

Demystifying Cannabis

A Review of Its Pharmacology, Use in Pain, and Safety Concerns

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The uses for cannabis and its synthetic derivatives continue to grow, as the regulatory status surrounding the drug becomes more legalized. Cannabis is composed of many chemical compounds, called cannabinoids, of which cannabidiol and 9-tetrahydrocannabinol have been studied for medicinal uses. As a modality for treatment of pain, cannabis may have benefit for use in treatment of neuropathic pain, with limited data for use in rheumatic pain. However, there are both short-term and long-term adverse effects with cannabis use that should be monitored in those who use cannabis for medicinal purposes, which include worsened anxiety and potential development of cannabis use disorder.

The role of cannabis in the pharmacotherapy of many disease states is ever evolving. There are a few synthetic cannabinoid prescription products that have Food and Drug Administration (FDA)-approved indications for use in certain disease states. However, the use of naturally derived cannabis as a treatment modality in various conditions is continuing to be more widely studied. More specifically, both the safety and efficacy of cannabis are being studied at this time. Some noteworthy research being conducted includes identifying whether cannabis has a role in treating different types of pain including neuropathic and rheumatic pain. The potential pain-negating effects of cannabis are produced due to the pharmacokinetics of cannabis in the body and its effects on cannabinoid 1 (CB1) and cannabinoid 2 (CB2) receptors (Mackie, 2008). Due to cannabis's effects on these receptors, it can also lead to potential side effects that a person may experience while using cannabis-derived products for treatment.

Pharmacology of Cannabis

Cannabis is derived from the *Cannabis sativa* plant that is believed to have originated in Central Asia (Mackie, 2008). The cannabis plant contains over 100 different active chemicals called cannabinoids. Cannabinoids work on different receptors within the body including CB1 and CB2. CB1 receptors are located mainly within the central nervous system (CNS) and are also found in peripheral organs. They have a role in motivation, cognition, emotions, pain regulation, memory processing,

and motor control. CB2 receptors are primarily located within the immune system and are present at lower level than CB1 in the CNS. CB2 receptors have a role in moderating inflammation and our immune response to pathogens. Both CB1 and CB2 receptors primarily signal through inhibitory G proteins, and the activation of the inhibitory G proteins is stimulation of CB1 receptors. This leads to the inhibition of adenylyl cyclase, the activation of mitogen-activated protein kinases and the inhibition of certain voltage-gated calcium channels, and the activation of G protein-linked potassium channels. Stimulation of CB2 receptors is similar, but the modulation of ion channels by CB2 receptors is more variable. Activation of the signaling pathways by the CB1 receptor and the elevated levels of these receptors on the presynaptic terminals means endocannabinoid stimulation of CB1 receptors suppresses neuronal excitability and inhibits neurotransmission.

Of the various cannabinoids that are present in cannabis, tetrahydrocannabinol (THC) and cannabidiol (CBD) are the two chemicals that have been found to have both therapeutic and psychoactive effects in the body (Koppel, 2014). When comparing THC and CBD, there will be similarities in the pain-negating effects and the role in reducing inflammation in the muscles, but the differences in the two compounds are observed from the start. THC is a partial agonist at CB1 and CB2 receptors with a high binding affinity to CB1. THC has psychoactive properties in that it is the compound responsible for the "high" effect from cannabis. CBD is harvested from the *C. sativa* strain and is used mostly for medicinal purposes. CBD has no psychoactive component and shows a low binding affinity for CB1 and

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CB2. The pharmacokinetics of THC are that it reaches peak serum concentrations 2–4 hours after ingestion or 3–10 minutes after smoking. THC is highly distributed to tissues like the liver, kidneys, heart, and muscles initially and will accumulate more slowly in less vascularized tissues and body fat. CBD's kinetics are affected significantly by first pass metabolism, with CBD being 6% bioavailable. CBD has a high volume of distribution and is rapidly distributed into the tissues. Both CBD and THC are highly protein-bound molecules.

