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Cannabinoids Can Serve As Alternatives To Narcotic Pain Medication For Fracture Healing

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Cannabidiol (CBD), a major nonpsychotropic cannabis constituent, has been shown to decrease pain—especially chronic and neuropathic pain—and may enhance bone metabolism. Currently, as the United States faces an opioid epidemic, many providers are either choosing or being forced to limit the number of narcotics they prescribe for pain in orthopaedic patients. Arthritis, osteoporosis, and low

back pain constitute the majority of musculoskeletal disease burden in the United States. All are expected to increase as the country's population ages. Pain management in orthopaedic patients can be challenging, especially chronic pain. There is a tremendous need for safe alternatives that do not result in tolerance or dependence. CBD has made headlines as a cure-all; Sanjay Gupta, MD, endorsed CBD on "The Dr. Oz Show," and The New York Times runs seemingly weekly coverage of the topic. Many patients have heard about and may want to try CBD. As with many trendy remedies, a great deal of misinformation is circulating in popular news outlets and on the internet. So, what is CBD, and should patients be using it for bone health or as part of a multimodal approach to pain control?

The science behind CBD

CBD is different from medical marijuana, but like tetrahydrocannabinol (THC), it is one of more than 100 naturally occurring cannabinoids found in cannabis plants. Cannabinoids bind endogenous cannabinoid receptors found throughout our bodies, which are mainly the two G protein-coupled receptors: CB1 and CB2. CB1 receptors are found in the central and peripheral nervous system and influence appetite, mood, and pain. CB2 receptors are found on immune cells and regulate cytokine production and inflammation. Those receptors are expressed by both osteoblasts and osteoclasts. The mechanism of action of CBD is not well understood, as CBD does not directly bind the receptors like THC but affects downstream signaling indirectly. Interestingly, CBD also shows affinity for binding noncannabinoid receptors, including the dopamine, serotonin, and opioid receptors.

CBD can be extracted from the stalks and stems of hemp

plants or the buds and flowers of marijuana plants. It also has been extracted from a new variety of hops. Hemp contains no more than 0.3 percent THC. By comparison, the THC content in marijuana ranges from 4 percent to 20 percent. Unlike cannabis and medical marijuana, CBD is nonpsychotropic, is nonpsychoactive, and does not produce a “high.” It does not increase appetite or produce withdrawal symptoms, and it is not addictive.

Hemp, like marijuana, has a complex history of being largely illegal to grow and sell in the United States under the Controlled Substance Act, although imported hemp products have been available for many years. The passage of the 2018 Farm Bill reclassified hemp from the domain of the Drug Enforcement Agency to the Department of Agriculture, opening up the possibility for industrial hemp production in the United States. Currently, hemp-derived CBD is fully legal in all 50 states regardless of the state’s laws on medical and recreational marijuana. By comparison, medical marijuana is legal in 33 states. However, some states are working with the Food and Drug Administration (FDA) to establish regulations for CBD.

CBD-related products

Recently, there has been a tremendous increase in demand for CBD, a nearly $1 billion industry. CBD-containing products—moisturizers, massage oils, gummies, beer, and much more— frequently are marketed as “hemp oil” or “CBD infused.” CBD products often are sold in natural medicine or supplement stores, in health food stores, and online. In the 10 states where recreational marijuana is currently legal (Alaska, California, Colorado, Maine, Massachusetts, Michigan, Nevada, Oregon, Vermont, and Washington), CBD products also are available at cannabis

dispensaries, where they may be sold separately or combined with THC.

Our orthopaedic practice, based in northern New Mexico, takes us to places like Santa Fe, where alternatives to traditional medications and holistic medicine are widely accepted. Nonetheless, CBD may still carry the stigma of marijuana, and patients often ask about becoming intoxicated, impaired, or even addicted. We also have patients who work at scientific laboratories or other jobs that require frequent drug testing who abstain from CBD due to concerns about strict workplace drug screening.

As dietary supplements, CBD products are not regulated like drugs or medications. Patients should choose reputable stores with high-quality, hemp-derived products to avoid potential cross-contamination with THC from marijuana-derived products. Patients may be advised to avoid cannabis dispensaries to mitigate confusion over THC content and potential mislabeling. Theoretically, it should be impossible to have a false-positive drug test from a purely hempderived CBD product.

