day. The response to treatment was evaluated as a parental-reported change in the mean monthly seizure frequency. Of the 74 patients, 66 (89%) reported reduction in seizure frequency. The reduction was 75% to 100% in 13 patients (18%), 50% to 75% in 25 (34%), 25% to 50% in 9 (12%), and

less than 25% in 19 (26%). Five (7%) patients reported aggravation of seizures, which led to discontinuation of use of the CBD (Tzadok et al., 2016).

Researchers suggest that future studies focus on the underlying mechanisms of alterations in the ECS in chronic epilepsy and other related pathological conditions, including autism, cell type-specific boosting of the ECS (for example, ECS-based gene therapy), physiological conditions that selectively control phasic or tonic ECS in vivo, and cannabinoid-based prophylaxis against epileptogenesis after various forms of brain injury (Soltesz et al., 2015).

Given the proven anticonvulsant effects from preclinical studies, and the lack of psychoactive properties, CBD is considered to be a promising alternative if not a candidate as a medication for epilepsy. Its safety record is strong to date but the long-term effects of CBD are unknown. Researching the long-term neuropsychological effects in the developing brains of children is particularly important.

Glaucoma

Glaucoma treatment focuses on the continuous reduction of intraocular pressure (IOP). Because marijuana smoking and THC ingestion have been found to reduce IOP by 60% to 65%, oral and topical cannabinoids show promise for future use in glaucoma treatment. The concern with smoking is that the effects on IOP last only 3 to 4 hours and the amount of smoking necessary may be prohibitive (Green, 1998). In a 2001 study, eight participants were given either two drops (50 mL) of a 25-mg or 50-mg WIN55212-2 solution or placebo solution. WIN55212-2 is a synthetic and selective CB1 receptor agonist. These drops decreased intraocular pressure within 30 minutes of application in participants with resistant glaucoma (Porcella, Maxia, Gessa, & Pani, 2001). Studies continue to explore the relationship between the ECS and the pathophysiology of glaucoma as well as the long-term treatment of glaucoma with cannabinoids as hypotensive and neuroprotective agents for the eye (Cairns, Baldridge, & Kelly, 2016).

Anxiety Disorders

Although marijuana use has been thought to be associated with a broad range of psychiatric disorders, statistical analysis has shown marijuana use to be associated only with increased

prevalence and incidence of alcohol and drug use disorders, including nicotine dependence (Blanco et al., 2016). However, marijuana use among people with anxiety or depression has been reported to be two to eight times higher than in the general population, with rates as high as 60% among people with panic symptoms (Bricker et al., 2007). Several studies suggest that marijuana, self-prescribed and smoked, or prescribed in pharmaceutical form, may be effective in treating symptoms related to anxiety, however, a 2015 review of the literature by Vorspan, Mehtelli, Dupuy, Bloch, and Lépine found that marijuana used in self-medication as a sedative can also be a "cause of anxiety disorders" (p. 4).

A review of the literature suggested that, as of 2009, frequent users of marijuana consistently had a high prevalence of anxiety disorders and people suffering from an anxiety disorder have often used marijuana. It was not clear from existing data if marijuana use increased the risk of developing long-lasting anxiety disorders (Crippa et al., 2009). Studies are needed to further understand and test the hypotheses regarding the relationship between anxiety and marijuana, taking into account neurobiological, environmental, and social influences.

One study found that social anxiety is positively associated with marijuana-related problems. Although no significant direct effect of social anxiety from marijuana use frequency was observed, a significant indirect effect on solitary marijuana use was found. This research suggests that social anxiety exerts its influence on marijuana use frequency indirectly via more frequent solitary use. Solitary marijuana use was related to more marijuana-related problems. This finding was congruent with the investigators' previous work, which found that socially anxious marijuana users tended to avoid social situations when marijuana was unavailable. Socially anxious persons used marijuana prior to social events to manage anticipatory anxiety about the event and/or used marijuana following the social event to manage their anxiety associated with review of negative aspects of their behavior during the social event (Buckner, Ecker, & Dean, 2016).

A study of 149 male and female participants, aged 18 to 36, used various statistics to investigate the factors, such as social anxiety, norms, and expectancies, that might be related to craving marijuana. The craving was greatest when marijuana use was viewed as acceptable and expected to reduce tension. Cravings due to social anxiety were low when expectations were low. The study found that non-Caucasian participants reported greater tension-reduction expectancies than Caucasian participants. This study suggests the importance of considering social norms,

expectancies, and social anxiety in understanding marijuana-related behaviors, given that craving is robustly related to marijuana use problems, such as relapse during an attempt to quit (Foster, Ecker, Zvolensky, & Buckner, 2015).

A meta-analysis included a total of 267 studies on marijuana use in anxiety. The results of 31 of those studies were re-analyzed using a random-effects meta-analysis with inverse variance weights. Analysis of the epidemiological data from this cohort representing 112,000 non-institutionalized members of the general population of 10 countries (the United States, Canada, Switzerland, Australia, France, Colombia, New Zealand, Netherlands, Germany, and the United Kingdom) found a small positive association between anxiety and either marijuana use (Odds ratio [OR] = 1.24, 95% confidence interval [CI], $p = 0.006$; $n = 15$ studies) or marijuana use disorders (OR = 1.68, 95% CI, $p = 0.001$; $n = 13$ studies) and between comorbid anxiety and depression and marijuana use (OR = 1.68, 95% CI, $p = 0.004$; $n = 5$ studies; Kedzior & Laeber, 2014).

A study conducted with 232 participants between the ages of 18 and 70 years who met the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for panic disorder tested an intervention that included cognitive-behavioral therapy (CBT; six sessions in 3 months followed by six follow-up 15- to 30-minute phone sessions) and marijuana use. Core panic symptoms were assessed using the Anxiety Sensitivity Index, social phobia by the social phobia subscale of the Fear Questionnaire, and depression by the 20-item Center for Epidemiological Studies Depression Scale. Recent marijuana use (smoking) was also recorded. Findings of the study suggested that monthly marijuana use combined with CBT did not significantly reduce anxiety, panic, or social phobia, but it was effective in persons with depression. The investigators noted significant comorbidity between anxiety and depression and suggested that the anxiety arm of the study may not have had sufficient power to detect the effect. The symptoms of persons with depression who smoked marijuana monthly showed no more improvement than the symptoms of persons who smoked less than monthly (Bricker et al., 2007).

Trauma and Stressor-Related Disorders

Rates of marijuana use have increased in the wake of major disasters. There are high rates of posttraumatic stress disorder (PTSD) in the United States, particularly in combat-exposed veterans, and marijuana use disorder is associated with PTSD (OR = 4.3). While some researchers

hypothesize that individuals with PTSD might benefit from marijuana use, one review of the literature found that the known risks of marijuana use outweigh the unknown benefits for PTSD (Steenkamp, Blessing, Galatzer-Levy, Hollahan, & Anderson, 2017). Posttraumatic stress disorder symptom severity is positively associated with (a) use of marijuana to cope, (b) marijuana use problems, (c) severity of marijuana withdrawal, and (d) experiences of craving related to compulsivity and emotionality, with findings regarding withdrawal and emotion-related craving remaining significant after adjusting for covariates. (Boden, Babson, Vujanovic, Short, & Bonn-Miller, 2013, p. 277)

Although a range of psychotherapies have been employed with varying degrees of effectiveness, persons who suffer with PTSD may not seek care, and a recent meta-analysis of pharmacotherapy for PTSD found only small effects (Steenkamp et al., 2017).