The products listed in Table 1 depict the FDA-approved prescription treatment options, but many non-FDA-approved CBD products are available over-the-counter (OTC) in a local drug store. These OTC products will contain a hemp-derived CBD with a THC content of less than 0.3%. The products most commonly found in local drug stores will be topical in nature including creams, patches, sprays, roll-ons, and lip balms. Other products on the market also include CBD oils, edibles, and infused food and drinks. All products available OTC are not approved by the FDA and data are limited in regard to safety and efficacy with the CBD products. Access to these products also varies state by state due to legislation.

Cannabis Use in Neuropathic Pain

One of the most closely researched modalities for cannabis include its use in treating pain, as evidenced by the presence of CB1 and CB2 receptors throughout the CNS (Mackie, 2008). Although there is an overwhelming lack of robust randomized clinical trials analyzing the efficacy of cannabis for use in skeletal muscle pain, there are still studies that may provide insight into the effect of cannabis for neuropathic pain. Neuropathy as a component of pain may affect up to 10% of patients who suffer from chronic pain (Mücke et al., 2018). Current treatment

options available for neuropathic pain may only yield substantial therapeutic benefit for a small subset of patients, and sustained relief may rarely be achieved.

A meta-analysis analyzed whether inhaled cannabis was efficacious for chronic neuropathic pain (Andreae et al., 2015). The meta-analysis included 5 randomized control trials, with a total of 178 participants and 405 observed responses. The neuropathic pain etiologies that were included in the studies were diabetic, traumatic, and HIV-related neuropathies. The meta-analysis only included studies that compared inhaled *C. sativa* strain to placebo. Pain relief was identified by those who reported at least 30% improvement in pain using a Visual Analogue Scale. Results showed that there was a short-term reduction in chronic neuropathic pain for one in every five to six patients. Notable side effects included anxiety, disorientation, and short-term decline in attention and memory with the treatment groups. Although the study concluded that inhaled cannabis may be beneficial with providing short-term relief of neuropathic pain, more long-term studies are needed to evaluate the risks versus benefit with continued use.

A Cochrane review evaluated the efficacy of cannabis-based medications for neuropathic pain in adults (Mücke et al., 2018). Sixteen studies were included in the review with a total of 1,750 participants across all studies: 15 were compared to placebo, and one study compared to dihydrocodeine as a control. The cannabis-containing medications that were used in the studies included oral-mucosal spray combination of THC/CBD (10), nabilone (2), dronabinol (2), and inhaled cannabis (2). Results of the studies showed that cannabis-containing medicines improved pain relief by 50% or greater in more patients as compared with placebo (21% vs. 17%). Additionally, more participants withdrew from the studies due to adverse events with the cannabis-containing products as compared with placebo (10% vs.

TABLE 1. PRESCRIPTION CANNABINOID PRODUCTS APPROVED BY THE FDA IN THE UNITED STATES

Brand/Generic Product	Indication	Mechanism of Action	THC vs. CBD	Dosing
Epidiolex/cannabidiol	Treatment of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome	The exact mechanism of action of the antiepileptic effect is unknown; however, it does not appear to involve its effects on cannabinoid receptors	CBD	Oral: Initial: 2.5 mg/kg twice daily, may increase after 1 week to a maintenance dose of 5 mg/kg twice daily. Max daily dose of 10 mg/kg twice daily. Taper dose if discontinuing, avoid abrupt discontinuation.
Marinol/dronabinol	Anorexia in patients with AIDS and Chemotherapy-induced nausea and vomiting	Marinol has approximately equal affinity for CB1 and CB2 receptors; however, efficacy is less at CB2. Activation of the cannabinoid system causes analgesia, appetite enhancement, muscle relaxation, and hormonal actions mediated by CB1 receptors	Delta-9-THC	Capsules: Initial: 2.5 mg twice daily (1 hr before lunch and dinner). Max daily dose of 20 mg/day in divided doses. Oral solution: Initial: 2.1 mg twice daily (1 hr before lunch and dinner). Max daily dose of 16.8 mg daily in divided doses.
Cesamet/nabilone	Treatment of refractory nausea and vomiting associated with cancer chemotherapy	Antiemetic activity may be due to effect on cannabinoid receptors (CB1) within the central nervous system	Delta-9-THC	Oral: Initial: 1–2 mg twice daily. Max daily dose of 6 mg/day divided in three doses.

