

CONTROLLING PAIN

Cannabinoids: An emerging role in pain management?

By Clifford Gevartz, MD, MPH

FIRST USED MEDICINALLY more than 5,000 years ago, cannabis has been attracting renewed interest lately as an analgesic.

The raw cannabis plant contains hundreds of chemical compounds, including about 70 cannabinoids. Three of these compounds have demonstrated psychoactive effects; delta-9-tetrahydrocannabinol (THC) is the most potent. The most important therapeutically active compound is cannabidiol (CBD), which has no psychoactive effect but significant analgesic, antioxidant, and anti-inflammatory effects. Cannabis-based medicinal extracts developed by pharmaceutical companies are distilled from cannabinoids without THC. In this article, I'll review the evidence, pro and con, for medicinal cannabis use. Because no studies have evaluated the analgesic effects of smoked cannabis, I'll focus on oral compounds. For more on the history of this drug, see *Cannabis through the centuries*.

How do cannabinoids work?

The body has two types of cannabinoid receptors: CB1 receptors in the central and peripheral nervous system and CB2 receptors located outside the central nervous system, particularly on macrophages. Researchers believe the CB2 receptor modulates anti-inflammatory and immunosuppressive activity. By chemically manipulating cannabinoids, drug developers can maximize selectivity for CB2 and avoid the psychoactive effects of cannabinoids.

Scientific literature before 1970 is mostly a collection of case studies and anecdotal reports about the analgesic efficacy of cannabinoids. Most of the more recent studies were small and examined different cannabinoids and

different regimens, so their data can't be pooled for a meta-analysis.

However, reviewing the therapeutic uses of cannabis and recent randomized controlled studies sets forth the areas of research needed to bring cannabis back to the bedside.

- **Cancer pain.** In a review of five cancer-pain studies (totalling 128 patients), a cannabinoid was found less effective than codeine and no more effective than placebo. Another study in the same review found that a cannabinoid had an analgesic effect when compared with placebo, but the dose-response relationship was complicated by increasing adverse reactions.¹

- **Chronic noncancer pain.** In one study of two patients with chronic pain, a cannabinoid was found no better than placebo based on visual analog scale scores for pain intensity. However, the patient used less morphine for breakthrough pain while also taking the cannabinoid, compared with placebo.¹ This is the typical morphine-sparing effect of a synergistic analgesic, but the small study size means the results can't be generalized.

In a patient with neuropathic pain and spasticity secondary to a spinal cord tumor, cannabinoids and codeine were equianalgesic, and both were better than placebo. Only the cannabinoid had a beneficial effect on spasticity. However, a single-patient study isn't acceptable scientific evidence.¹

In a crossover study of 21 patients with chronic neuropathic pain and significant hyperalgesia or allodynia, researchers found that patients taking the cannabinoid had significantly improved pain intensity ratings on a visual analog scale, and no major adverse reactions.


CANNABIS THROUGH THE CENTURIES

Cannabis was used in China some 5,000 years ago to treat malaria, constipation, and rheumatic pains. Mixed with wine, it was a surgical anesthetic. In the mid-19th century, cannabis was used in India as an analgesic, anticonvulsant, antispasmodic, antiemetic, and hypnotic. In the United States, the drug was part of dozens of home remedies. Sir William Osler, widely regarded as the father of internal medicine, recommended cannabis for migraine treatment.

However, concerns about the recreational use of cannabis led to it being outlawed in 1937. Exceptions for compassionate use of medicinal cannabis were made from 1976 to 1992, when the loophole was tightened. A 1996 California law lets patients use medicinal marijuana if a physician provides a written endorsement.

Although the study is promising, a much larger study is needed to confirm the researchers' conclusions that this cannabinoid would be suitable for neuropathic pain.¹

- **Acute pain.** A study of the cannabinoid plant extract Cannador found that it was as effective as commonly used oral drugs, such as morphine and non-steroidal anti-inflammatory drugs, for moderate pain intensity. This suggests that cannabinoids may have a role in postoperative pain management.²

- **Arthritis pain.** A double-blind trial compared cannabinoid-based Sativex oral spray with placebo, and found that patients who took Sativex had significant improvements in pain on movement, pain at rest, quality of sleep, inflammation, and intensity of pain. 

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Adverse reactions were mild or moderate (dizziness, light-headedness, dry mouth, and nausea). Although the therapeutic benefits were small and variable across the patient group, they're clinically relevant because of the minimal adverse reactions. Also, no cases of Sativex abuse from patients seeking psychotropic effects have been documented. More detailed investigation through larger trials is needed.³

Considering the downside

THC has a dose-response relationship for adverse reactions, including sedation, ataxia, vertigo, numbness, disorientation, disconnected thought, slurred speech, muscle twitching, impaired memory, dry mouth, and blurred vision. A 20-mg dose is sedating in all

patients, so this is considered the upper limit for clinical use. A 10-mg dose is better-tolerated, but causes more adverse reactions than 60-mg or 120-mg doses of codeine. For neuropathic pain, a 5-mg dose of THC is well tolerated and doesn't alter consciousness. The nitrogen analog of THC doesn't affect heart rate but causes drowsiness in 40% of patients, so it isn't clinically useful. Benzopyranoperidine causes a similar degree of sedation as codeine, but is ineffective as an analgesic.

Cannabinoids vary widely in efficacy, and increasing doses to improve analgesia also increases adverse reactions. If the right balance or strain of cannabis could be bred, the drug might have more options for analgesic use. At present, research doesn't support widespread use

of cannabinoids for pain management. And although the drug may be useful for spasticity and neuropathic pain, larger studies are needed. ✧

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