CBD has been purported to treat a wide array of conditions, including but not limited to acne, anxiety, depression, inflammation, insomnia, and post-traumatic stress disorder. CBD may even have anticancer properties. But does it work, and is it safe? Epidiolex®, from GW Pharmaceuticals, is an FDA-approved oral CBD medication used to treat certain epilepsy conditions, prescribed at 5–20 mg/kg/day. However, the FDA does not regulate CBD for most conditions. As a result, indications and dosages are open to interpretation. The usual starting dose is around 15–25 mg per day, but doses of 80–120 mg per day may be common. For seizures, 200–300 mg daily may be prescribed, as studies show that

CBD is well tolerated in daily doses up to 600 mg. This wide safety range means there is a low risk of overdose or adverse events.

Products like hemp oil, honey, and beer generally contain 5–30 mg per serving. Such products typically cost more than similar products without CBD, but a 30-day supply of hemp oil only costs around $15 to $30. Unfortunately, the production of CBD products is largely unregulated and has the potential for false advertising, which could be misleading to patients. Therefore, it is recommended that patients consider purchasing products from companies and retailers that provide independent third-party laboratory results that verify actual CBD content.

Courtesy of Jeremy Korsh, MD

Incorporating CBD products into orthopaedics

What is the role of CBD in orthopaedics? CBD is most commonly used to treat epilepsy, neuropathic pain, and

anxiety. The best available evidence suggests CBD may be effective for musculoskeletal pain. Conditions studied include arthritic pain (including rheumatoid arthritis), back pain, and trauma-related pain. Many of the studies tested THC alone or in combination with CBD.

For postoperative pain, the evidence is mixed. Unfortunately, we are not left with many other alternatives when nonsteroidal anti-inflammatory drugs are contraindicated due to patient comorbidities or held following surgery due to concerns that they may interfere with soft tissue or bony healing. Anti-inflammatory properties of CBD are promising, but the evidence is mostly limited to animal and laboratory studies. There is insufficient evidence to currently make strong conclusions about the efficacy of CBD for acute, arthritic, or postoperative pain. However, there is better evidence that CBD provides analgesia for patients with cancer and chronic, neuropathic pain.

Most practitioners recognize the importance of identifying alternative treatment strategies other than narcotic pain medications. Many patients are reluctant to use their prescribed opioids out of fear of developing addiction or dependency, and there is emerging evidence that CBD can be used to treat chronic pain and combat opioid abuse.

Another consideration is that a large, probably underappreciated, component of pain is anxiety. CBD has been shown in multiple studies to have considerable potential as an anxiolytic. If CBD can attenuate anxiety, patients may experience less pain overall. Animal models also have shown synergy between CBD and opioids in treating pain. Despite the fact that animals receiving CBD consumed fewer opioids in those studies, the opioid-sparing effect has not yet been demonstrated in any clinical trials.

Animal and basic science studies also suggest that CBD may play a role in bone regeneration. One study in rats showed decreased osteoclastic bone resorption via CBD attenuation of receptor activator of nuclear factor-kappa B pathway. Another study in rats showed reduced bone mineral density (BMD) loss in a spinal cord injury model. A third and frequently cited study showed that CBD may enhance bone healing and decrease time to fracture union by stimulating osteoblastic expression of lysyl hydroxylase, an enzyme involved in collagen cross-linking and stabilization. The authors found that rats with closed midshaft femur fractures treated with CBD demonstrated stronger fracture callus at earlier time points versus the group treated with THC and the control group. The potential benefits were unique to CBD and not shared with THC, which is consistent with a previous human study from 2008 that showed that smoking marijuana was associated with decreased bone filling around titanium implants. Lastly, antiepileptic drugs (AEDs) are associated with disordered bone turnover, decreased BMD, and an increased risk of fracture. CBD may be an option for some patients to avoid AED-related bone disease.

Public perception of CBD as a panacea is not currently supported by evidence. In fact, current literature on the topic is heterogenous and low quality, precluding strong conclusions regarding many of the potential benefits of CBD. The limited numbers of studies specific to CBD, not including THC, are often preclinical (test tube, cell culture, or animal models). Given the large overall burden of musculoskeletal diseases on the health system, therapeutic uses for CBD certainly will continue to develop. Future research should focus on CBD use for acute and perioperative pain, especially any opioid-synergy or -sparing

effects. Further studies should investigate the role of CBD in human bone metabolism, including potential use in fracture healing and osteoporosis.

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