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Cannabis & Chronic Pain

Separating Science from Stigma

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ACCORDING TO THE WORLD HEALTH ORGANIZATION, cannabis is the most widely cultivated illicit herbal treatment, used by 147 million people worldwide. Historical records going back thousands of years show the cannabis plant being used to treat maladies including pain, muscle spasms, and nausea in China, India, Greece, and the Middle East. Although it fell out of favor in the last century, recent changes in the social, political and legal climate, plus scientific advances, have led researchers to reexamine the therapeutic potential of cannabis, and to explore its possible role in alleviating the opioid crisis.

In the United States, cannabis was prescribed for a variety of ailments well into the 20th century. Because of its perceived association with mental illness and violent crime—and for economic reasons—the Marihuana Tax Act of 1937 levied high taxes on its commercial use. In 1970, marijuana was classified as a Schedule 1 substance based on high abuse liability and lack of demonstrated medical use and safety. Although that federal regulation is still in place, California legalized the medical use of marijuana by popular vote in 1996, and by 2018 medical use of cannabis in various forms was legal in 29 states and the District of Columbia.

CANNABIS COMPOUNDS

Many of our current medicines have their origins in compounds found in plants used for herbal treatments of disease symptoms. Of the nearly 500 compounds found in cannabis, few have been characterized to any degree. Tetrahydrocannabinol (THC) was determined in 1964 as responsible for the psychoactive effects (the "high") of cannabis. Strains of cannabis with large amounts of THC are known as marijuana, whereas strains with low levels of THC are industrial hemp, which is used for textiles, paper, food, and other products. Synthetic THC, (dronabinol) and a similar compound nabilone, have been approved by the Food and Drug Administration (FDA) for relief of nausea in chemotherapy patients and to stimulate appetite in patients infected with human immunodeficiency virus, HIV.

Cannabidiol (CBD), another component of cannabis, was also isolated in the 1960s. It has no psychoactive effects, but has been studied for its potential to relieve pain, nausea, inflammation, and seizures. CBD was recently approved by the FDA for the treatment of some forms of epilepsy. Nabiximols, a combination of THC and CBD, is approved in Canada and other countries for relief of spasms and pain associated with multiple sclerosis, and pain in advanced cancer. Other compounds in cannabis—including more than 100 cannabinoids, as well as flavonoids, proteins, terpenes, and fatty acids—have not been characterized, but may have potential therapeutic value.

In the late 1980s, researchers at Saint Louis University in collaboration with chemists at Pfizer Pharmaceutical Company identified receptors in the nervous system to which THC binds that correlates with pain relief. These cannabinoid receptors were part of the endocannabinoid system (ECS) and bound naturally occurring molecules found in the body called "endogenous cannabinoids" or endocannabiniods. This receptor-ligand pair affects mood, pain, memory, appetite; in the immune system it affects inflammation. Cannabinoid compounds in cannabis, including THC, but not CBD, can also bind to these receptors, affecting multiple chemical messengers in many parts of the body. Cannabinoid effects can vary depending on which of the compounds is being considered (e.g. THC, CBD, another cannabinoid from the plant, an endocannabinoid or a synthetic molecule made to resemble one of the compounds in the plant). Our understanding of this important signaling system is incomplete, requiring additional studies. However, it is clear that the study of the ECS will be important for understanding how we can create better medicines to treat target diseases while at the same time avoiding unwanted side effects.

THERAPEUTIC POTENTIAL OF CANNABINOIDS

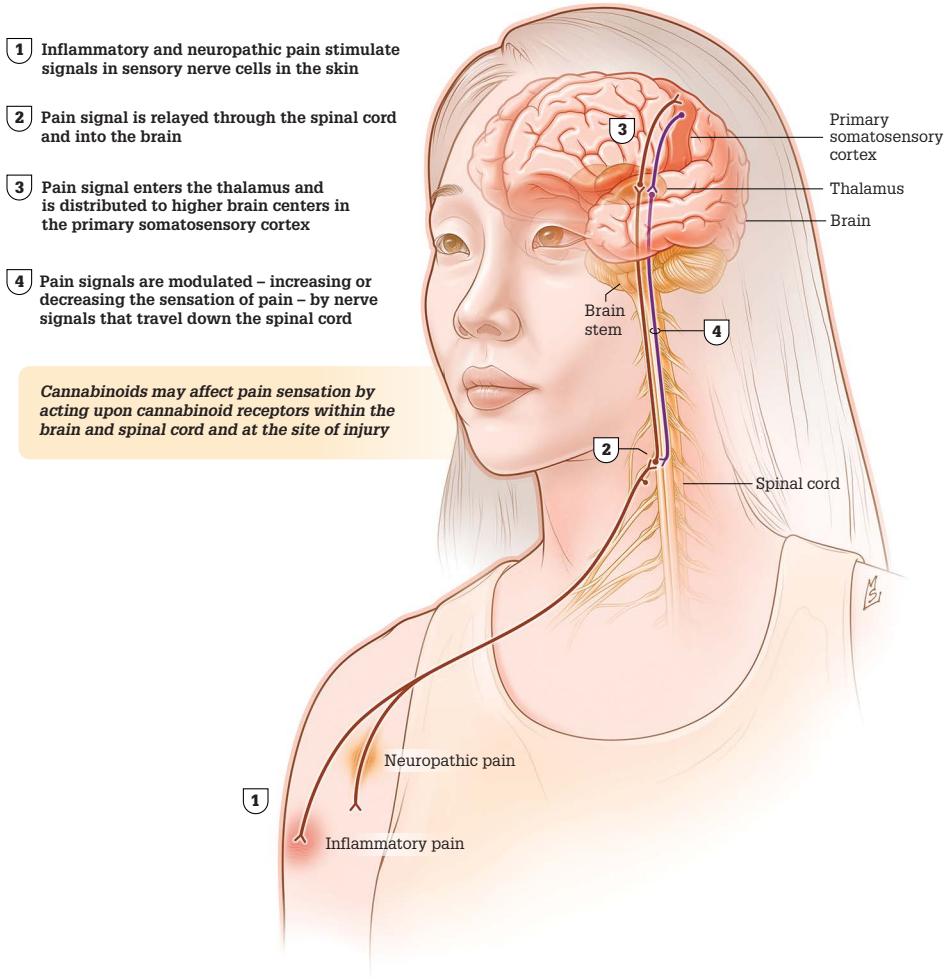
SUBSTANTIAL OR MODERATE EVIDENCE
Chronic pain in adults
Nausea and vomiting from cancer chemotherapy
Spasticity in multiple sclerosis
Sleep disturbances due to sleep apnea, fibromyalgia, chronic pain, and multiple sclerosis
LIMITED EVIDENCE
Appetite stimulation in HIV/AIDS and cancer
Symptoms of Tourette's syndrome
Symptoms of anxiety and post-traumatic stress disorder
Better outcomes for traumatic brain injury and intracranial hemorrhage

