REVIEW

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Cannabis for peripheral neuropathy: The good, the bad, and the unknown

ABSTRACT

Cannabis may be an effective alternative or adjunctive treatment for peripheral neuropathy, an often debilitating condition for which standard treatments often provide little relief. Most studies show moderately improved pain from inhaled cannabis use, but adverse effects such as impaired cognition and respiratory problems are common, especially at high doses. Data on the long-term safety of cannabis treatments are limited. Until risk-benefit profiles are better characterized, doctors in states where cannabis therapy is legal should recommend it for peripheral neuropathy only after careful consideration.

KEY POINTS

Small clinical studies have found that cannabis provides benefits for peripheral neuropathy, including pain reduction, better sleep, and improved function, even in patients with symptoms refractory to standard therapies.

Adverse effects such as throat irritation, headache, and dizziness are common, and serious neuropsychiatric effects can occur at high doses.

Safety may not be adequately assessed in US trials because cannabis supplied by the National Institute of Drug Abuse is less potent than commercially available products.

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Marijuana, which is still illegal under federal law but legal in 30 states for medical purposes as of this writing, has shown promising results for treating peripheral neuropathy. Studies suggest that cannabis may be an option for patients whose pain responds poorly to standard treatments; however, its use may be restricted by cognitive and psychiatric adverse effects, particularly at high doses.[1]

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In this article, we discuss the basic pharmacology of cannabis and how it may affect neuropathic pain. We review clinical trials on its use for peripheral neuropathy and provide guidance for its use.

PERIPHERAL NEUROPATHY IS COMMON AND COMPLEX

An estimated 20 million people in the United States suffer from neuropathic pain. The prevalence is higher in certain populations, with 26% of people over age 65 and 30% of patients with diabetes mellitus affected.[2–4]

Peripheral neuropathy is a complex, chronic state that occurs when nerve fibers are damaged, dysfunctional, or injured, sending incorrect signals to pain centers in the central nervous system.[5] It is characterized by weakness, pain, and paresthesias that typically begin in the hands or feet and progress proximally.[4] Symptoms depend on the number and types of nerves affected.

In many cases, peripheral neuropathy is idiopathic, but common causes include diabetes, alcoholism, human immunodeficiency virus (HIV) infection, and autoimmune disease. Others include toxicity from chemotherapy and heavy metals.

Peripheral neuropathy significantly worsens quality of life and function. Many patients experience emotional, cognitive, and functional problems, resulting in high rates of medical and psychiatric comorbidities and occupational impairment.[4,6,7] Yet despite its clinical and epidemiologic significance, it is often undertreated.[8]

STANDARD TREATMENTS INADEQUATE

Peripheral neuropathy occurs in patients with a wide range of comorbidities and is especially difficult to treat. Mainstays of therapy include anticonvulsants, tricyclic antidepressants, and serotonin-norepinephrine reuptake inhibitors.[9] A more invasive option is spinal cord stimulation.

These treatments can have considerable adverse effects, and response rates remain suboptimal, with pain relief insufficient to improve quality of life for many patients.[9,10] Better treatments are needed to improve clinical outcomes and patient experience.[11]

CANNABIS: A MIX OF COMPOUNDS

Peripheral neuropathy is often undertreated

Cannabis sativa has been used as an analgesic for centuries. The plant contains more than 400 chemical compounds and is often used for its euphoric properties. Long-term use may lead to addiction and cognitive impairment.[12,13]

Tetrahydrocannabinol (THC) and cannabidiol (CBD) are the main components and the 2 best-studied cannabinoids with analgesic effects.

THC is the primary psychoactive component of cannabis. Its effects include relaxation, altered perception, heightened sensations, increased libido, and perceptual distortions of time and space. Temporary effects may include decreased short-term memory, dry mouth, impaired motor function, conjunctival injection, paranoia, and anxiety.

CBD is nonpsychoactive and has anti-inflammatory and antioxidant properties. It has been shown to reduce pain and inflammation without the effects of THC.[14]

Other compounds in the cannabis plant include phytocannabinoids, flavonoids, and tapenoids, which may produce individual, interactive, or synergistic effects.[15] Different strains of cannabis have varying amounts of the individual components, making comparisons among clinical studies difficult.

THE ENDOCANNABINOID SYSTEM

The endogenous mammalian cannabinoid system plays a regulatory role in the development, homeostasis, and neuroplasticity of the central nervous system. It is also involved in modulating pain transmission in the nociceptive pathway.