Depressive and Bipolar Disorders

A recent survey measured the statistical association between the age at which people first used marijuana and depression in two ways. First, two statistics (linear regressions) used scores from three assessments – the 12-Item Short-Form Health Survey, the Mental Component Summary, and the Major Depression Inventory – as the dependent variables, with the age at first use of marijuana as the independent variable. Second, two regression analyses used age at marijuana first use as the independent variable (with lifetime nonusers as a reference), and poor mental health and major depression as the dependent variables. The results confirmed that marijuana first use at a young age is an important risk factor in the progression to other drug use. Mental health and depression were significantly predicted by age at marijuana first use. However, after controlling for the frequency of marijuana use and for the misuse of alcohol, cigarettes, and other drugs, the association with depression did not persist and the association with poor mental health was reduced. These results underscore the importance of preventing early marijuana users from progressing to other drugs. Among individuals whose first use of marijuana is early in life, these results suggest that the risks of mental health problems and depression are subsequently mediated by abusive consumption of marijuana or other substances. Early onset does not appear to be an indicator of later mental health problems per se, as long as it is not followed by harmful patterns of substance use.

Major depressive disorder is known to be more common in women. Conflicting reports exist concerning the relationship between gender and the prevalence of the use of marijuana to cope with emotional distress. Researchers conducted a secondary analysis of the results of a marijuana intervention trial involving 332 young adult women. Changes in depression symptoms (categorized as minimal, mild, and moderate or more severe depression) were assessed using Beck's Depression Scale in relation to changes in marijuana use at 3 and 6 months after the baseline assessment. The purpose of the study was to examine reduction in marijuana use and its impact on depression symptoms. After controlling for alcohol, investigators found a significant relationship between reductions in marijuana use and reductions in depression symptoms among young women who reported at least some mild depression symptoms (Moitra, Anderson, & Stein, 2016).

Recently, the European Mania in Bipolar Longitudinal Evaluation of Medication study analyzed a sample of 1,922 adults who had experienced a manic/mixed episode of bipolar disorder. Participants' data were organized into three groups: current use of marijuana (between 12-week and 24-month visits), no current but previous use (during first 12 weeks), and never use marijuana. The study found that people with bipolar disorder who stopped using marijuana during their manic/mixed episode had similar clinical and functional outcomes to those who had never used marijuana. People who continued to use marijuana had a higher risk of recurrence and poorer functioning, such as work impairment and not living with a partner.

Investigators surmised that the clinical implications of the findings were that a holistic management plan for bipolar patients should include psychoeducation and other treatments/interventions that focus on stopping use of marijuana, alcohol, and other drugs, as well as on improving adherence and preventing relapses (Zorrilla et al., 2015).

Schizophrenia and Other Psychoses

One of the primary concerns cited in the controversy over decriminalization and legalization of marijuana is its causal relationship with psychosis. Debate is ongoing concerning whether ingesting or smoking marijuana increases the risk for psychosis or, conversely, whether marijuana use contributes to the alleviation of symptoms associated with schizophrenia. Marijuana, while not seeming to cause any basic structural changes in the brain, does appear to

make changes in areas of the brain responsible for memory and emotion. Whether these changes are transitory or permanent and whether they contribute to the pathophysiology of schizophrenia are unknown. Many studies now show a robust and consistent association between marijuana consumption and the development of psychosis, but this may not be the case for schizophrenia specifically. Two primary kinds of data inform this issue: studies done with people with schizophrenia and studies of first-episode psychosis. Evidence suggests that the use of marijuana does not in itself cause a psychotic disorder. Rather, the evidence suggests that both early and heavy use of marijuana are more likely in individuals with a vulnerability to psychosis (Ksir & Hart, 2016). Longitudinal studies show a consistent association between adolescent initiation of marijuana use, in a dose-dependent fashion, and the emergence of psychotic symptoms and their severity, along with functional impairment and worse outcomes (Bagot, Milin, & Kaminer, 2015). A study of 64 participants who were followed for 5 years demonstrated that continued marijuana use with subclinical depression symptoms is associated with poorer clinical outcome, and may be a predictor of negative outcomes in persons experiencing their first episode of psychosis (González-Ortega et al., 2015). Another study found a dose-dependent association between change in marijuana use (from intermittent to continual use) and relapse of psychosis that is not thought to be the result of self-medication or genetic or environmental variables (Schoeler et al., 2016). Such findings are helpful for healthcare professionals, who can test them in practice. For example, a person considering the benefits and risks of marijuana use might be told that a study by Schoeler and colleagues in 2016 found that when users who had experienced psychosis changed from intermittent or occasional use to more continual use, such as smoking marijuana every day, they had a statistically greater risk of psychosis relapse.

According to a Cochrane review (McLoughlin et al., 2014), the evidence from research is unclear concerning a possible relationship between marijuana and schizophrenia. For some people with schizophrenia, positive symptoms are worse when they use marijuana. “For many, however, using marijuana seems only to have the expected mild soporific effects that probably compound negative symptoms” (McLoughlin et al., 2014, p. 41) such as blunted affect, anhedonia, and asociality. Upon reinspection with lead investigators of the studies covered in the Cochrane review on marijuana and schizophrenia, researchers concluded that there was as yet no evidence to demonstrate that one type of adjunct psychological therapy or one type of drug therapy was more effective than another and that there was also insufficient evidence to show that CBD had an

antipsychotic effect (Pushpa-Rajah et al., 2015). Alcohol use is known to confound data in studies on psychosis risk related to marijuana use (Auther et al. 2015), as could any substance, such as stimulants. Research also differentiates the amount of marijuana use in self-care as a factor in research outcomes. For example, "heavy" marijuana consumption (defined as smoking more than three marijuana cigarettes per day) seems to impair verbal memory in first-psychotic-episode patients. Heavy users also perform worse than medium users in other neurocognitive tasks. Medium users (one to three "joints" or marijuana cigarettes per day) did not show any greater risk than nonusers. Based on these results, investigators inferred the existence of a dose-related effect of marijuana consumption (Núñez et al., 2015).

Multiple Sclerosis and Spasticity

Data from more than 40 clinical trials of marijuana and cannabinoids have been published. Beyond the two indications for which dronabinol and nabilone are already approved by the FDA, the strongest evidence exists for the use of marijuana and cannabinoids as phytotherapies for chronic pain, neuropathic pain, and spasticity associated with multiple sclerosis. As of March 2015, there had been six trials (n = 325 patients) that examined chronic pain, six trials (n = 396 patients) that investigated neuropathic pain, and 12 trials (n = 1,600 patients) that focused on multiple sclerosis. Several of these trials had positive results, suggesting that marijuana or cannabinoids may be effective therapies. In 2014, the American Academy of Neurology published evidence-based guidelines that recommended an oral marijuana extract containing both THC and CBD (not yet available in the United States as an FDA-approved medication) as having the highest level of empirical support as a treatment for spasticity and pain associated with multiple sclerosis. Synthetic oral THC and Sativex© (THC and CBD) oromucosal spray followed with "effective" ratings (Yadav et al., 2014). One systematic review of the literature suggests a clear role for marijuana preparations in symptom management of movement disorders that are known to worsen in people who are anxious. The review found that marijuana in various formulations is effective in reducing symptoms, especially hyperkinetic symptoms, or the anxiety that aggravates symptoms in some conditions (Koppel, 2015).

Cancer and Pain Management

Cannabinoids have known antineoplastic and antitumor effects (Ramer & Hinz, 2008, as cited in Kendall & Alexander, 2017). Marijuana use is not a new subject for healthcare professionals who care for people being treated for cancer and the discomfort related to the disease and treatments. Nor is it new to those who care for people being treated for chronic and intractable non-cancer pain. According to Donald Abrams (2016, p. 404), who has been an oncologist for 35 years and has advised patients about the use of marijuana for some time, "We recommend a self-titrated dosing regimen for the patient as the safest option, rather than attempting to prescribe an actual dose." Dr. Abrams expresses caution in recommending marijuana to older adults because of the plant's ability to lower blood pressure and raise the heart rate. Older adults can experience postural hypotension, leading to falls. He remarks that he has found that his patients generally tolerate the mild euphoria that they feel as an effect of marijuana. Dr. Abrams (2016, p. 404) notes that, "If I have a single medicine that I can recommend to assist with nausea, anorexia, insomnia, depression, and pain rather than prescribing five or six pharmaceuticals that may interact with each other or the patient's chemotherapy, I consider it an attractive option for my patients." This experienced physician takes a pragmatic approach. He understands that a person who has been told to eat only a quarter of a marijuana cookie might then consume the rest of the cookie if his or her pain is not relieved quickly. However, the person may then suffer discomfort from the psychoactive effects of the plant. Helping a person who has had an experience such as this could be compared to guiding the behavior of someone who has been overeating or over-exercising to a level of discomfort or injury. Self-care is a vital part of a person's healing process. It is a time when a person learns about his or her own body's needs in new ways. Nurse-scientist Dorothea Orem wrote, "Self-care is not the performance of this act or that act. Self-care requires the seeing of relationships among factors, for example, diet, activity, and insulin in the management of a diabetic condition. It requires the making of adjustments in care actions on a day-to-day basis or more frequently. It requires the incorporation of self-care into the pattern of daily living" (Orem, Renpenning & Taylor, 2003, p. 213). Marijuana self-care compels a period of time spent adapting to its effects and titrating to the right dose as the person incorporates the plant into his or her lifestyle.

