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CONTINUING EDUCATION ACTIVITY

Cannabis: A Review of the Good and the Bad

Elizabeth A.M. Frost, MD

Purpose statement: To provide information about the current state of research and the use of marijuana for medical, religious/spiritual, and recreational purposes.

Learning Objectives/Outcomes: After participating in this CME/CNE activity, the provider should be better able to:

1. List the conditions for which cannabis use has the strongest evidence of benefit.
2. Identify the risks of long-term cannabis use both for those younger than 18 years and for adults.
3. Outline the physiologic actions of some of the specific cannabinoids present in the marijuana plant.

Key Words: Cannabinoids, Cannabis, Indications for use, Marijuana, Side effects

After many years of uncertainty, a majority of states have approved the medical use of marijuana over the last 2 decades in the United States, although it remains illegal and with no approved medical use according to the US Department of Justice. Nonetheless, at least 8 states have

legalized recreational marijuana in addition to medical use, and at least 12 states will see their legislatures considering medical and/or recreational use during 2018.

In fact, recent production and sale of the herb have skyrocketed. Along with this great increase in availability, many claims have been made as to the efficacy of daily ingestion of marijuana, some with merit but many others of dubious nature. Medical practitioners in all disciplines must be aware of the current evidence regarding marijuana and the cannabinoids it

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contains, as their patient population is bound to include some who are using it in one form or another. This article provides background on cannabis, along with a review of physiologic actions, uses, and side effects.

Legal marijuana is set to be the fastest-growing industry in the United States today. A recent report from *Marijuana Business Day*, "Marijuana Business Factbook 2017," quotes legal sales growth in the United States of 30% in 2017, and predicts 45% this year, and 300% as an aggregate between 2016 and 2021, representing a \$17 billion market. The stock market has certainly also paid attention, attracting investment dollars. Other sources consider marijuana the largest cash crop in the United States, enjoying a growth rate of 77% over the last few years and an estimated 700% growth rate by this year.^{1,2} Several pharmaceutical companies such as AbbVie Inc, Corbus Pharmaceutical Holdings, and Insys Therapeutics Inc have marijuana-based drugs either in development or approved. Supplements for cannabis growers and insecticides for these plants are commercially available.

Legal marijuana is set to be the fastest-growing industry in the United States.

Although cannabis is mostly used recreationally or as a medicinal drug, it may also be used for religious or spiritual purposes. In 2013, between 128 million and 232 million people

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used cannabis (2.7%–4.9% of the global population between the ages of 15 and 65 years). By 2015, 43% of Americans had used cannabis, a number that increased to 51% in 2016, making it the most commonly used illegal drug both in the world and in the United States.³

To the US federal government, the drug remains categorized as Schedule 1,⁴ meaning it has no recognized medical benefits and its use is illegal—the same status as heroin. Nevertheless, the debate continues at local and state levels as to whether marijuana, both for medical and recreational uses, should be legal.

The 2 most prominent cannabinoids that have mind-altering properties are cannabidiol and tetrahydrocannabinol, but some 400 other compounds from the cannabis plants have been identified.

Basic Facts About Marijuana

Marijuana refers to the dried leaves, flowers, stems, and seeds from the *Cannabis sativa* or *Cannabis indica* plant. Cannabis comes from the flowering tops and leaves of the hemp plant, and has long been used for hemp fiber, hemp oils, medicinal purposes, and as a recreational drug. The 2 most prominent cannabinoids that have mind-altering properties are cannabidiol (CBD) and tetrahydrocannabinol (THC), but some 400 other compounds from the cannabis plants have been identified, even if their actions have not been determined. CBD and THC both interact with the body through the endocannabinoid system, a vital signaling system responsible for regulating a wide array of functions, including pain, appetite, memory, moods, and sleep. The chemical composition of the 2 compounds is similar to the human endocannabinoid system, allowing them to interact with cannabinoid receptors, altering the release of neurotransmitters in the brain.

CBD and THC, although they are structural isomers, have distinct differences between them that influence how they interact with the endocannabinoid system and, subsequently, the effects they elicit. THC is a direct agonist of the cannabinoid-1 receptors (CB-1), found primarily in the brain and the central nervous system. The psychoactive effect associated with recreational or medical marijuana use is due to activation of CB-1 receptors. On the other hand, CBD does not bind with CB-1 receptors and may be described as an antagonist of CB-1 agonists. Thus, CBD does not cause a high, no matter how much is consumed, and it also acts to suppress the CB-1-activating qualities of compounds like THC.

Terminology: Cannabis, Hemp, and Marijuana

Both CBD and THC are found throughout the seeds, stalks, and flowers of both hemp and marijuana. The 2 exist in cannabis plants in a wide range of proportions. However,

although THC is most plentiful in marijuana, CBD is present in higher quantities in hemp.^{4,5} The International Association of Plant Taxonomy concluded “both hemp varieties and marijuana varieties are of the same genus, *Cannabis*, and the same species, *Cannabis sativa*. Further, there are countless varieties that fall into further classifications within the species *Cannabis sativa*.”

Thus, depending on how the plant is grown and used determines whether hemp or marijuana is the correct term. Cannabis (or marijuana) is used when describing a *C. sativa*

plant that is grown for its potent, resinous glands (known as trichomes) that contain high amounts of THC. Currently, marijuana is cultivated specifically to maximize its THC content. It has been altered and

cloned with particular emphasis on increasing its THC concentration and producing more powerful intoxicating effects. Although THC content can be as low as 3%, on average, marijuana strains today contain approximately 12% THC.