Two of the most abundant cannabinoid endogenous ligands are anandamide and 2-arachidonylglycerol.[9] These endocannabinoids are produced on demand in the central nervous system to reduce pain by acting as a circuit breaker.[16–18] They target the G protein-coupled cannabinoid receptors CB1 and CB2, located throughout the central and peripheral nervous system and in organs and tissues.[12]

CB1 receptors are found primarily in the central nervous system, specifically in areas involved in movement, such as the basal ganglia and cerebellum, as well as in areas involved in memory, such as the hippocampus.[12] They are also abundant in brain regions implicated in conducting and modulating pain signals, including the periaqueductal gray and the dorsal horn of the spinal cord.[16–20]

CB2 receptors are mostly found in peripheral tissues and organs, mainly those involved in the immune system, including splenic, tonsillar, and hematopoietic cells.[12] They help regulate inflammation, allodynia, and hyperalgesia.[17]

Modifying response to injury

Following a nerve injury, neurons along the nociceptive pathway may become more reactive and responsive in a process known as sensitization.[21] The process involves a cascade of cellular events that result in sprouting of pain-sensitive nerve endings.[21,22]

Cannabinoids are thought to reduce pain by modifying these cellular events. They also inhibit nociceptive conduction in the dorsal horn of the spinal cord and in the ascending spinothalamic tract.[20] CB1 receptors found in nociceptive terminals along the peripheral nervous system impede pain conduction, while activation of CB2 receptors in immune cells decreases the release of nociceptive agents.

STUDIES OF CANNABIS FOR NEUROPATHIC PAIN

A number of studies have evaluated cannabis for treating neuropathic pain. Overall, available data support the efficacy of smoked or inhaled cannabis in its flower form when used as monotherapy or adjunctive therapy for relief of neuropathic pain of various etiologies. Many studies also report secondary benefits, including better sleep and functional improvement.[23,24]

However, adverse effects are common, especially at high doses, and include difficulty concentrating, lightheadedness, fatigue, and tachycardia. More serious reported adverse effects include anxiety, paranoia, and psychosis.

Wilsey et al, 2008: Neuropathic pain reduced

Wilsey et al[25] conducted a double-blind, placebo-controlled crossover study that assessed the effects of smoking cannabis in 38 patients with central or peripheral neuropathic pain. Participants were assigned to smoke either high- or low-dose cannabis (7% or 3.5% delta-9-THC) or placebo cigarettes. Cigarettes were smoked during treatment sessions using the following regimen: 2 puffs at 60 minutes from baseline, 3 puffs at 120 minutes, and 4 puffs at 180 minutes. Patients were assessed after each set of puffs and for 2 hours afterwards. The primary outcome was spontaneous relief of pain as measured by a visual analog scale.

Pain intensity was comparable and significantly reduced in both treatment groups compared with placebo. At the high dose, some participants experienced neurocognitive impairment in attention, learning, memory, and psychomotor speed; only learning and memory declined at the low dose.

Ellis et al, 2009: Pain reduction in HIV neuropathy

Ellis et al[23] conducted a double-blind, placebo-controlled crossover trial in patients with HIV neuropathy that was unresponsive to at least 2 analgesics with different modes of action. During each treatment week, participants were randomly assigned to smoke either active cannabis or placebo, while continuing their standard therapy. Titration started at 4% THC and was adjusted based on tolerability and efficacy. Twenty-eight of the 34 enrolled patients completed both cannabis and placebo treatments. The principal outcome was change in pain intensity from baseline at the end of each week, using the Descriptor Differential Scale of Pain Intensity.

Of the 28 patients, 46% achieved an average pain reduction of 3.3 points (30%). One patient experienced cannabis-induced psychosis, and another developed an intractable cough, which resolved with smoking cessation.

Ware et al, 2010: Reduced posttraumatic or postsurgical neuropathic pain

Ware et al[24] performed a randomized crossover trial in 21 patients with posttraumatic or postsurgical neuropathic pain. Participants inhaled 4 different formulations of cannabis (containing 0%, 2.5%, 6.0%, and 9.4% THC) during 4 14-day periods. They inhaled a 25-mg dose through a pipe 3 times a day for the first 5 days of each cycle, followed by a 9-day washout period. Daily average pain intensity was measured using a numeric rating scale. The investigators also assessed mood, sleep, quality of life, and adverse effects.