Marijuana has also been used extensively by people who suffer from nausea and vomiting during chemotherapy treatment. Cotter (2009) conducted a systematic literature review to evaluate the efficacy of smoked marijuana and THC as treatment for chemotherapy-induced nausea and

vomiting (CINV), a well-documented concern. A synthesis of the data in the review shows that marijuana and synthetic oral THC are more effective than placebo in treating CINV from unnamed chemotherapeutic drugs with a high emetic potential. When using traditional oral antiemetics or drugs of a moderate to high potential for CINV, smoked marijuana and oral THC were found to be equally effective. Oral THC and smoked marijuana have similar efficacy, but with smoked marijuana having the additional risk related to inhalation of smoke (Cotter, 2009).

Whiting and colleagues (2015) published a systematic review considering 28 studies involving a total of 2,454 participants and preparations including inhaled marijuana, dronabinol, nabilone, and Sativex©, among others. Twelve of the studies investigated neuropathic pain, and three looked at patients with cancer pain. The studies generally showed improvement in pain measures, with an overall OR of 1.41 (95% CI: 0.99 to 2.00) for improvement in pain with the use of cannabinoids compared with placebo. An earlier systematic review (Lynch & Campbell, 2011) of 18 randomized controlled trials of cannabinoids in 766 participants with chronic noncancer pain found that 15 of the studies reported a significant analgesic effect for the cannabinoids compared with placebo, and a number of the studies also noted improvements in sleep.

Neuropathic pain is also a concern in the care of cancer patients. A systematic review was conducted of the randomized controlled trials involving marijuana and cannabinoids for the treatment of chronic nonmalignant neuropathic pain. Analysis of the 13 included studies showed that cannabinoids may provide effective analgesia in chronic neuropathic pain that is unresponsive to other treatment (Boychuk, Goddard, Maurio, & Orellana, 2015). Another systematic review of six randomized, double-blind, placebo-controlled trials of cannabinoids (five specifically addressing neuropathic pain) found evidence for the use of low-dose medicinal marijuana in refractory neuropathic pain in conjunction with traditional analgesics (Deshpande, Mailis-Gagnon, Zoheiry, & Lakha, 2015). A randomized controlled trial of Sativex© in 359 cancer patients with poorly controlled pain despite a stable opioid regimen found that the sublingual preparation (4, 10, or 16 sprays daily for 5 weeks) reduced both pain and sleep disruption (Portenoy et al., 2012). A pharmacokinetic interaction study of vaporized marijuana in 21 patients with chronic – mostly non-cancer – pain taking sustained-release morphine or sustained-release oxycodone showed no significant effect on plasma levels of the opiates but did suggest enhanced analgesia. The investigators added anecdotal evidence for the decreasing need for opiates when patients began taking marijuana (Abrams, 2016).

In a randomized placebo-controlled trial, Sativex© did not show a statistically significant improvement in symptoms in those with intractable diabetic peripheral neuropathy pain. Participants were divided into those with and without a history of depression because people with depression have higher baseline pain scores. This study had a large placebo effect, possibly accounting for the failure to show differences between experimental and control groups (Selvarajah, Ghandi, Emery, & Tesgaye, 2010).

A systematic review performed by Fitzcharles, Baerwald, Ablin, and Hauser in 2016 concluded that the finding that cannabinoids are superior to placebo in reducing chronic pain was valid only for neuropathic pain. The evidence for efficacy of cannabinoids reducing pain in people diagnosed with fibromyalgia syndrome (FMS) is inconsistent. However, many people with FMS do seem to think that marijuana is effective. In a study conducted by the U.S. National Pain Foundation, more than 1,339 people with FMS rated marijuana more effective than FDA-approved duloxetine, milnacipran, and pregabalin. The survey showed that only 8% of duloxetine users, 10% of pregabalin users, and 10% of milnacipran users found the prescribed medication to be "very effective," while 60% of duloxetine users, 61% of pregabalin users, and 68% of milnacipran users replied that the medications "do not help at all." In contrast, 62% of marijuana users rated the plant "very effective." Only 5% said that marijuana did not help at all (Fitzcharles et al., 2016).

MRSA and Antibacterial Action

Methicillin-resistant *Staphylococcus aureus* (MRSA) is an antibiotic-resistant gram-positive bacteria. Studies show that about one in three people in the United States carry S. aureus in their noses, usually without any signs of illness, and two in 100 people carry MRSA (Centers for Disease Control and Prevention, 2017). Terpenoids are aromatic compounds found in the essential oil molecules of plants that can act as a part of the broader immune response of a plant; they may be a protectant for a plant against a predator or an attractant for pollinators. Current research on the terpenoids in marijuana, such as alpha-pinene and limonene, could be explored to see if they, like the alpha-pinene in *Sideritis erythrantha* essential oil, are effective against MRSA and other antibiotic-resistant bacterial strains (Köse, Deniz, Sarikürkçü, Aktaş, & Yavuz, 2010). Pure CBD powerfully inhibits MRSA (minimum inhibitory concentration 0.5 to 2 mg/mL; Appendino et al., 2008). The ability of monoterpenoids to enhance skin permeability and entry of

other drugs may further increase antibiotic benefits (Russo, 2011).

A study tested hemp seed oil, as well as its emulsion, against the growth of selected bacteria using disk diffusion and broth microdilution methods. The antibacterial effect of hemp seed oil was documented against *Micrococcus luteus, Staphylococcus aureus,* and *Salmonella.* Oil quality depends on seed origin and extraction method. The formulated emulsions did not exhibit the anticipated antibacterial activity. However, unrefined cold-pressed hemp seed oil did show activity (Mikulcová, Kašpárková, Humpoliček, & Buňková, 2017).

Marijuana for Other Diseases and Health Concerns

Researchers are examining marijuana's role in the relief of symptoms related to a number of disease and health concerns. The following are a few examples of published studies.

Crohn's Disease

Anecdotally, people have reported marijuana as having a positive effect on Crohn's disease symptoms. In one study (Naftali et al., 2013), the sample size was 21 patients (mean age 40 years ± 14 years; 13 men) with Crohn's Disease Activity Index (CDAI) scores greater than 200/600 (disease severity) who had not responded to therapy with steroids, immunomodulators, or antitumor necrosis factor-alpha agents. Patients were assigned randomly to two groups, one given marijuana cigarettes containing 115 mg of THC twice daily and the other given cigarettes containing marijuana flowers from which the THC had been extracted. Disease activity and laboratory tests were assessed during 8 weeks of treatment and then 2 weeks thereafter. Complete remission (CDAI score < 150) was achieved by 5 of 11 subjects in the marijuana group (45%) and 1 of 10 in the placebo group (10%; $p = 0.43$). A clinical response (decrease in CDAI score of >100) was observed in 10 of 11 subjects in the marijuana cigarettes group (90%; from 330 ± 105 to 152 ± 109) and 4 of 10 in the placebo group (40%; from 373 ± 94 to 306 ± 143; $p = 0.028$).

