

Chronic Pain

As many as one in five Americans lives with chronic pain.[1] Many of these people suffer from neuropathic pain (nerve-related pain) -- a condition that is associated with numerous diseases, including diabetes, cancer, multiple sclerosis, and HIV. In most cases, the use of standard analgesic medications such as opiates and NSAIDs (non-steroidal anti-inflammatory drugs) is ineffective at relieving neuropathic pain. Further, long-term use of most conventional pain relievers, including acetaminophen, opioids, and NSAIDs, is associated with a host of potential adverse side effects, including stroke, erectile dysfunction, heart-attack, hepatotoxicity, and accidental overdose death.

Survey data indicates that the use of cannabis is common among patients with chronic pain[2] and a majority of patients who use it for this indication report it as being effective.[3] In addition to anecdotal claims, several recent FDA-designed clinical trials report that inhaled inhaled marijuana can significantly alleviate neuropathic pain. These include a pair of randomized, placebo-controlled clinical trials demonstrating that smoking cannabis reduces neuropathy in patients with HIV by more than 30 percent compared to placebo.[4-5] (Additional details on these studies appear in the HIV section of this book.) In addition, a 2007 University of California at San Diego double-blind, placebo-controlled trial reported that inhaled cannabis significantly reduced capsaicin-induced pain in healthy volunteers.[6] A 2008 University of California at Davis double-blind, randomized clinical trial reported both high and low doses of inhaled cannabis reduced neuropathic pain of diverse causes in subjects unresponsive to standard pain therapies.[7] A 2010 McGill University study reported that smoked cannabis significantly improved measures of pain, sleep quality and anxiety in participants with refractory pain for which conventional therapies had failed.[8] A 2013 clinical trial reported that both inhaled cannabis and oral THC significantly decreased pain sensitivity and increased pain tolerance in healthy subjects exposed to experimental painful stimuli.[9]

Clinical trials also report that vaporized cannabis is effective at mitigating pain. 2013 FDA-approved trial assessing the impact of vaporized cannabis on neuropathic pain reported that even low doses of THC (1.29 percent) "provided statistically significant 30% reductions in pain intensity when compared to placebo." [10] A 2014 Israeli open-label clinical trial reported that the administration of a single dose of whole-plant cannabis via a thermal-metered inhaler was effective and well tolerated among patients suffering from nerve pain.[11] Placebo-controlled data published in 2015 in *The Journal of Pain* further reported

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that vaporized cannabis provides "a dose-dependent reduction in diabetic peripheral neuropathy pain in patients with treatment-refractory pain." [12]

A review of these and other trials the *British Journal of Clinical Pharmacology* concluded, "[I]t is reasonable to consider cannabinoids as a treatment option for the management of chronic neuropathic pain with evidence of efficacy in other types of chronic pain such as fibromyalgia and rheumatoid arthritis as well." [13] A separate review published in *The Clinical Journal of Pain* further concluded, "Overall, based on the existing clinical trials database, cannabinergic pain medicines have been shown to be modestly effective and safe treatments in patients with a variety of chronic pain conditions. ... Incorporating cannabinergic medicine topics into pain medicine education seems warranted and continuing clinical research and empiric treatment trials are appropriate." [14]

Most recently, a one-year assessment of Canadian chronic pain patients reported that daily use of herbal cannabis was associated with sufficient safety and efficacy. Compared to controls, patients in the cannabis use group experienced a significant reduction in average pain intensity while reporting no increased risk of adverse cognitive or pulmonary events. Authors concluded: "[T]his study suggests that the adverse effects of medical cannabis are modest and comparable quantitatively and qualitatively to prescription cannabinoids. The results suggest that cannabis at average doses of 2.5g/d in current cannabis users may be safe as part of carefully monitored pain management program when conventional treatments have been considered medically inappropriate or inadequate." [15]

Preclinical data indicates that cannabinoids, when administered in concert with one another, are more effective at ameliorating neuropathic pain than the use of a single agent. Investigators at the University of Milan reported in 2008 that the administration of single cannabinoids such as THC or CBD produce limited relief compared to the administration of plant extracts containing multiple cannabinoids, terpenes (oils), and flavonoids (pigments). Researchers concluded: "[T]he use of a standardized extract of *Cannabis sativa* ... evoked a total relief of thermal hyperalgesia, in an experimental model of neuropathic pain, ... ameliorating the effect of single cannabinoids," investigators concluded. ... "Collectively, these findings strongly support the idea that the combination of cannabinoid and non-cannabinoid compounds, as present in [plant-derived] extracts, provide significant advantages in the relief of neuropathic pain compared with pure cannabinoids alone." [16]

In 2009, an international team of investigators from the United Kingdom, Belgium and Romania affirmed these preclinical findings in a clinical study of intractable cancer pain

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patients. They concluded: "[I]n this study, the THC/CBD extract showed a more promising efficacy profile than the THC extract alone. This finding is supported by evidence of additional synergy between THC and CBD. CBD may enhance the analgesic potential of THC by means of potent inverse agonism at CB2 receptors, which may produce anti-inflammatory effects, along with its ability to inhibit immune cell migration. ... These results are very encouraging and merit further study." [17]

Cannabis may also permit some chronic pain patients to significantly reduce their use of opioids. A 2011 clinical trial assessing the administration of vaporized plant cannabis in chronic pain patients on a daily regimen of morphine or oxycodone reported that inhaled "cannabis augments the analgesic effect of opioids." Authors concluded, "The combination (of opioids and cannabinoids) may allow for opioid treatment at lower doses with fewer side effects." [18] Patients appear to be taking this advice in jurisdictions where they have medical marijuana access. According to the findings of a 2015 National Bureau of Economic Research study, "[S]tates permitting medical marijuana dispensaries experience a relative decrease in both opioid addictions and opioid overdose deaths compared to states that do not." [19] The NBER findings are similar to those published in 2014 in the *Journal of the American Medical Association (JAMA) Internal Medicine* which also reported that the enactment of statewide medicinal marijuana laws is associated with a 24.8 percent lower mean annual opioid overdose mortality rate compared with states without medical cannabis laws. [20] Consequently, some pain experts are now advising that physicians recommend cannabis therapy in addition to or in lieu of opiate medications to "reduce the morbidity and mortality rates associated with prescription pain medications." [21] Yet, inexplicably, in some jurisdictions lawmakers have refused to include analgesia as a qualifying condition for medical cannabis.

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