Hemp describes a *C. sativa* plant that contains only trace amounts of THC and is mainly used for industrial purposes such as oils and topical ointments, and fiber for clothing and construction. The chemical composition of hemp is dominated by CBD. By definition, THC content of hemp is no more than 0.3%, nearly 10 times less than the least potent strain of marijuana. Rather, hemp naturally has more CBD than THC, making it an ideal source of CBD from cannabis.

History of Cannabis Use

Cannabis has been used in a religious, shamanic, or spiritual context in India and Nepal since the Vedic period (approximately 1500 BCE) and perhaps even as early as 2000 BCE.⁶ Greek mythology refers to a powerful drug to eliminate anguish and sorrow. Herodotus wrote of ceremonial practices by the Scythians, occurring from the fifth- to second-century BCE. Itinerant Hindu religious men have used it in Nepal and India for centuries.⁷ There is evidence of inhalation of cannabis smoke from the Third Millennium BCE. Charred cannabis seeds were found in a ritual brazier at an ancient burial site in present-day Romania.⁸ The earliest written reference to cannabis dates back to around 2727 BCE, from the Chinese emperor Shen Nung, who is considered the father of herbal medicine and agriculture.⁹ He advocated the use of cannabis not only to treat some 100 illnesses but also to make rope, fibers, and paper. He experimented widely on himself and died of a toxic overdose, but not of cannabis.

Cannabis leaf fragments and seeds have been found next to a 2500- to 2800-year-old mummified shaman in China. Evidence of cannabis consumption was also found in Egyptian mummies dated about 950 BCE, and cannabis

pollen was detected on the mummified body of Ramses II, who died in 1213 BCE¹⁰ Cannabis was also known to the ancient Assyrians, Scythians, Thracians, and Dacians. It was used by Muslims in various Sufi orders as early as the Mamluk period, by the Qalandars. Smoking pipes uncovered in Ethiopia and carbon-dated to around 1320 were found with traces of cannabis.¹¹

The oil of holy ointment, said to be told to Moses by God, calls for 250 shekels of cannabis in the Hebrew version (*kaneh bosc*), although in the King James Bible version it was mistakenly changed to the plant *calamus*.¹²

An early Chinese surgeon, Hua Tuo (c. 140-208) may have been the first recorded person to use cannabis as an anesthetic. After powderizing the plant he mixed it with wine for administration before conducting surgery.¹³ The Chinese term for “anesthesia” (*mázui*) literally means “cannabis intoxication.”

Throughout the 17th Century, there were many references to cannabis. It was endorsed by Shakespeare. The Jamestown settlers imported large quantities to North America. The British herbalist Culpeper extolled its virtues in his famous text, “The English Physician.”¹⁴ During the 18th Century, George Washington grew large amounts of hemp and described its medicinal effects.¹⁴

An Irish physician, William Brooke O’Shaughnessy, reintroduced cannabis to Britain in 1842 when he returned from Bengal. By 1850, marijuana appeared in the US Pharmacopeia and was listed as treatment for neuralgia, tetanus, typhus, cholera, rabies, dysentery, alcoholism, opiate addiction, anthrax, leprosy, incontinence, gout, convulsive disorders, tonsillitis, insanity, excessive menstrual bleeding, and uterine bleeding, among others.¹⁴

Legal History and Status in the United States

President Theodore Roosevelt signed the Pure Food and Drug Act in 1906. Enforcement of the act was assigned to the Bureau of Chemistry in the US Department of Agriculture, later renamed the US Food and Drug Administration (FDA) in 1930.¹⁵ This first federal law regulating foods and drugs was limited to foods and drugs in interstate commerce. The law was principally a “truth in labeling” law designed to raise standards in the food and drug industries. Drug labels had to list any of 10 ingredients that were deemed “addictive” and/or “dangerous” on the product label. Alcohol, morphine, opium, and cannabis were all included on the list of these “addictive” and/or “dangerous” drugs.

The use of cannabis was declared illegal by the beginning of the 20th century in several countries including South Africa, the United Kingdom, New Zealand, and Canada. The Marihuana Tax Act of 1937 (Pub. 238, 75th Congress, 50 Stat. 551, enacted August 2, 1937) placed a tax imposed on physicians, pharmacists, and producers of medical marijuana

on the sale of cannabis.¹⁶ Hemp was also included in this law, perhaps because tycoons such as the Mellon, Hearst, and the Du Pont families wanted to safeguard their timber industries for paper manufacturing.

Although many politicians claimed that cannabis use would lead to the decline of society, others were less sure of its addictive effects. In New York City in 1938, Mayor Fiorello LaGuardia commissioned the New York Academy of Medicine to conduct an investigation of marijuana. The 1944 report, “The Marihuana Problem in the City of New York,” also referred to as the “LaGuardia Report,” concludes that many claims about the dangers of marijuana are exaggerated or untrue.¹⁷

“The practice of smoking marihuana does not lead to addiction in the medical sense of the word. ... The use of marihuana does not lead to morphine or heroin or cocaine addiction and no effort is made to create a market for these narcotics by stimulating the practice of marihuana smoking. ... Marihuana is not the determining factor in the commission of major crimes. ... The publicity concerning the catastrophic effects of marihuana smoking in New York City is unfounded.”