Three patients in the marijuana group were weaned from steroid dependency. Subjects receiving marijuana cigarettes reported improved appetite and sleep, with no significant side effects. Although the primary end point of the study (induction of remission) was not achieved, a short course (8 weeks) of THC-rich marijuana produced significant clinical, steroid-free benefits in 10 of 11 people with active Crohn's disease as compared with those who received placebo, without side effects. Although this study had a small sample, the attention given to the botanical

detail of the study design is superior. The investigators acknowledged and accounted for the problem that medicinal marijuana and all plants contain various constituents in a mixture, making it difficult to measure the contribution of each one. They dealt with the standardization issue by choosing marijuana for the study from genetically identical plants grown from twigs of the same mother plant and in equal conditions. Plants were tested to verify an equal content of active ingredients. The investigators also standardized the machine-made cigarettes to contain equal weights of marijuana flowers (Naftali et al., 2013).

Nonalcoholic Fatty Liver Disease

A population-based, case-controlled correlational study tested the hypothesis that marijuana is associated with reduction in non-alcoholic fatty liver disease. The risk factors identified from more than 6 million patient records included age 40 to 60 years, being female, hyperlipidemia, hypertension, alcohol use, diabetes, metabolic syndrome, and being a non-Hispanic Caucasian person. The study found the hypothesis to be supported (Adejumo et al., 2017).

AIDS-Associated Anorexia

According to Lutge, Gray, and Siegfried (2013), the FDA approved dronabinol for the treatment of AIDS-associated anorexia using a study published in 1995 that at the time was the only study amenable to further analysis. The study, with a sample size of 139 (88 evaluable), found that participants administered dronabinol were twice as likely to gain 2 kg or more in body weight. The mean weight gain was 0.1 kg, as compared to a loss of 0.4 kg in the placebo group.

Sleep Disturbances

Sleep disturbances are prominent symptoms in individuals with substance use disorders. A self-report online survey of 248 people suggests that those who are “risky” marijuana and/or alcohol users are likely to report poor sleep quality rather than daytime sleepiness. Riskiness was determined by a score of lower than 6 for a 39-item instrument called the Marijuana Screening Inventory. Women typically have poorer sleep outcomes than men, as do people who use both alcohol and marijuana (Ogeil, Phillips, Rajaratnam, & Broadbear, 2015).

A study of 13 daily marijuana users, all men, examined the effects of around-the-clock dosing with oral THC on sleep latency and ability to fall asleep. The participants were given an escalating dose up to 120 mg on days 5 and 6. The overall amount of nighttime sleep decreased slightly during the study. Although other reports have suggested that people typically have

somnolent side effects after receiving oral THC, this study suggests, although it had a very small number of participants, that people may become tolerant to the effects of THC through sustained use (Gorelick et al., 2013).

Rapid eye movement sleep behavior disorder (RBD), in which people act out their dreams, is considered a prodromal symptom of Parkinson's disease (PD). Marijuana is being explored for its neuroprotective effects in RBD/PD. Four patients with RBD/PD were treated with CBD for 6 weeks. Three received 75 mg per day and one person 300 mg per day. All four subjects had a significant decrease in symptoms (Chagas et al., 2014).

ORAL HEALTHCARE CONCERNS AND THE MARIJUANA USER

Smoking tobacco products has been linked to health hazards related to the heat of combustion and the inhalation of many chemicals and adjuvants into the lungs. Users of marijuana and healthcare professionals hold similar concerns about marijuana smoking. The herb can be rolled into a cigarette for smoking, called a "joint," or smoked using a water pipe or "bong." In a bong, the smoke from the burning marijuana bubbles through the bong water, where it is cooled. It is important to note that particulate matter from the burning action is not removed by the water. Hashish is typically smoked using a pipe or bong, or mixed with marijuana and smoked as a joint or vaporized.

There are many people who smoke both tobacco and marijuana. A joint (marijuana cigarette) prepared with tobacco is known as a "spliff" or "kiff." A systematic review of 28 studies showed that marijuana users who also smoked tobacco were more dependent on marijuana, had more psychosocial problems, and had poorer cessation outcomes than those who used marijuana but not tobacco (Peters, Budney, & Carroll, 2012).

As electronic cigarettes (e-cigarettes) are becoming more popular with tobacco smokers, "vaping" with e-cigarettes and electronic vaporizers is emerging as a possible method for inhaling marijuana (Tashkin, 2015). People who use e-cigarettes believe that vaping is healthier, as well as more discreet because it produces less odor than smoking. Disadvantages are that vaping produces dry mouth and fewer positive marijuana effects (Etter, 2015). Marijuana buds and oil are often the

product of choice for these devices rather than hashish, wax, or butane honey oil. In an exploratory study (Etter, 2015), 45% of individuals who smoked and vaped marijuana reported that vaping reduced their marijuana use, 37% said it had no impact on their marijuana use, and 6% said that it increased their marijuana use. Vaping is also less expensive than traditional smoking. One in vitro study concluded that "temperature-controlled, electrically-driven vaporizers efficiently decarboxylate inactive acidic cannabinoids and reliably release their corresponding neutral, active cannabinoids. Thus, they offer a promising application mode for the safe and efficient administration of medicinal cannabis" (Lanz, Mattson, Soydaner, & Brenneisen, 2016).

One literature review revealed something about marijuana that is somewhat counterintuitive: It suggests that marijuana increases rather than reduces forced vital capacity (FVC) in patients (Ribeiro & Ind, 2016). This effect may be related to the anti-inflammatory effects of the plant. However, the review also cited several community-based studies, all but one of which showed significant increase in symptoms of chronic bronchitis and use of acute care services for respiratory illness in people who frequently smoke marijuana.

An analysis of survey questions and standardized spirometry data from a cross-sectional study of adults in the United States who participated in the National Health and Nutrition Examination Survey from 2007 to 2010, showed that 59.1% had used marijuana and 12.2% had used marijuana in the last month. The effect of smoking marijuana was measured as the ratio or relationship between lung function scores recorded as forced expiratory volume and FVC. The study concluded that, despite marijuana smoke being a known irritant to the airways of the lungs, cumulative lifetime marijuana use, up to 20 joint-years, is not associated with adverse changes in the above spirometric measures of lung health. However, people who smoke marijuana for more than 20 joint-years may have a significant increased risk of lung disease when compared with those who have never smoked marijuana (Kemper, Honig, & Martin, 2015).

Marijuana-Induced Oral Pathology

In general, marijuana users have poorer oral health than non-users, with higher plaque scores, higher decayed, missing and filled (DMF) teeth scores, and less healthy gingiva (Darling & Arendorf, 1992). One of the most significant adverse effects of marijuana use is xerostomia, thus, chronic use of marijuana increases the risk of caries (Darling & Arendorf, 1993 and Cho, Hirsch & Johnstone, 2005). Marijuana smoking causes changes in the oral epithelium, termed

‘cannabis stomatitis’; this includes hyperkeratosis and leukoedema of the buccal mucosa. Acute signs and symptoms include sialostasia, xerostomia and irritation and superficial anaesthesia of the oral epithelium (Maloney, 2011). With chronic use, ‘cannabis stomatitis’ presents as chronic inflammation of the oral epithelium and leukoplakia, which may progress to neoplasia. Marijuana can elicit variable parasympathetic effects, which in combination with a stress response, such as a visit to the dentist, may be associated with syncopal episodes. Dental treatment on patients who are active users or intoxicated can result in acute anxiety, psychotic-like paranoiac thoughts and dysphoria. The use of local anesthetic solutions containing epinephrine may seriously prolong tachycardia already induced by an acute dose of marijuana (Maloney, 2011, and Cho, Hirsch & Johnstone, 2005, and Jones, 2002). Table 3 summarizes the dental implications of treating marijuana users.