Patients in the 9.4% THC group reported significantly less pain and better sleep, with average pain scores decreasing from 6.1 to 5.4 on an 11-point scale. Although the benefit was modest, the authors noted that the pain had been refractory to standard treatments.

Cannabidiol is not psychoactive and is effective against pain and inflammation

The number of reported adverse events increased with greater potency and were most commonly throat irritation, burning sensation, headache, dizziness, and fatigue. This study suggests that THC potency affects tolerability, with higher doses eliciting clinically important adverse effects, some of which may reduce the ability to perform activities of daily living, such as driving.

Wilsey et al, 2013: Use in resistant neuropathic pain

Wilsey et al[26] conducted another double-blind, placebo-controlled crossover study assessing the effect of vaporized cannabis on central and peripheral neuropathic pain resistant to first-line pharmacotherapies. Dose-effect relationships were explored using medium-dose (3.5%), low-dose (1.3%), and placebo cannabis. The primary outcome measure was a 30%

reduction in pain intensity based on a visual analog scale.

In the placebo group, 26% of patients achieved this vs 57% of the low-dose cannabis group and 61% of those receiving the medium dose. No significant difference was found between the 2 active doses in reducing neuropathic pain, and both were more effective than placebo. The number needed to treat to achieve a 30% reduction in pain was about 3 for both cannabis groups compared with placebo. Psychoactive effects were minimal, of short duration, and reversible.

Wallace et al, 2015: Use in diabetic peripheral neuropathy

Wallace et al[27] conducted a randomized, double-blind, placebo-controlled crossover study evaluating cannabis for diabetic peripheral neuropathy in 16 patients. Each had experienced at least 6 months of neuropathic pain in their feet. The participants inhaled a single dose of 1%, 4%, or 7% THC cannabis or placebo. Spontaneous pain was reported with a visual analog scale and also tested with a foam brush and von Frey filament at intervals until 4 hours after treatment.

Data support the efficacy of smoked or inhaled cannabis for neuropathic pain

Pain scores were lower with treatment compared with placebo, with high-dose cannabis having the greatest analgesic effect. Pain reduction lasted for the full duration of the test. Cannabis recipients had declines in attention and working memory, with the high-dose group experiencing the greatest impact 15 minutes after treatment. High-dose recipients also had poorer scores on testing of quick task-switching, with the greatest effect at 2 hours.[27]

Research and market cannabis are not equal

Results of US studies must be qualified. Most have used cannabis provided by the National Institute of Drug Abuse (NIDA),[23–26] which differs in potency from commercially available preparations. This limits the clinical usefulness of the analysis of benefits and risks.

Vergara et al[28] found that NIDA varieties contained much lower THC levels and as much as 23 times the cannabinol content as cannabis in state-legalized markets.

Studies based on NIDA varieties likely underestimate the risks of consumer-purchased cannabis, as THC is believed to be most responsible for the risk of psychosis and impaired driving and cognition.[24,28]

CBD MAY PROTECT AGAINST ADVERSE EFFECTS

Studies of CBD alone are limited to preclinical data.[29] Evidence suggests that CBD alone or combined with THC can suppress chronic neuropathic pain, and that CBD may have a protective effect after nerve injury.[30]

Nabiximols, an oromucosal spray preparation with equal amounts of THC and CBD, has been approved in Canada as well as in European countries including the United Kingdom. Although its use has not been associated with many of the adverse effects of inhaled cannabis,[30–32] evidence of efficacy from clinical trials has been mixed.

Lynch et al,[31] in a 2014 randomized, double-blind, placebo-controlled crossover pilot study[31] evaluated nabiximols in 16 patients with neuropathic pain related to chemotherapy. No statistically significant difference was found between treatment and placebo. However, the trial was underpowered.

Serpell et al,[32] in a 2014 European randomized, placebo-controlled parallel-group study, evaluated 246 patients with peripheral neuropathy with allodynia, with 128 receiving active treatment (THC-CBD oromucosal spray) and 118 receiving placebo. Over the 15-week study, participants continued their current analgesic treatments.

Pain was reduced in the treatment group, but the difference from placebo was not statistically significant. However, the treatment group reported significantly better sleep quality and Patient Global Impression of Change measures (reflecting a patient's belief of treatment efficacy).

META-ANALYSES CONFIRM EFFECT

Three meta-analyses of available studies of the effects of cannabis on neuropathic pain have been completed.