California voters passed Proposition 215 in 1996, making it the first state to allow the medical use of marijuana. By 2018, a total of 29 states, and the District of Columbia, Guam, and Puerto Rico, have enacted similar laws, allowing for comprehensive public medical marijuana and cannabis programs.¹⁸ In these states, the use of medical marijuana with high levels of THC must be recommended by a licensed provider. Recreational use of marijuana and THC is now legal in 8 states and Washington, District of Columbia.

CBD is legally available in the United States, but it must be derived from imported high-CBD, low-THC hemp. CBD itself is not listed under the Controlled Substances Act, and is legal in all 50 states, provided it is not extracted from marijuana. If CBD is derived from marijuana, its use is illegal unless obtained through a state-regulated medical marijuana program or in a state that permits recreational marijuana use. It is important to note that the regulations regarding the sale, potency, and use of marijuana differ among states.

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Some other states allow the use of “low THC, high-cannabidiol (CBD)” products for medical reasons in limited situations or as a legal defense. Those programs are not counted as comprehensive medical marijuana programs. Some forms of hemp are considered dietary supplements and thus are legal to buy and sell.

Pros and Cons of Marijuana Legalization

There are arguments for and against why legalization of marijuana should proceed¹⁹ (Sean Williams, *The Motley Fool*, October 2017). First of all, a majority of the public is in favor of it, according to recent polls (Gallup October 2016, *CBS News*, and Quinnipiac April 2017). Clinical data suggest that marijuana can improve quality of life for some patients. Moreover, the cannabis industry has the potential to create thousands of jobs and also become a source of tax revenue for states and the federal government.

On the other hand, heavy use in adolescents may later affect long- and short-term memory. Long-term effects are unknown. Although blood alcohol levels that prove dangerous have been set by states, such values are unknown regarding marijuana, although it is recognized that driving may be impaired but less so than occurs with alcohol. Also, THC can stay in the blood for extended periods, again making it difficult to assess when the drug was used. Finally, the amount of electricity required to grow marijuana from lighting to temperature needs, such as air-conditioning systems, could impose enormous strain on the nation's electric grids if the practice becomes legal throughout the United States.

Medical Uses of Marijuana

Although the recreational use of marijuana is well known, it is important to recognize that medical uses have been known for thousands of years. THC is known to produce negative side effects, including dry mouth, light-headedness, anxiety, paranoia, and drowsiness, but death from marijuana alone has not been reported. Similarly, large doses of CBD are well tolerated and safe. A recent research review examining the safety and side effects of CBD concluded that CBD seemed to be safe in humans and animals.²⁰ Even chronic use of CBD by humans has been shown to cause no adverse neurologic, psychiatric, or clinical effects. Use of marijuana with high levels of THC can lead to a substance use disorder, and no medications are currently available to treat this addiction.

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In a recent study of Californians, becoming a medical marijuana user was influenced by early discoveries of effective medicinal use, interaction with proponents of medical use at dispensaries, experiences with new kinds of medical use, and especially the demands of particular health conditions improved by marijuana.²¹

Because the legal status of marijuana has been so uncertain, there are few large studies examining the effectiveness of marijuana for medical conditions. Preliminary studies suggest that medical marijuana legalization might be associated with decreased prescription opioid use and overdose deaths.²² A more detailed National Institute on Drug Abuse-funded analysis showed that legally protected medical marijuana dispensaries, not just medical marijuana laws, were also associated with a decrease in opioid prescribing, self-reports of opioid misuse, and treatment admissions for opioid addiction.²³

It has been suggested that medical marijuana treatment may reduce the opioid dose prescribed for pain patients,^{24,25} and a recent study showed that availability of medical marijuana for Medicare patients reduced prescribing of medications, including opioids, for their pain.²⁶ Additional studies are being funded to determine the link between medical marijuana use and the use or misuse of opioids for pain.

Patients and employees whose urine is tested for THC could test positive for as many as 30 days after their most recent use. However, passive exposure by inhaling secondhand marijuana smoke will not cause a person to fail a drug test, as very little THC is released in the air when a person exhales. The most common medical uses of marijuana include relief of neuropathic pain and muscle spasms caused by multiple sclerosis (nabiximols oromucosal spray), nausea from cancer chemotherapy, as a means of increasing appetite and preventing weight loss caused by chronic illness (such as HIV), or nerve pain, seizure disorders, and Crohn disease.

The FDA has approved THC to treat nausea and improve appetite, and it is available by prescription (dronabinol and nabilone). Other approved uses include psoriasis, lupus, nail-patella syndrome, and severe dermatologic pain.²⁷ Small studies have considered anti-inflammatory and neuroprotective effects of cannabis, suggesting a use in traumatic brain injury, and as a means to increase memory in patients with Alzheimer disease, to mitigate bipolar disorders, or to reduce

intraocular pressure in glaucoma. Very preliminary studies have suggested cannabis and its derivatives might have use in acne, dermatitis, pruritus, wound healing, and skin cancer. It is important to note that most studies

remain inconclusive until larger numbers can be obtained. However, medical cannabis use does seem to serve as a complementary therapy for symptom management and treatment of medication side effects associated with certain chronic conditions, and as an alternative method for treatment of pain, seizures, and inflammation.²⁸

Conclusion

Marijuana use in medicine goes back many thousands of years, and in recent decades has been at least somewhat validated by the discovery of an endocannabinoid system and cannabinoid receptors within the human body. After several decades of being classified as illegal and having no medical use by the federal government, marijuana is now being produced, regulated, and recommended by physicians in more than half of the US states, as well as in some territories.