Marijuana-related oral cancer usually occurs on the tongue and the anterior floor of the mouth (Zhang et al, 1999, and Marks et al, 2014, and Firth, 1997). The mechanism by which marijuana smoke acts as a carcinogen relates to the presence of benzopyrene, nitrosamines and aromatic hydrocarbons, in twice the concentration as found in the same amount of tobacco smoke (Tashkin, 2018). Marijuana smoke is associated with dysplastic changes within the epithelium of the buccal mucosa (immature cell forms, anucleated squamous cells, increased nuclear pleomorphism and increased mitotic activity and abnormalities). Smoking marijuana is associated with oral premalignant lesions, including erythroplakia and leukoplakia. One study found that the association between marijuana use and head and neck cancer was stronger among younger patients (less than 50 years old) (Zhang et al, 1999). The long-term prognosis in young patients with head and neck cancer is poorer than in older patients because tumors appear more aggressive in younger patients, and require more extreme treatment such as radiotherapy and surgical resection. A synergistic effect between marijuana and tobacco smoke has also been observed, suggesting the interactions of different risk factors further increases the risk of developing oral cancer (Zhang et al, 1999). The relationship between the presence of oral papilloma and marijuana smoking may be related to suppression of the immune response by different cannabinoids, although the human papilloma virus may also play a significant role (Darling & Arendorf, 1993).

Oral candidiasis and the density and intra-oral prevalence of candidal species are increased in marijuana smokers, most likely due to the presence of hydrocarbons in marijuana, which act as an energy source for certain candida species (Marks et al, 2014). Additional factors such as a

compromised immune response due to chronic marijuana use, nutritional factors and poor denture hygiene should also be considered.

A fiery-red and painful gingivitis with associated white patches has been documented on the gingiva of marijuana smokers (Darling & Arendorf, 1993). Diffuse gingival hyperplasia and concurrent alveolar bone loss was also noted in this study in chronic abusers of marijuana. However, for both conditions, other etiologies were not fully considered, and therefore supporting evidence is lacking. Current knowledge on the effects of cannabinoids on periodontal health is inadequate because the frequency, amount, duration and mode of administration of marijuana differs amongst individuals, rendering controlled epidemiological studies difficult to undertake. Personal risk factors including oral hygiene, general health, age, concurrent tobacco smoking and polypharmacology make it difficult to identify the specific influence of cannabis abuse on susceptibility to periodontitis.

Marijuana-Dental Drug Interactions

Table 4 delineates the medications most commonly used in dentistry (Donaldson & Goodchild, 2012, and Rosenberg, 2010). In reviewing potential drug interactions between marijuana and these particular medications, there are only a few, but important, considerations.

Analgesics and Antiinflammatory Agents

Acetaminophen has a synergistic effect when administered with a nonsteroidal anti-inflammatory drug (NSAID) and the combination has repeatedly shown superior analgesic efficacy compared to either drug alone (Moore & Hersch, 2013 and Aminoshariae, Kulild, Donaldson, & Hersch, 2016). This therapeutic combination also has a better side effect profile and less potential for abuse compared to opioids. For example, NSAIDs have been shown to be associated with a reduced incidence of postoperative nausea and vomiting by up to 30% compared to narcotics (Elia, Lysakowski, & Tramer, 2005). Knowledge and understanding of individual maximum recommended doses cannot be over-emphasized since the most effective dose for the shortest period of time will provide the greatest pain relief balanced against patient safety concerns. There are no specific concerns in combining acetaminophen with an NSAID to insure appropriate pain relief in patients who may be concurrently taking marijuana. While this is also true for the coadministration of glucocorticoids, the same cannot be said for narcotic-

containing analgesics (i.e., codeine, hydrocodone and oxycodone).

Unfortunately, there is an historical and unfounded belief that patients with significant orofacial pain should be prescribed opioid-containing analgesics and this misinformation has added to our current opioid epidemic. Opioids are frequently prescribed for short-term orofacial pain management associated with dental procedures in emergency and clinical settings, despite the fact that they are not anti-inflammatory agents, and therefore do not target the underlying pathophysiology of orofacial pain (Moore & Hersch, 2013 and Aminoshariae, Kulild, Donaldson, & Hersch, 2016). Opioids should definitely not be prescribed in patients who may be concurrently taking marijuana because both of these agents act as central nervous system (CNS) depressants.

Antibiotics and Antifungals

While there are no specific drug interactions between the most common antibiotics prescribed in dentistry and the use of marijuana, certain antibiotics can increase the effects of specific cannabinoids such as cannabidiol which are metabolized through the cytochrome (CYP) isoenzyme system. Erythromycin may be the classic example of a drug which acts as an inhibitor of CYP3A4. Taking erythromycin with cannabidiol can lead to increased effects of cannabidiol, because cannabidiol is also metabolized by CYP3A4. The best strategy would be to avoid this combination, and if a macrolide antibiotic is indicated, prescribing azithromycin instead of erythromycin would be an excellent alternative. Azithromycin is not metabolized through the cytochrome enzyme system.

The antifungal fluconazole is a strong CYP2C19 inhibitor and moderate inhibitor of CYP3A4, therefore concurrent administration with marijuana can lead to the increased effects and side effects of cannabidiol. If an antifungal agent is desired to help treat oral candidiasis in a marijuana user, the swish and swallow approach with nystatin would be a better choice in order to avoid this drug interaction.

Local and Topical Anesthetics

There are no drug interaction concerns between marijuana and the local or topical anesthetics typically used in dentistry.

Sedative Agents

Given the high incidence of dental fear in the general population, many patients who visit the dentist will inquire about the opportunity for sedation services. In most cases the intervention will be with either oral or inhalational pharmacological modalities, and each of these present specific concerns in the marijuana user. In the case of the marijuana smoker, an odor from the patient may be indicative of recent usage, even if the patient does not admit this directly. These patients have already self-medicated with a sedative and the addition of another oral or inhalational sedative would be moot. It is more difficult to discern patients who may have recently ingested marijuana in a topical or edible formulation. If the practitioner's level of suspicion is high, but unconfirmed by the patient, the prudent practitioner may choose to avoid additional sedative(s). In the highly fearful patient, low, conservative doses of any additional CNS depressant may be considered (i.e., nitrous oxide – oxygen inhalational sedation, or oral medicines such as the benzodiazepines).

Chronic marijuana users who have severe dental anxiety may choose to work with oral healthcare professionals to insure their oral or inhalational sedation is not compromised by their marijuana use. In these cases, topical and edible formulations of marijuana should be avoided for at least twenty-four hours prior to the dental appointment (or longer if possible), in order to avoid the potentiated effects of this drug combination.

In the case of chronic marijuana smokers, there is a greater concern as to the overall respiratory health of the patient, in which case nitrous oxide – oxygen inhalational sedation may in fact be contraindicated. According to one study, smoking both tobacco and marijuana synergistically increased the risk of respiratory symptoms two and a half times over baseline while the risk of developing chronic obstructive pulmonary disease (COPD) increased three fold (Tan et al, 2009). If the patient has COPD, nitrous oxide – oxygen inhalational sedation is contraindicated, and the OHCP is therefore left with oral sedation as the pharmacological alternative (Donaldson, Donaldson, & Quarnstrom, 2012).

Similar to the analgesics above, in patients who may concurrently take marijuana and another CNS depressant, monitor for excessive sedation and somnolence during coadministration is advisable.

A recent study of 138 tobacco smokers surveyed concerning their marijuana use found that anxiety sensitivity was related to marijuana use. In other words, users of marijuana seemed to

experience anxiety more easily than they might when not using marijuana. The 25-item and 5-subscale Marijuana Motives Measure and the Anxiety Sensitivity Index-3 were the instruments employed in the study (Norberg, Olivier, Schmidt, & Zvolensky, 2014). Healthcare professionals may want to consider helping clients who are low in anxiety sensitivity and who use both marijuana and tobacco to focus on choosing alternative recreational behaviors that are associated with less health risk than smoking marijuana.