Credit: National Academies of Sciences, Engineering, and Medicine. 2017. The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research. Washington, DC: The National Academies Press. https://doi.org/10.17226/24625.

MARIJUANA AS MEDICINE

Cannabinoid compounds have been studied as potential treatments for a variety of conditions (see table); one of the most promising may be as a pain reliever. Although there have been relatively few well-designed clinical trials assessing effects of cannabis on pain, a 2017 report by the National Academy of Sciences, Engineering, and Medicine concluded that cannabinoid compounds are an effective treatment in adults for chronic pain due to neuropathy, cancer, multiple sclerosis, chemotherapy, and musculoskeletal disorders.

Pain is a complex phenomenon. It can be caused by direct damage to tissues or by incorrect pain messages relayed by damaged or malfunctioning nerve cells (neuropathic pain).



CANNABINOID RECEPTORS MAY EFFECT PAIN SIGNALING » Cannabinoids likely act by binding to cannabinoid receptors on cell surfaces in the nervous system, immune system, and other sites to inhibit the transmission and perception of pain. *Illustration: © Michael Linkinhoker, Link Studio, LLC.*

The cannabinoids in cannabis likely act by binding to receptors on cells in the nervous system, immune system, and other sites to inhibit the transmission and perception of pain and emotional responses to pain (see figure). In addition, cannabinoids may have anti-inflammatory actions, which can also reduce pain.

Because of their potential effectiveness against pain, cannabinoid compounds may provide an alternative to opioid medications such as morphine, codeine, oxycodone and fentanyl. Long-term use of opioids can require increasingly higher doses to alleviate pain. Recent increases in opioid abuse and deaths resulting from overdose are a current public health crisis. According to the Centers for Disease Control and Prevention, deaths from prescription opioids have increased fivefold since 1999, and more than 42,000 people in the US died of opioid overdoses in 2016. Opioids can cause depressed breathing and death though overstimulation of opioid receptors, which are abundant in brain regions controlling breathing. Cannabinoid receptors, in contrast, are sparse in parts of the brain that control breathing. For this and other reasons, cannabinoid medications have been proposed as a safer alternative to opioids, or in addition to opioids to reduce the opioid dose required for pain relief. This is supported by studies in the 1990's at Virginia Commonwealth University. An analysis published in 2014 in JAMA Internal Medicine showed a 24.8% reduction in opioid overdose deaths between 1999 and 2010 in states where medical marijuana was legal.

Only after further investigation on the health aspects of cannabis will we know whether it can replace opioid pain relievers. Well-designed, randomized clinical trials are necessary, as they are before any medication can be approved for use. Researchers must be licensed and registered with the Drug Enforcement Administration, receive approval on dosing from the FDA, and obtain their cannabis for research through the National Institute on Drug Abuse. Currently, cannabis provided for research has much lower levels of THC than varieties available for herbal treatment and recreational purposes. Selective breeding has generated strains that vary greatly in levels of THC and CBD, as well as the hundreds of other less-characterized components. Many currently published studies on pain in patients are not randomized or controlled clinical trials, but instead rely on anecdotal accounts, or have unclear distinctions between medical or recreational use of marijuana. In addition, dosing is difficult to control and the route of administration (smoking, vaporized, oral, injection) affects the bioavailability of the active compounds and the possibility of side effects.

Clearly, the benefits and risks need to be more extensively studied, including the potential for addiction and the effects of childhood and adolescent exposure (see sidebar). Political, social, legal, and regulatory barriers to this research are often based on incomplete or erroneous information, or may be biased by preconceived notions of the positive or negative effects of cannabis. Reduction of these barriers and adequate research funding will allow decisions about medical use of cannabis to be based on scientific evidence.

EFFECTS ON THE DEVELOPING BRAIN

While the therapeutic use of cannabis holds promise, it is not without adverse effects, including impaired learning, memory, and attention, with increased risk of automobile accidents. These risks are enhanced in young users, whose brains continue to develop into their early 20s. Both the American Academy of Pediatrics and the Canadian Pediatric Society oppose the use of cannabis by children and teens, citing deficits in motor control, coordination and cognitive function, as well as increased risk for mental illness and substance abuse. Structural changes have also been observed in the brains of young cannabis users.

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