With polls showing that the majority of people in the United States support the use of marijuana as medicine, practitioners should learn enough about the drug's risks and benefits to advise their patients on the evidence, even if they do not actively recommend the drug itself. With marijuana continuing to be illegal from the standpoint of the federal government, some providers and health care organizations may elect not to actively participate even if their state has legalized it, as some fear it could put their privileges, licenses, and practices at risk.

Still, physicians, nurses, and other clinicians should be aware of the conditions that could benefit from medical marijuana—and those for which it would not seem to make a difference in a choice between THC, the psychoactive and most prevalent cannabinoid in marijuana plants, and CBD, which has different properties and does not provide a high or any psychoactive effect.

The most common medical uses of marijuana include relief of neuropathic pain and muscle spasms caused by multiple sclerosis, nausea from cancer chemotherapy, as a means of increasing appetite and preventing weight loss caused by HIV, cancer and other chronic illness, or nerve pain, seizure disorders, and Crohn disease. ■

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As Patients Seek Botanical Relief, Industry Sprouts Around Cannabis

Anne Haddad

Looking at medical cannabis in the United States, the pictures that emerge are more like digital graphic art, with color-coding, overlay panels, many shades of gray, and constant change.

It is still unclear whether physicians and health care organizations with federal contracts are vulnerable to sanctions even if they follow state laws in approving cannabis for patients. MedChi, the Maryland state medical society, has chosen not to take a position on medical cannabis, leaving it to individual members to decide whether to register with the state.

Warren Ross, MD, a physician with Lifebridge Health in Ellicott City, Maryland, has been practicing medicine for more than 40 years. An internal medicine specialist, he registered with the Maryland Medical Cannabis Commission when it began accepting applications, but he had to withdraw his name later.

“My employer is a large health system that has to be fully compliant with federal regulations,” Ross said. He can discuss cannabis with his patients, but they will ultimately have to decide on their own whether to seek a recommendation from one of the physicians certified by the state.

“There are patients in my practice who will definitely benefit,” Ross said, and those for whom medical cannabis would probably carry more risk than benefit.

“It’s not right to think of it in a simplistic way,” Ross said, adding that researchers are still working to understand the endocannabinoid system.

As of mid-January, 29 states and the District of Columbia had approved at least medical cannabis, and 8 of those states also had approved it for recreational purposes. If we had printed a map in this issue of *Topics in Pain Management*, it would have been out of date by the time it reached the reader. Legislators in 12 states are expected to vote on legalizing marijuana in some form during the first half of 2018. Some of these 12 are states considering legalizing medical use, and some are states that already have legal medical use and are now considering recreational use.

The gray area is federal law, under which there is no such thing as medical marijuana—but only marijuana, and it is a Schedule 1 drug with no medical use, just like heroin. President Barack Obama’s administration adopted the policy of not pursuing prosecution in states that had made marijuana legal, but current US Attorney General Jeff Sessions said in January that he is opposed to marijuana in all forms—legal, medical, and otherwise—and that US attorneys should use their discretion in deciding what resources to devote to prosecuting it.

Looking at the larger political picture, however, a vast majority of Americans believe medical marijuana should be available, and for the first time, polls show that even a majority of Republicans agree with that.

Case Study: Maryland’s New Law

So, despite the gray areas, states are proceeding and industry is expanding around the drug to meet the demand. In Maryland, the state legislature approved a bill 2 years ago allowing medical cannabis, but it was only in December 2017 that it was finally made available statewide.

During those 2 years, there was groundwork to be laid by training and certifying physicians, growers, distributors, testing laboratories, and dispensaries. The original list of contractors was criticized after minority business owners argued the state had not worked hard enough to make sure the list of approved contractors included minority business owners.

No Credit Cards, No Guns

Once the legal sales began on December 1, 2017, in Maryland, issues emerged.

Patients who want to use medical cannabis must surrender their rights to buy or own a gun. Federal law prohibits drug users from owning a gun, and authorities have made it clear to gun dealers that they must ask buyers this question, and they cannot sell guns to people using medical marijuana. Because medical marijuana users must first register with the state, they are on record, and gun dealers must ask them to answer that question.

Payment also requires some planning on the part of the patient and the dispensary. Prescription plans do not cover cannabis (to start with, it is not Food and Drug Administration-approved). Banks and credit card companies have to comply with federal laws, so patients have had to pay with cash. This led to safety concerns, because of the dangers to the dispensaries and patients of being robbed.

Entrepreneurship has stepped in to fill the void: an app called “CanPay” works as a legal bridge for patients to pay participating dispensaries in states with legal cannabis, using a debit card. But as of early January 2018, only one local bank in Maryland allows entrepreneurs in the state’s fledgling cannabis industry to set up a bank account.

Patient Registration and Access

The rules are many, and patients must start by registering online with the Maryland Medical Cannabis Commission at

<http://mmcc.maryland.gov>, where they also find information on the process and the providers.

Patients should discuss cannabis with their own primary care providers, but most will need to see another doctor from a list of about 20 physicians registered with the state commission. These state-certified doctors determine whether cannabis is appropriate for the patient.