Marijuana-Herbal Interactions

One reason for the record of safe use of herbal remedies is that plants are made up of hundreds of different biochemical constituents. Used in whole form, whether decocted as tea or used as an extract or salve, the action of whole-plant therapies is complex when looked at through a reductionist lens. The chemical constituents in plants occur in very small amounts. Herbs, although they have healing properties and the ability to create change and can even cause chemical reactions in the body, are not pharmaceutical drugs typically produced from one substance. They are much more complex. When people ingest, apply, or inhale herbs, they are taking in very small "doses" of particular substances that are in a natural, rather than synthetic, state and are in formulation, so to speak, as they occur in nature. The safe use of whole plants is related to the use of a plant in its complex natural state. Often, botanical science reveals that medicinal plants contain constituents in balance, with seemingly opposing actions. Plant pharmacology is replete with examples of such balance or contradiction. For example, the hypericin constituent in St. John's wort (*Hypericum perforatum*) "induces the cytochrome P450 system (inducing CYP3A4 in hepatocyte cells) and at the same time contains the bioflavonoid quercetin, which is a 3A4 inhibitor" (Libster, 2002, p. 74). However, when people decide to use a standardized extract of a single constituent of an herb, such as hypericin, much like a drug, or use an herb in a form that departs from traditional use, the historical safety record is no longer applicable. For example, if the safety record of traditional medicinal use of garlic is related to eating the fresh chopped bulb in food or as an infused oil, new safety data will have to be collected for use of powdered garlic tablets. Whereas safety "information" related to traditional use of herbs is shared through oral tradition (e.g., where and when to harvest, how to gather and prepare and apply, how much to take and when) biomedical use of herbs compels research and further gathering of population safety information about new forms of herbal remedies and applications. When herbs are used in the

treatment of biomedically defined diseases, the same safety standards are followed as are used with drugs. Marijuana has been used for centuries and is relatively safe when compared with other illicit drugs. However, when the herbs' constituents are removed and placed in pharmaceutical single-constituent drug form, a new history of use begins. Safety cannot be inferred for these or any whole-plant products that diverge from traditional use. Marijuana-based pharmaceuticals and innovative products such as cannabinoid-terpenoid synergy drugs require a clinical-trial evidence base. At this time, herbal medications are not part of the typical dental armamentarium so that herbal interactions with marijuana are not a specific current concern. The interaction between herbal medicines and dental drugs has been covered in other modules (Donaldson, 2016).

LEGAL STATUS OF MARIJUANA

Marijuana is the most commonly used illicit drug in the United States. In 1 month in 2014, as reported by the Substance Abuse and Mental Health Services Administration (SAMHSA), more than 22 million people aged 12 years and older used marijuana. According to the 2014 survey, 4.2 million people had disorders related to the use of marijuana. Among adolescents aged 12 to 17, 2.7%, or 667,000, were found to have marijuana use disorder (SAMHSA, 2015).

Now that the use of marijuana is becoming legal in many states (30 at the time of publication), healthcare professionals are well positioned to affect the choices communities make about the supply, distribution, prescription, and care of people using marijuana, as well as the regulatory developments surrounding marijuana's future, its use, and abuse. Worldwide, the growing development of marijuana-based medicines has led to greater discussion among prescribers, the public, and policy makers. Ethical principles in health care mandate a degree of separation between the prescribing of a drug and its supply, thus necessitating the need for independent channels of distribution. In the case of marijuana, growers are engaged in distribution and quality control of supply, and marijuana dispensaries are being established in states where marijuana is legal. Should the federal prohibition on marijuana be lifted and medical marijuana be legalized, pharmacists may also be responsible for the handling, supply, counsel, and oversight of the safe use of the plant as well as its related products and drugs.

The line between medicinal and recreational use of marijuana is often blurred. Greater

awareness and education can clarify distinctions between these two purposes for using marijuana (Isaac, Saini, & Chaar, 2016). The first part of this module provided insight into the cultural and historical context of both medicinal and recreational uses. Marijuana's legal status has often been contrasted with that of legal opioids, which have killed thousands more people than marijuana. (States that have legalized marijuana have reported a substantial decline in opiate and pain medication prescription overdose rates; Schepker, 2017). Use of both illicit and prescription opioids has reached the status of a "public health emergency" (U.S. Department of Health and Human Services, 2017). This is not to say that there are not significant potential risks in the legalization of marijuana. A published review of drug policy publications suggests that it is plausible that legalizing recreational marijuana use in the United States could substantially reduce its price and increase heavy use and marijuana-related problems such as dependence and substance misuse among those who already use the drug. In the longer term, legalization may also increase the number of new users (Hall & Lynskey, 2016).

To provide background to the issue of legalization of marijuana, the following is a brief outline of the history:

1850: In the United States, marijuana was sold over the counter and was commonly used as treatment for such diseases as cholera, alcoholism, opiate addiction, and convulsive disorders.

1906: Congress passed the Pure Food and Drug Act, a piece of legislation designed to restrain abuses in the patent-medicine industry. It was also the first piece of legislation in the United States to mention marijuana. Until this time, there was no concerted effort on the part of the government to regulate psychoactive substances. Cocaine was still in Coca-Cola; heroin kits were available for sale at Sears. No drug was illegal.

1930: The Federal Bureau of Narcotics (FBN) was formed in Washington, DC.

1936: Every state then in the union passed a law restricting possession of marijuana and eliminating its availability as an over-the-counter drug.

1937: Although opposed by the American Medical Association, the Marihuana Tax Act of 1937 was passed to prohibit all nonmedical use of marijuana in the United States. However, the law also limited medical use with fees and regulatory restrictions that imposed a significant burden on physicians prescribing marijuana.

1970: On October 27, 1970, the Comprehensive Drug Abuse Prevention and Control Act was enacted. Title II of the act – The Controlled Substances Act – established categories varying from Schedule I (the strictest classification) to Schedule V (the least strict). Marijuana was placed in the Schedule I category, thereby prohibiting its use for any purpose.

1996: California voters approved Proposition 215 to legalize medical marijuana. However, the Clinton Administration opposed the proposition and threatened to revoke the prescription-writing privileges of doctors who prescribed the drug. Since the passage of Proposition 215, marijuana use among youth in California has declined significantly (Lee, 2012).

Although the federal government of the United States currently prohibits the sale and use of marijuana, thirty U.S. states and the nation's capital have made marijuana legal for all adults, and most states allow for some use of medicinal marijuana. A total of 29 states, the District of Columbia, Guam, and Puerto Rico allow for comprehensive public medicinal marijuana programs. The Marijuana Policy Project (2018) and the National Conference of State Legislatures (2017) provide web-based resources that detail each state's legalization status for medicinal marijuana. Contained within the federal budget are provisions to protect a state's right to responsibly regulate medical marijuana programs. Since December 2014, the Rohrabacher-Farr amendment has prohibited the Justice Department from spending funds to interfere with the implementation of state medical marijuana laws. This amendment must be renewed each fiscal year to remain in effect and was included in a series of spending bills approved in 2016 and 2017, with the most recent extension being approved with the passage of the budget on February 9, 2018. Several states and the District of Columbia have stopped jailing individuals for possession of small amounts of marijuana (Marijuana Policy Project, 2017).

Despite concerns that legalization of marijuana could increase crime risk, several studies have shown that instating laws allowing for medical marijuana and dispensaries is not associated with increased crime. In 2012, a study published in the Journal of Studies on Alcohol and Drugs found that the density of medical marijuana dispensaries was not associated with violent or property crime rates (Kepple & Freisthler, 2012). In 1914, the Harrison Act placed narcotics under the regulatory control of the federal government, restricting access to nonmedical consumers. The Harrison Act made the first legal distinction between recreational and medical use of drugs. That year, undercover sting operations led to the arrest of 25,000 physicians on narcotics charges. Three

thousand were given prison sentences and “thousands had their licenses revoked for giving out opiates” (Lee, 2012, p. 41). The pharmaceutical industry’s lobby did, however, keep marijuana from being covered by the Harrison Act. Few people were smoking marijuana at the time, although some were still eating hashish. Prohibition of marijuana began in California, where it was outlawed in 1915. The political rationale was control of Mexicans in the labor force. “Arrests and convictions of ‘Mexican’ workers for marijuana possession were most concentrated during the years of, and in the areas with, the highest levels of labor organization and action” (Lee, 2012, p. 42). During most of the Prohibition era, marijuana was exempt from national crime legislation; however, in 1929 Congress passed the Narcotic Farms Act (later repealed in 1944), which misclassified Indian hemp as a habit-forming narcotic (Lee, 2012) and authorized construction of two hospitals in the prison system for treating drug addicts, including non-medical marijuana users deemed addicts (Lee, 2012). As a social upside, marijuana was at the center of the jazz culture that brought together Black and White Americans interested in the emerging music genre. By 1931, when the FBN was formed in Washington, D.C., many states had banned marijuana.