Note. CBD = cannabidiol; THC = tetrahydrocannabinol.

5%). Moreover, 17% of participants who used cannabis-containing products experienced psychiatric disorders, as compared with 5% of participants in the placebo group. Other adverse effects seen in the studies included somnolence, sedation, confusion, and psychosis. Overall, the authors of the Cochrane review found that cannabis-based medicines show potential benefit in alleviating neuropathic pain; however, there still remains increased risk of potential harm with its use.

Cannabis Use in Rheumatic Pain

Cannabis has also been studied in rheumatic pain, as currently there is no ideal treatment available. A Cochrane review evaluated the use of cannabis or cannabinoid-containing products in the following rheumatic conditions: fibromyalgia, osteoarthritis, chronic spinal pain, and rheumatoid arthritis (Fitzcharles et al., 2016). Two randomized controlled trials were included in the review. The first study compared nabilone to placebo and reported decreased pain intensity as a result. The other trial included in the study was comparing CBD/THC to placebo and reported decreased morning pain in patients who had rheumatoid arthritis. Some of the adverse effects that were reported in the individual studies included dizziness, lightheadedness, dry mouth, fatigue, vertigo, confusion, decreased concentration, and constipation. Overall, the Cochrane review concluded that there was insufficient evidence to recommend the use of cannabis-containing products for pain relief in patients with rheumatic diseases.

Short-Term Effects of Cannabis

As evidenced by the reported adverse side effects in the studies earlier, there are short-term adverse effects with cannabis use that should be of concern (Koppel, 2014). Cognitive impairment is particularly significant. Other effects include increased weakness, fatigue, dizziness, and feeling of intoxication. More serious short-term adverse effects that are typically associated with higher concentrations of THC include dysphoria, anxiety, and psychosis. Sleep disturbances may also be evidenced by a decrease in rapid-eye-movement (REM) sleep, and an increase in non-REM sleep, which has shown to be non-restorative. Behavioral changes and even suicidal ideation have been evidenced with short-term use.

Long-Term Effects of Cannabis

Although there is well-established documentation of the short-term effects of cannabis, the long-term adverse effects may seem unclear. However, more studies are being conducted to identify what are the long-term ramifications of cannabis use (Volkow, 2014). What can appear to be the most obvious, is the risk of developing cannabis use disorder, a physical and psychological dependence on cannabis that is well defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). Smoking cannabis has been associated with inflammation of the large airways, increased airway resistance, and lung hyperinflation with long-term use. Additionally, long-term use has been associated with

vascular conditions: increased risk of myocardial infarction, stroke, and transient ischemic attacks. There are also data that identified long-term risk in adolescents who smoked cannabis (deShazo et al., 2019). These results included poorer school and work performance, increased risk of developing mood or psychotic disorders, and decline in short-term memory and cognitive function. There were also adverse effects on executive functioning, and verbal deficits in adolescents who began using cannabis when compared with adults. Cessation of cannabis did not fully restore any diminished neuropsychological functioning that was present in those who began using cannabis prior to age 21 years.

Summary

Although the full therapeutic potential of cannabis may still be unknown at this time, there is existing literature for its potential effect in various forms of pain relief. Cannabis has shown some benefit in relieving neuropathic pain, a condition that many who suffer from its chronic effects rarely achieve complete remission. However, there are both short-term and long-term effects that should be discussed prior to considering cannabis as a modality for pain treatment. Some serious short-term adverse effects that may occur include worsened anxiety, dysphoria, and psychosis. For those who use cannabis for an extended period of time, some long-term effects include developing cannabis use disorder, neurocognitive deficits in adolescents, and development of cardiovascular conditions. These effects should be discussed when considering if cannabis is an appropriate modality for pain treatment. The availability of cannabis to be utilized for medical use via a medical marijuana card will vary across the United States, as it is currently enforced through state legislation. State-specific laws should be taken into consideration prior to identifying if cannabis for medicinal purposes is a feasible treatment option.

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