To be approved, the patients must have been unable to find other relief for certain conditions, including anorexia, wasting syndrome (such as with AIDS or cancer), severe pain, severe nausea, seizures, severe or persistent muscle spasms, glaucoma, posttraumatic stress disorder, and chronic pain.

The products include unprocessed dried flowers from the plant, topical balms and creams, and liquids that can be inhaled through a smokeless vaporizer. For now, the law in Maryland does not allow for “edibles,” such as gummy candies that contain cannabis. All of the cannabis products sold by the dispensaries must come from the state-certified growers and processors in Maryland.

Focus on Smokeless

“We focus on the smokeless products,” said Leslie Apgar, MD, a Maryland obstetrician-gynecologist who cofounded Greenhouse Wellness with her entrepreneur neighbor, Gina Dubbé, and also serves as its medical director.

“We feel very strongly about having a medical staff on site,” Dubbé said. “We’re trying to elevate this and talk about disease prevention and treatment.” Much of their work, she says, is educational.

Patients, especially in the first wave of legal access, are not likely to know about the various products available and which ones would be best for them, point out the Greenhouse Wellness founders. So patients first sit down with a nurse to discuss their conditions and preferences, before selecting and purchasing products.

“We’re medically directed,” Apgar said. “This is a clean and comfortable environment that is welcoming, safe, and secure.” To further ensure product safety, the company has formed partnerships with growers and processors.

Dubbé cofounded TheraPearl, the company that produces the now-ubiquitous hot or cold compresses filled with gel beads, after realizing that she could go at least one better than the bag of frozen peas everyone was using. She wanted a reusable, mess-free, drug-free way of relieving pain and inflammation, and which could get cold in the freezer—or warm in the microwave.

The innovation got her named by *Forbes* magazine in 2014 as one of the Women Who Built Outstanding Companies, and TheraPearl made the Inc 500 list of the Fastest Growing Private Companies in the United States for 2 consecutive years. After selling the company in 2014, Dubbé started

looking for a new project, just as Maryland passed a law allowing medical use of cannabis.

Apgar has practiced medicine for 17 years as an obstetrician-gynecologist. Born and raised in the Pacific Northwest, she graduated from the Penn State University College of Medicine in 2000 and completed her residency at the Penn State Health Milton S. Hershey Medical Center. Her familiar last name is associated with the Apgar score, a 0-to-10 scale for measuring the health of a newborn. The test was developed by the pioneering physician Virginia Apgar, a distant relative of Leslie Apgar’s first husband.

As a physician, Apgar said, she follows research on medical cannabis and looks forward to future studies that will explore the role of cannabinoids on pain, inflammation, gut health, cancer, and other diseases. Evidence indicates that in states where medical cannabis is available, opioid overdoses have declined, she says.

Although cannabis can be addictive, even an overdose is not fatal, although it could cause feelings of paranoia and other physical and psychological symptoms.

The products include unprocessed flowers, topical balms, oils, and liquids.

Soothing green and white décor at Greenhouse Wellness makes this state-certified dispensary look more like a private medical office—albeit with a high level of security. The building also houses several other medical offices, including a large diagnostic radiology and imaging practice.

Visitors and patients must first be buzzed in—the front door and the subsequent door are locked. Only patients registered with the state and their designated caregivers are permitted into this inner sanctum.

Quality Control: Independent Testing Laboratories

The Maryland law set up a fully self-sustaining medical cannabis infrastructure in which all the product sold must have been grown by certified growers, tested by certified independent laboratories in the state, and dispensed by licensed dispensaries in Maryland.

Shannon Hoffman was a chemical analyst in the cosmetics industry for nearly 2 decades, most recently at Covergirl. Last June, when her job was moved out of state, she chose not to follow it. “I saw that medical cannabis was an emerging industry that was coming to life in the next six months,” Hoffman says. “I knew it was something I could be excited about and contribute to, because of my experience.”

Hoffman is the regional director of operations and the certifying chemist for Steep Hill Maryland in Columbia, one of

Scientific Resources

Please see page 1 of this issue for a continuing education article that provides a comprehensive review of medical cannabis for pain practitioners.

Journal of the American Medical Association

Bachhuber MA, Saloner B, Cunningham CO, Barry CL. Medical cannabis laws and opioid analgesic overdose mortality in the United States, 1999-2010. *JAMA Intern Med.* 2014;174(10):1668-1673. doi:10.1001/jamainternmed.2014.4005.

National Academies Press

To learn about the most recent scientific studies of the effects of cannabis, one trustworthy source is the National Academies Press, part of the National Academies of Science, Engineering, and Medicine.

Go to www.nap.edu and search “cannabis” to find all reports on medical cannabis. Download free PDF or read online buttons (prices are only for ordering the printed book).

The latest report is a comprehensive one called “The Health Effects of Cannabis and Cannabinoids” (December 2017).

4 independent laboratories that Maryland has certified to test the quality and safety of medical cannabis products sold to consumers under the new state law. Steep Hill, a cannabis science company headquartered in Berkeley, California, operates laboratories in several of the 29 states that have legalized medical cannabis.

Just as when she worked at Covergirl, when Hoffman mentions to people what she does for a living, they ask whether she can get them free samples.

“The answer, in both cases, is ‘No,’” Hoffman says.