Marijuana is currently listed as a Schedule I substance under the Controlled Substances Act of 1970, the highest classification under the legislation, and remains illegal at the federal level. The Controlled Substances Act regulates the manufacture, importation, possession, use, and distribution of substances such as marijuana. A Schedule I drug, as defined by the U.S. Drug Enforcement Administration (DEA), is a substance that has a high potential of being abused by its users and has no acceptable medical use (DEA, n.d.). Recently, however, legislation has been rapidly changing at the state level. Health professionals, along with the public and legislators, are reviewing the evidence resulting from marijuana prohibition. Some evidence suggests that marijuana laws have contributed to increased prevalence of illicit marijuana use and marijuana use disorders (Hasin et al., 2017). States recognize (make the policy for) medical use, limited medical use, no access laws, or some recreational use.

EMPLOYER CONSIDERATIONS AND CONCERNS

No single constituent determines the risks to public health from illicit marijuana use or

misuse of medicinal marijuana. Apples, after all, are not removed from the market or banned from farms because the seeds contain cyanide. The risk is weighed against the benefit, which is often a matter of degree. The people and their state legislatures seem to be weighing risks against benefits as, one by one, states are voting to legalize marijuana in varying degrees after decades of prohibition. This section focuses on community health and education considerations and concerns related to the growth of the marijuana industry in American communities. When weighing the benefits and risks of using marijuana, some basic questions arise that are relevant to healthcare professionals as represented in professional white papers, position statements, and scientific discussions and publications:

- What do people who use marijuana in their self-care practices need in order to do so safely?
- What is the new role of government in protecting the public if it abandons marijuana prohibition?
- What are the roles and responsibilities of healthcare professionals related to marijuana use?
- What are emerging issues in states that have legalized marijuana related to widespread use?

It is important to consider some of the identified health considerations and concerns related to the growth of the marijuana industry in American communities. In general, healthcare professionals' approach to shared decision making and person-centered care suggests that they will take a client's personal experience into account. People have various reasons for choosing their self-care practices. Research has shown that they are often quite rational in their thought processes concerning their health choices, even when they seem to be making choices "alternative" to mainstream biomedical culture's view of safe and effective care (O'Connor, 1995). They may request further information, but such requests should not be interpreted necessarily as a sign of ignorance. The medicinal marijuana culture is a dominant subculture of the larger self-care culture, identified by social scientists as the "hidden health care system" (Levin & Idler, 2010). Medicinal plants have been part of the foundation of healthcare systems for centuries (Libster, 2004), yet many people may feel disconnected from their environment and the plants that are responsible for their food, shelter, and medicine. They may have no knowledge of what it takes to grow the tomato and prepare the tomato sauce that is on their pizza, or what plant has been the prototype for the newest cancer drug. Then, lacking this knowledge, they are faced with the decision points that have always come with use of medicinal plants. Marijuana is a plant no different from any other. It has many uses and forms, as well as hundreds of constituents, all seemingly at odds when the

plant is examined in its reduced parts – but with scientific evidence of an intricate and powerful synergy of substances, an "entourage of effects," when examined as a whole (Russo, 2011). Herbalists, who are often community experts on the subject of the application of medicinal plants, are an excellent referral resource for healthcare professionals who are learning to counsel people considering or already taking plant medicines such as marijuana (Libster, 1999). Nurses, pharmacists, and behavioral health practitioners can forge partnerships with knowledgeable herbalists to begin to address existing and emerging public health considerations and concerns.

Screening instruments commonly employed in assessing marijuana-related problems because they are brief and easy to use are the Severity of Dependence Scale (SDS – symptoms of dependence), Cannabis Use Disorders Identification Test (CUDIT – motivational aspects of use), Cannabis Abuse Screening Test (CAST – social and health problems), and Problematic Use of Marijuana (PUM). All scales have shown moderate to high internal consistency (Cronbach's alpha ranging from 0.72 to 0.92), which means that the scales are good at measuring what they are supposed to measure. The SDS is a five-item scale that measures the degree of psychological dependence, that is, the individual's feeling of impaired control and anxiety toward drug taking. The CUDIT screens for current marijuana use disorders (abuse or dependence), whereas the PUM measures harmful use, problems in interpersonal relationships, and psychophysical functioning. Basically designed for adolescents or young adults, the CAST identifies patterns of marijuana use leading to social or health problems for the user or others in society (Piontek, Kraus, & Klempova, 2008).

Marijuana Drug Screening Issues

Finally, while marijuana is legal for medical and recreational use in some U.S. states, under federal law, cannabis use is illegal, and employers in industries that are heavily regulated by the federal government screen their employees randomly and include drug testing as part of their hiring process. For non-federally regulated employers, federal law doesn't require drug testing. However, there are state and local governments that enforce laws regulating drug testing. Employers have the legal right to maintain a drug- and alcohol-free work environment, and are allowed to test applicants and employees as long as the employer clearly informs those applicants and employees of the company's drug testing policies, including pre-employment screening and random drug testing. In some cases, an offer of employment may be conditional pending the results

of a drug test. These policies may be stated in the job description, but most often will be stated in a clearly written agreement within the application or employee handbook, which applicants and employees are required to agree to and sign in order to be hired or maintain employment. Some employers have a company policy that directly addresses marijuana use, while others do not.

Drug screening for marijuana has become a debated topic in states where medical and/or recreational use is legal. The biggest difference between alcohol and cannabis is how they are detected through testing. Alcohol does not linger in the bloodstream like marijuana does. Someone can fail a marijuana drug test weeks after using marijuana because THC takes a long time to leave the bloodstream. A positive test does not mean the person is impaired at that moment. Instead, it just shows that they used marijuana within the last few weeks.

On the other hand, there are on-the-spot tests like the breathalyzer to determine the alcohol level and subsequent impairment of an individual at that moment. This enables lawmakers to create laws regarding the consequences of having more than the legal limit of alcohol in your system. The technology to test marijuana levels with such accuracy has yet to be created. Without the ability to do accurate on-the-spot testing, it is challenging to determine what a legal level (the lowest level that does not cause impairment) of THC would be. Therefore, any trace can be considered exceeding the legal limit.

SUMMARY

Oral healthcare practitioners face significant challenges today as patients are living longer, collecting chronic diseases and the myriad of medications to treat these, all while retaining their dentition and requiring the services of dental professionals. In the management of oral health dentists will often employ surgical as well as pharmacological interventions which have been time tested yet continue to evolve based on current medical evidence. Keeping current with the latest therapies to treat patients, while trying to keep a pulse on the many more medications patients may be taking outside of the office (nutraceuticals, herbals, botanicals, prescription, non-prescription, social and illicit drugs), adds to this overall challenge of being able to treat patients both safely and effectively.

Medicinal marijuana is a highly controversial topic in the United States today. While it is

unlikely to play a role at this time in patient management from a dental perspective. The number of patients using marijuana is steadily increasing, therefore, OHCPs need to understand and be able to manage patients who are using marijuana for both recreational and medical purposes. There is much to learn about medicinal marijuana from evidence other than clinical trials since many more patients are exposed to this medicine. This course includes historical data and evidence from in vitro studies, literature reviews, meta-analyses, surveys, and community health studies that have contributed in a meaningful way to current scientific understanding of the health outcomes witnessed in the public sphere, where marijuana use is proliferating. It is now up to oral healthcare practitioners to learn about the pharmacology and current state of medicinal marijuana since the impact of this drug has specific consequences on oral pathology, drug interactions and oral health care.