Andreae et al, 2015: 5 trials, 178 patients

Andreae et al[1] evaluated 5 randomized controlled trials in 178 patients in North America. All had had neuropathy for at least 3

months, with a pain level of at least about 3 on a scale of 10. Two studies had patients with HIV-related neuropathy; the other 3 involved patients with neuropathy related to trauma, diabetes, complex regional pain syndrome, or spinal cord injury. All trials used whole cannabis plant provided by NIDA, and the main outcomes were patient-reported pain scales. No study evaluated pain beyond 2 weeks after trial termination.

They found that 1 of every 5 to 6 patients treated with cannabis had at least a 30% pain reduction.

Nugent et al, 2017: 13 trials, 246 patients

Nugent et al[33] reviewed 13 trials in 246 patients that evaluated the effects of different cannabis-based preparations on either central or peripheral neuropathic pain from various conditions. Actively treated patients were more likely to report a 30% improvement in neuropathic pain. Again, studies tended to be small and brief.

Cochrane review, 2018: 16 trials, 1,750 patients

A Cochrane review[34] analyzed 16 trials (in 1,750 patients) lasting 2 to 26 weeks. Treatments included an oromucosal spray with a plant-derived combination of THC and CBD, nabilone, inhaled herbal cannabis, and plant-derived THC.

With cannabis-based treatments, significantly more people achieved 50% or greater pain relief than with placebo (21% vs 17%, number needed to treat 20); 30% pain reduction was achieved in 39% of treated patients vs 33% of patients taking placebo (number needed to treat 11).

On the other hand, significantly more participants withdrew from studies because of adverse events with cannabis-based treatments than placebo (10% vs 5%), with psychiatric disorders occurring in 17% of patients receiving active treatment vs 5% of those receiving placebo (number needed to harm 10).

The primary studies suffered from methodologic limitations including small size, short duration, and inconsistency of formulations and study designs. Further evaluation of long-term efficacy, tolerability, and addiction potential is critical to determine the risk-benefit ratio.

RISKS OF CANNABIS USE

Like any drug therapy, cannabis has effects that may limit its use. Cannabis can affect a person's psyche, physiology, and lifestyle.

Impaired attention, task speed

Neurocognitive changes associated with cannabis use—especially dizziness, fatigue, and slowed task-switching—could affect driving and other complex tasks. Evidence indicates that such activities should be avoided in the hours after treatment.[26,27,32,33]

Concern over brain development

Most worrisome is the effect of long-term cannabis use on brain development in young adults. Regular use of cannabis at an early age is associated with lower IQ, decline in school performance, and lower rates of high school graduation.[35]

Avoid in psychiatric patients

It is unlikely that cannabis can be safely used in patients with psychiatric illnesses. Anxiety, depression, and psychotic disorders can be exacerbated by the regular use of cannabis, and the risk of developing these conditions is increased while using cannabis.[36,37]

High concentrations of THC (the highest concentration used in the above studies was 9.5%) can cause anxiety, paranoia, and psychosis.

THC potency affects tolerability

Respiratory effects

Long-term cannabis smoking may cause wheezing, cough, dyspnea, and exacerbations of chronic bronchitis. There is some evidence that symptoms improve after stopping smoking.[33,38]

SHOULD WE RECOMMEND CANNABIS?

Where cannabis can be legally used, doctors should be familiar with the literature and its limitations so that they can counsel patients on the best use and potential risks and benefits of cannabis treatment.

A recent conceptualization of pain suggests that a pain score reflects a composite of sensory factors (eg, tissue damage), cognitive factors (eg, beliefs about pain), and affective factors (eg, anxiety, depression).[39] Physicians should keep this in mind when evaluating patients to better assess the risks and benefits

of cannabis. While pharmacotherapy may address sensory factors, cognitive behavioral therapy may help alter beliefs about the pain as well as anxiety and depressive symptoms that might influence subjective reports.

Ideally, patients being considered for cannabis treatment would have a type of neuropathic pain proven to respond to cannabis in randomized, controlled studies, as well as evidence of failed first-line treatments.

Relative contraindications include depression, anxiety, substance use, psychotic disorders, and respiratory conditions, and these should also be considered.

Although current research shows an analgesic benefit of cannabis on neuropathic pain comparable to that of gabapentin,[40] further investigation is needed to better evaluate long-term safety, efficacy, and interactions with standard therapies. Until we have a more complete picture, we should use the current literature, along with a thorough knowledge of each patient, to determine if the benefits of cannabis therapy outweigh the risks.

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