But conversations now have a more earnest tone; Hoffman said people open up to her about how a relative suffering from chemotherapy-induced nausea was helped by cannabis, or how another has been waiting for it to become legal.

“Everyone has a story, and everyone has a family member or friend who has suffered,” Hoffman said.

Some of these confessions have gone out of state or tapped into the illegal marketplace to alleviate their loved ones’ suffering. But things are changing, she points out.

“People can access it now without fear of [criminal] charges. It’s really inspiring and it gives a sense of purpose.”

In some ways, Hoffman’s job is the same as it was at Covergirl—making sure the products are safe and effective by running tests for specific active ingredients, potential contaminants, and harmful substances.

In the case of cannabis products, chemists test for the amount of active ingredient, such as cannabidiol (CBD) and tetrahydrocannabinol (THC), the primary molecules in the cannabis plant that have been shown to have medical use. State-regulated dispensaries are able to recommend some products over others, based on such qualities as the ratio of CBD to THC.

Chemists also test for molecules that should *not* be there, such as heavy metals, pesticides, mold, yeast, foreign matter, and other contaminants.

Natural plants can be affected by the soil, fertilizer, and water they are exposed to.

“The cannabis plant is very happy to absorb heavy metals from whatever it’s growing in,” Hoffman said.

Addiction and Overdose Concerns

Cannabis itself has no lethal dose, and medical evidence supports some benefits for certain conditions (see Scientific Resources [sidebar] to find a summary of the research), although the number of studies and participants is small because the drug’s federal status is that it is illegal with no medical use. However, one study in 2014 in the *Journal of the American Medical Association* indicated that medical marijuana legalization might be associated with decreased use of prescription opioids and fewer deaths from opioid overdose.

Cannabis can still be psychologically addictive, but it does not lead to physical dependence, experts say. Much of the current opioid crisis stems from the 1990s and early 2000s, when undertreatment of pain was a real issue, and pharmaceutical companies and some physicians began asserting that opioids could be used more widely.

“With opioids, we were burned very badly,” said Ross, the internal medicine physician. As with any drug, cannabis could become overprescribed, diverted, or otherwise abused.

“Everyone is looking for the pill that will make their pain go away,” he said.

Ross said he hopes people will understand that the product is not a cure-all but a tool for moving toward better health. “The worst thing that could happen is it becomes too casual, so that someone who doesn’t have a medical need can just access it.”

Coming Soon:

- Sleep Interventions for Patients with Chronic Pain

ICYMI: IN CASE YOU MISSED IT

Notes from recent studies related to pain management, compiled by Elizabeth A.M. Frost, MD

Is Parecoxib Safe for Postoperative Pain?

Nonselective, nonsteroidal anti-inflammatory drugs (NSAIDs) and selective cyclooxygenase-2 (COX-2) inhibitors have been associated with adverse cardiovascular, renal, and gastrointestinal (GI) events. Authors Schug et al. conducted a pooled analysis of 28 placebo-controlled trials of parecoxib and reviewed postauthorization safety data. Prespecified safety events commonly associated with COX-2 inhibitors, and the frequency of each event, were compared among treatment groups using the chi-square test. In the postauthorization review, the number of confirmed cases, along with outcome, was presented for each event.

Gastrointestinal events occurred in approximately 0.2% of patients in both the parecoxib and placebo groups. The rate of renal complications associated with parecoxib was 1.0%, and for placebo, 0.9%. Arterial (parecoxib = 0.3%, placebo = 0.2%) and venous (parecoxib = 0.2%, placebo = 0.1%) cardiovascular embolic and thrombotic events were similar between the groups.

Other complications were described as follows: hypersensitivity reactions (anaphylactic reactions): 8.7% for parecoxib and 8.6% for placebo; hypotension: 2.6% for parecoxib and 2.1% for placebo; angioedema: 2.5% for parecoxib and 2.8% for placebo. There were no severe cutaneous adverse reactions in either group; and incision site or other skin or tissue infections occurred in less than 0.1% of patients in both groups.

The ratio of total reports to serious reports in the postauthorization database, based on 69,567,300 units of parecoxib, was as follows: GI ulceration-related events (35 total/all serious); renal failure and impairment (77 total/68 serious); cardiovascular embolic and thrombotic events (66 total/64 serious); hypersensitivity reactions, including hypotension-related events (32 total/25 serious); severe cutaneous adverse events (17 total, all serious); and masking signs of inflammation (18 total, all serious).

A majority of reported outcomes were classified as recovered or recovering.

The authors concluded that serious safety events are rare after use of parecoxib, making it safe to use for patients with postoperative pain. (See: Schug SA, et al. The safety profile of parecoxib for the treatment of postoperative pain: a pooled analysis of 28 randomized, double-blind, placebo-controlled clinical trials and a review of over 10 years of postauthorization data. *J Pain Res.* 2017;10:2451-2459. doi: 10.2147/JPR.S136052.)

Postoperative Pain Management in Children With Developmental Delay

A randomized, controlled study of outcomes compared the effectiveness of parent/nurse-controlled analgesia (PNCA), with and without a basal opioid infusion, with IV opioids administered on an “as needed” basis (PRN) for postoperative pain management in 81 children with developmental delay (DD). The children had undergone extensive surgery, and they were expected to require opioid medication for more than 24 hours afterward.