EXAM QUESTIONS

Questions 1–20

Note: Choose the one option that BEST answers each question.

1. Recreational use of marijuana is best defined as the user's intention to
    a. become intoxicated.
    b. relieve pain.
    c. sleep.
    d. exercise.

2. The resin or sap that forms on marijuana and is collected for use is known as
    a. dope.
    b. joint.
    c. hashish.
    d. smack.

3. The main psychoactive constituent in marijuana is
    a. cannabidiol.
    b. Cannabis indica.
    c. lysergic acid diethylamide (LSD).
    d. delta-9-tetrahydrocannabinol (THC).

4. The paradoxical stimulating and sedating effect produced by smoking marijuana is similar to the effect produced by
    a. alcohol.

b. LSD.

c. antidepressants.

d. coffee.

5. Hemp is a strain of *Cannabis*

a. *indica* that is high in THC.

b. sativa that is low in THC.

c. *indica* with no THC.

d. *sativa* that is high in THC.

6. In the 1800s, marijuana was used by physicians in the treatment of

a. migraine headaches.

b. cancer.

c. osteoporosis.

d. tetanus.

7. The effects of eating hashish are not felt for at least

a. 5 to 10 minutes.

b. 15 to 20 minutes.

c. 30 to 60 minutes.

d. 70 to 90 minutes.

8. Common effects of smoking *Cannabis sativa* include

a. whole-body relaxation.

b. sleepiness.

c. calmness.

d. optimism.

9. A major risk factor for marijuana use disorder is

a. use before age 18.

b. eating hashish.

c. adulteration.

d. use of *Cannabis indica.*

10. Marijuana withdrawal symptoms can be similar to those of

a. cocaine.

b. LSD.

c. nicotine.

d. alcohol.

11. Two major phytocannabinoids responsible for medicinal effects of marijuana are delta-9-tetrahydrocannabinol (THC) and

a. cannabidiol.

b. 3-hydroxycannabidiol.

c. cannabis.

d. endocannabioid.

12. The two drugs the U.S. food and Drug Administration has approved for use in chemotherapy-induced nausea and vomiting are dronabinol and

a. nabitan.

b. nabilone.

c. nabumetone.

d. nabazenil.

13. Cannabinoid type 1 (CB1) receptors are found mainly in the

a. immune system.

b. gut.

c. brain.

d. lungs.

14. Anandamide is an examples of a/an

a. hormones.

b. phytocannabinoids.

c. glutamate.

d. endocannabinoids.

15. The reason for marijuana's effect on the human brain is thought to be that

a. delta-9-tetrahydrocannabinol (THC) is similar to endocannabinoids.

b. cannabinoid type 1 (CB1) is similar to endocannabinoids.

c. cannabidiol (CBD) is similar to endocannabinoids.

d. gamma-aminobutyric acid (GABA) is similar to endocannabinoids.

16. A new physiological theory about endocannabinoid system (ECS) deficiency has been supported by some evidence from studies of people with

a. bipolar disorder.

b. allergies.

c. chronic obstructive pulmonary disorder.

d. posttraumatic stress disorder.

17. According to a 1999 Institute of Medicine report, the major adverse effect of oral THC in older adults with no previous experience with taking marijuana is

a. stroke.

b. nausea.

c. disorientation.

d. depression.

18. The gateway theory, when applied to marijuana use, is unsupported mostly due to

a. confounding effects of the environment.

b. evidence for previous drug use.

c. increased public acceptance of marijuana.

d. lack of clear evidence for causation.

19. The major difference between federal and state marijuana law is that

a. federal law prohibits marijuana use for all purposes and by anyone.

b. state laws prohibit marijuana use for all purposes and by anyone.

c. federal law allows marijuana use for medical purposes only.

d. state laws allow marijuana use for palliative care only.

20. A systematic review of the literature shows that marijuana users who smoke tobacco are

a. less dependent on marijuana.

b. more dependent on marijuana.

c. equally dependent on marijuana and tobacco.

d. not dependent on marijuana.

This concludes the final examination.

Please answer the evaluation questions found on page v of this course book.

RESOURCES

Helpful websites and literature to enhance further learning:

National Institute on Drug Abuse

The National Institute on Drug Abuse aims to advance science on the causes and consequences of drug use and addiction and to apply that knowledge to improve individual and public health. This involves: strategically supporting and conducting basic and clinical research on drug use (including nicotine), its consequences, and the underlying neurobiological, behavioral, and social mechanisms involved and; ensuring the effective translation, implementation, and dissemination of scientific research findings to improve the prevention and treatment of substance use disorders and enhance public awareness of addiction as a brain disorder.

Website: https://www.drugabuse.gov/

Washington State Department of Health

One of the first States to legalize marijuana, Washington Initiative 502 passed in November of 2012 and went into effect July 1, 2015. I-502 directed the Washington State Department of Health to implement: a marijuana use public health hotline that provides referrals to substance abuse treatment providers, utilizes evidence-based or researched-based public health approaches to minimizing the harms associated with marijuana use, and does not solely advocate an abstinence-only approach; agrants program for local health departments or other local community agencies that supports development and implementation of coordinated intervention strategies for the prevention and reduction of marijuana use by youth and; a media-based education campaigns across television, internet, radio, print, and out-of-home advertising, separately reaching youth and adults, that provide medically and scientifically accurate information about the health and safety risks posed by marijuana use.

Website: https://www.doh.wa.gov/YouandYourFamily/Marijuana

U.S. National Library of Medicine

MedlinePlus is the National Institutes of Health's Web site for patients and their families and friends. Produced by the National Library of Medicine, the world's largest medical library, it brings you information about diseases, conditions, and wellness issues in language you can understand. MedlinePlus offers reliable, up-to-date health information, anytime, anywhere, for free.

Website: https://medlineplus.gov/marijuana.html

The Centers for Disease Control and Prevention

The Centers for Disease Control and Prevention provides up-to-date information to identify and address the public health impacts of marijuana use and improve our knowledge about the health effects of marijuana use. The CDC's goals are threefold: to increase the capacity of CDC and state and local jurisdictions to monitor use patterns and the public health effects of marijuana use through existing surveillance systems; to increase the capacity to identify, monitor, and evaluate effective public health and regulatory practices and policies to prevent marijuana-related harms and; to support state and local efforts to create and disseminate evidence-based information describing the health effects of marijuana.

Website: https://www.cdc.gov/marijuana/index.htm

U.S. Department of Health and Human Services

The National Center for Complementary and Integrative Health (NCCIH), is the Federal Government's lead agency for scientific research on the diverse medical and health care systems, practices, and products that are not generally considered part of conventional medicine. NCCIH was formerly known as the National Center for Complementary and Alternative Medicine.

Website: https://nccih.nih.gov/health/marijuana

In addition to electronic resources, the reader is also directed to more traditional textbooks that focus specifically on medical marijuana:

- M. Backes 2017, *Cannabis Pharmacy: The Practical Guide to Medical Marijuana -- Revised and Updated,* (1st ed.). New York, NY: Hachette Book Group (ISBN: 978-0-316-46418-5)

- J. Fahl, 2017, *Medical Marijuana: Complete Guide To Pain Management and Treatment Using Cannabis (Anxiety, Cancer, Symptoms, Illness, Epilepsy, CDB Oil, Hemp Oil, Cures, Growing, Dispensary*,(1st ed.). Colorado Springs, CO: CreateSpace Independent Publishing Platform (ISBN: 978-154-729102-1)
- M.H. Moskowitz, 2017, *Medical Cannabis: A Guide for Patients, Practitioners, and Caregivers,* (1st ed.). Virginia Beach, VA: Koehler Books. (ISBN 978-163-393538-9)

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