Three medication groups were identified: (1) PNCA with a basal infusion; (2) PNCA without a basal infusion; and (3) IV PRN opioids. Demographics, pain scores, opioid consumption, and frequency of side effects were collected beginning 12 hours after surgery to decrease the impact of anesthetic agents.

The proportion of patients in each group with pain scores of 3 vs 4 indicated no between-group differences in any epoch ($P = 0.09$ – 0.27). Patients in the group receiving PNCA with an infusion received significantly more opioid than those receiving PNCA without a basal infusion, but more patients in both of these groups required supplemental oxygen ($P = 0.05$). No difference was demonstrated between the PNCA-without-a-basal-infusion and the PRN groups. There were no statistically significant differences in side effects.

The authors concluded that their results suggest there may be no advantage to PNCA over PRN opioids in this patient population after the first 12 postoperative hours on the basis of pain scores, opioid consumption, or side effects. (See: Czarnecki ML, et al. Parent/nurse-controlled analgesia compared with intravenous PRN opioids for postsurgical pain management in children with developmental delay: a randomized controlled trial. *Pain Med.* 2017 Nov 1 [Epub ahead of print]. doi: 10.1093/pm/pnx257.)

RF Ablation vs Intra-Articular Steroids in Knee Osteoarthritis

A prospective, multicenter, randomized trial of 151 subjects with chronic (>6 months) knee pain that was unresponsive to conservative therapy analyzed the efficacy of cooled radiofrequency ablation (CRFA) and intra-articular steroid injection (IAS). Knee pain as measured by Numeric Rating Scale (NRS), Oxford Knee Score, overall treatment effect (Global
(Continued on page 12)

Topics in Pain Management CE Quiz

To earn CME credit using the enclosed form, you must read the CME article and complete the quiz and evaluation assessment survey on the enclosed form, answering at least 70% of the quiz questions correctly. **Select the best answer and use a blue or black pen to completely fill in the corresponding box on the enclosed answer form.** Please indicate any name and address changes directly on the answer form. If your name and address do not appear on the answer form, please print that information in the blank space at the top left of the page. Make a photocopy of the completed answer form for your own files and mail the original answer form in the enclosed postage-paid business reply envelope. Your answer form must be received by Lippincott CME Institute by **February 29, 2019**. Only two entries will be considered for credit.

Online CME quiz instructions: Go to <http://cme.lww.com> and click on "Newsletters," then select *Topics in Pain Management*. Enter your *username* and *password*. First-time users must register. After log-in, follow the instructions on the quiz site. You may print your official certificate **immediately**. **Please note:** Lippincott CME Institute, Inc., **will not** mail certificates to online participants. **Online quizzes expire on the due date.**

To earn nursing CNE credit, you must take the quiz online. Go to www.nursingcenter.com, click on CE Connection on the toolbar at the top, select Browse Newsletters, and select *Topics in Pain Management*.

Log-in (upper right hand corner) to enter your *username* and *password*. First-time users must register. As a subscriber benefit, nurses can earn contact hours when taking CE activities from *Topics in Pain Management* for free. You must enter your subscription number preceded by LWW, in your registration profile where there is a field for **Link to my subscription**. The 100% discount is applied when payment is requested. Non-subscribers pay a \$49.00 fee to earn ANCC contact hours for this activity.

After log-in, locate and click on the CE activity in which you are interested. There is only one correct answer for each question. A passing score for this test is 7 correct answers. If you fail, you have the option of taking the test again. When you pass, you can print your certificate of earned contact hours and access the answer key. For questions, contact Lippincott Professional Development: 1-800-787-8985. The registration deadline for CNE credit is **March 1, 2019**.

1. **Marijuana sales in the United States**
 - A. represent about a \$17 billion market
 - B. are decreasing annually
 - C. will increase at the rate of 1% to 3%/year
 - D. remain static
2. **Estimates of the number of Americans who have used marijuana in 2016**
 - A. approach 10%
 - B. exceed 50%
 - C. are unknown
 - D. have decreased over the past 3 years
3. **According to the federal government, marijuana**
 - A. is categorized as a Schedule 1 substance, as is heroin
 - B. has stayed as a Schedule 4 drug
 - C. does not require any categorization
 - D. should be legalized by all states for all uses
4. **Cannabidiol**
 - A. is a structural isomer of THC
 - B. binds with CB-1 receptors
 - C. has marked psychotropic effects
 - D. does not affect the CB-1-activating qualities of THC
5. **THC**
 - A. is isolated from the seeds and flowers of hemp and marijuana
 - B. acts as a direct agonist of CB-1 receptors
 - C. causes the "high" associated with marijuana
 - D. all of the above
6. **Studies have shown that medical marijuana may reduce the opioid dose prescribed for pain patients.**
 - A. True
 - B. False
7. **Regarding the approval of marijuana use, the FDA**
 - A. supports its use in the treatment of Alzheimer disease
 - B. approved its use to treat nausea associated with chemotherapy
 - C. does not approve its use for pain and muscle spasm
 - D. has had nothing to do with the drug
8. **Which one of the following statements regarding factors against the legalization of marijuana is false?**
 - A. Cultivation places a large load on the electrical grid system.
 - B. The long-term effects are largely unknown.
 - C. The US Federal Government categorizes it as a Schedule 4 drug.
 - D. Blood levels that cause impairment have not been determined.
9. **Which of the following statements regarding factors supporting the legalization of marijuana is/are true?**
 - A. Tax revenue for states could be increased.
 - B. Significant jobs would be created.
 - C. A recent Gallup poll found that the majority of the public is in favor of legalization.
 - D. All of the above
10. **In states that have approved it, medical marijuana**
 - A. must be recommended by a licensed provider
 - B. should contain no more than 3% THC
 - C. is legal in only about 25% of US states
 - D. can be dangerous as secondhand smoke

(Continued from page 10)

Perceived Effect), analgesic drug use, and adverse events were compared at 1, 3, and 6 months after the intervention.

At 6 months, the CRFA group had more favorable outcomes in NRS scores, with pain reduction of at least 50%: 74.1% versus 16.2%, $P < 0.0001$ (25.9% and 83.8% of these study cohorts, respectively, were nonresponders).

Mean NRS score reduction was 4.9 ± 2.4 versus 1.3 ± 2.2 , $P < 0.0001$; mean Oxford Knee Score was 35.7 ± 8.8 vs 22.4 ± 8.5 , $P < 0.0001$; mean improved Global Perceived Effect was 91.4% vs 23.9%, $P < 0.0001$; and mean change in nonopioid medication use favored CRFA over IAS ($P = 0.02$). No serious adverse events were reported.

The authors concluded that CRFA is an effective long-term therapeutic option for managing pain and improving physical function and quality of life for patients with painful knee osteoarthritis. (See: Davis T, et al. Prospective, multicenter, randomized, crossover clinical trial comparing the safety and effectiveness of cooled radiofrequency ablation with corticosteroid injection in the management of knee pain from osteoarthritis. *Reg Anesth Pain Med*. 2018;43(1):84-91. doi: 10.1097/AAP.0000000000000690.)

Does Nerve Blockade Decrease Risk of Continued Postoperative Opioid Use?

Two recent articles questioned whether the use of perioperative nerve blocks would alter the need for continued opioid use after shoulder and knee surgery.

In the first study, Mueller et al. used health care claims data to construct a sample of 6695 patients who underwent shoulder arthroplasty between 2002 and 2012¹. Billing data identified use of nerve blockade. A multivariable logistic regression estimated the association between nerve blockade and 2 measures of opioid use: filling at least 1 prescription for an opioid between postoperative day (POD) 0 and 90 and between POD 91 and 365. Potential confounders, such as preoperative opioid use and medical history, were adjusted by this regression analysis.

No association between nerve blockade and the 2 measures of persistent opioid use were identified. The adjusted odds ratios were 1.12 (97.5% confidence interval [CI], 0.939–1.34; $P = .15$) for opioid use between POD 0 and 90; and 0.997 (97.5% CI, 0.875–1.14; $P = .95$) for opioid use between POD 91 and 365.

In the second study, Sun et al. used health care data to constructed a sample of 120,080 patients who underwent total knee arthroplasty between 2002 and 2012.² As with the first study, billing data indicated the use of nerve blockade.

Multivariable logistic regression estimated the association between nerve blockade and the risk of chronic opioid use, ie, filling at least 10 prescriptions or at least 120 days' supply for an opioid in the first postsurgical year. No association was established between nerve blockade and the risk of postoperative chronic opioid use across 3 groups. The adjusted relative risk was 0.984 for patients who were opioid-naïve in the year before surgery (98.3% CI, 0.870–1.12, $P = .794$); 1.02 for intermittent opioid users (98.3% CI, 0.948–1.09, $P = .617$); and 0.986 (98.3% CI, 0.963–1.01, $P = .257$) for chronic opioid users. Similar results held for alternative measures of postsurgical opioid use.

The authors of both studies concluded that although use of perioperative nerve blockade for shoulder and knee surgeries may improve short-term outcomes, the analyzed types of blocks do not appear to decrease the risk of persistent opioid use in the longer term. (See: Mueller KG, et al. Lack of association between the use of nerve blockade and the risk of persistent opioid use among patients undergoing shoulder arthroplasty: evidence from the MarketScan Database. *Anesth Analg*. 2017;125(3):1014-1020. doi: 10.1213/ANE.00000000000002031; and Sun EC, et al. Lack of association between the use of nerve blockade and the risk of postoperative chronic opioid use among patients undergoing total knee arthroplasty: evidence from the MarketScan Database. *Anesth Analg*. 2017;125(3):999-1007. doi: 10.1213/ANE.0000000000001943.)

Diversions to Decrease Pain During IV Cannulation

In a single-blind, randomized controlled study, 120 males who were donating blood were divided by into 4 groups. One was a control group, and 3 groups each used a different tactic to divert their attention from pain during cannulation: coughing, blowing into a spirometer, or squeezing a stress ball. During the procedure, the pain levels felt by the individuals were assessed using the visual analog scale by a nurse who was blinded to the procedure.

Statistical analysis showed a significant difference between the mean pain scores of individuals in the control group and those of individuals in the coughing, spirometer, and stress-ball groups. While all treatment groups reduced the appreciation of pain, that of the coughing group was the most successful.

The authors concluded that nurses, aware of pain and stress experienced by patients during invasive procedures, should also have knowledge of proven nonpharmacologic methods that can reduce pain to a minimum. (See: Yilmaz D, Gunes UY. The effect on pain of three different nonpharmacological methods in peripheral intravenous catheterisation in adults. *J Clin Nurs*. 2017 Oct 27 [Epub ahead of print]. doi: 10.1111/jocn.14133.)