

# MARIJUANA IN ORTHOPAEDICS: EFFECTS ON BONE HEALTH, WOUND-HEALING, SURGICAL COMPLICATIONS, AND PAIN MANAGEMENT

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## Abstract

» Marijuana use is on the rise in the United States, and there is a paucity of information on the effects of cannabis and its chemical constituents on bone health, wound-healing, surgical complications, and pain management.

» Current evidence suggests that cannabidiol (CBD) may enhance bone health and metabolism, while  $\Delta 9$ -tetrahydrocannabinol ( $\Delta 9$ -THC), the major psychoactive component in marijuana, has an inhibitory effect.

» Marijuana users are at higher risk for delayed bone-healing, demonstrate lower bone mineral density, are at increased risk for fracture, and may experience postoperative complications such as increased opioid use and hyperemesis.

The legalization of marijuana in the United States is quickly increasing, and it is now legal in 36 states for medical use only and in 17 states for both medical and recreational use. As medical marijuana has become more acceptable both legally and socially, its perceived risk of deleterious effects has decreased. Overall use has increased, and there are >20 million current marijuana users in the United States<sup>1</sup>. The Annual Surveillance Report of Drug-Related Risks and Outcomes revealed that 15.9% of individuals who are  $\geq 12$  years of age used marijuana in 2020<sup>1</sup>. This is far greater than for any other illicit substance, with 3.7% of individuals reporting opiate misuse and 2% reporting cocaine use<sup>1</sup>. This is also a considerable increase from previous years: surveys from 2015 and 2010 reported marijuana use as 13.2% and 11.5%, respectively, in those who are  $\geq 12$  years of age<sup>1</sup>. Reported daily use of marijuana also increased from 2.1% in 2016 to 3.4% in 2019 according to the National Survey on Drug Use<sup>2</sup>. Increased use among youth over the last decade has been demonstrated, with >11.8 million reporting mari-

juana use. Daily use in the youth population has been noted to increase over time: 2017 data reported use as 0.8%, 2.9%, and 5.9% for eighth, tenth, and twelfth graders, and 2020 data reported use as 1.1%, 4.4%, and 6.9%, respectively<sup>1</sup>. The elderly population ( $\geq 65$  years of age) has likewise had a dramatic increase in marijuana use, from 0.4% in 2006 to 2.9% in 2015<sup>3</sup>.

With this rise in marijuana use, interest has been piqued in the medical community concerning the effects of marijuana and its chemical constituents on human physiology. Within the field of orthopaedics, there have been investigations on the effects of marijuana on bone mineral density, bone-healing, fracture risk, and postoperative outcomes<sup>4-10</sup>. However, the current literature is scarce, and additional investigation is needed on the effects of marijuana and its constituents on the musculoskeletal system. The purpose of this article is to review the literature that is currently available on this topic.

## The Chemistry of Cannabis

Cannabis is a plant with psychoactive chemical properties; it contains >500

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components, including 104 cannabinoids that have been identified. The pharmacological properties of 2 of the cannabinoids,  $\Delta^9$ -tetrahydrocannabinol ( $\Delta^9$ -THC) and cannabidiol (CBD), have been the subject of scientific investigation<sup>11</sup>. Because of the psychoactive nature of  $\Delta^9$ -THC, there has also been a large commercial interest in increasing the amount that is contained in products, with  $\Delta^9$ -THC concentrations being consistently >15% in recreational marijuana, and CBD concentrations range from 0.5% to 4.0%<sup>12</sup>. Vaping methods with distilled resins have allowed for further variation of the relative amounts of these compounds.

The primary methods of intake of cannabinoids are inhalation and oral ingestion. When comparing the absorption rates and bioavailability of these compounds, inhalation results in a rapid onset of effects within 10 minutes of peak plasma concentrations; the effects after oral ingestion are delayed, with lower peak concentrations occurring at around 5 hours<sup>13</sup>. Because the nature of these molecules is highly lipophilic, they are primarily distributed to highly vascular tissues. These compounds are then conjugated with fatty acids and stored within fatty tissues. These molecules are metabolized by the cytochrome P450 enzyme system, more specifically the CYP2C9 and CYP2C19 enzymes, via hydroxylation and oxidation in the liver. They are primarily eliminated in the feces (65%) and urine (20%)<sup>13</sup>.

Endocannabinoids and their receptors are involved in the regulation of numerous physiological processes, including pain perception, bone health, neurotransmission, memory, appetite, motor function, and immune response<sup>4,11,13-15</sup>. Cannabinoid receptors 1 and 2 (CB-1 and CB-2) have been the primary focus of most investigations. These receptors are G protein-coupled receptors located on the cell surface that are activated by phytocannabinoids, endocannabinoids, and synthetic cannabinoid analogs. The mechanism of these G-protein receptors has been demonstrated through the inhibition of

adenylyl cyclase and the subsequent increase of cyclic adenosine monophosphate (cAMP) by influence of the RAS pathway. Cannabinoids bind to tissues and exhibit carrying effects on these receptors.

CB-1 is primarily expressed throughout the central nervous system (CNS) and peripheral nerve axons; it is thought to be involved primarily in analgesic effects<sup>16,17</sup>. Although CB-1 has predominantly been located within the CNS, it is also found on nerve fibers innervating bone, and to a lesser extent within the immune cells of the bone marrow. CB-2, although also located in the CNS, is found throughout the immune system<sup>17</sup>. CB-2 has been shown to be involved in neurodefense, as well as in reduction of inflammation through activation of various cytokines, including interleukin-1 (IL-1), IL-2, IL-6, and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ )<sup>14</sup>. G protein-coupled receptor 55 (GPR55) is a third cannabinoid receptor that has been found to be located on osteoblasts and osteoclasts and in the gastrointestinal tract and adrenal glands. Endogenous cannabinoids, including anandamide and 2-arachidonoylglycerol, have been studied for their primary interactions on these 2 receptors<sup>15</sup>. In orthopaedics, our focus is to determine how these cannabinoids affect tissue-healing and bone health.

### **Bone Health and Healing: Effects of CB-1, CB-2, and GPR55 on Bone Function**

Several compounds have been determined to affect bone turnover and osteogenesis, including vitamin D and bisphosphonates. The extent to which the cannabinoid system affects these processes is under ongoing investigation. There have been multiple studies evaluating the effects of cannabinoid receptors on bone health. One of the first studies to stimulate interest evaluated mice with knockout of the CB-1 cannabinoid receptor, which initially showed increased bone mass after oophorectomy but subsequent increased osteoporosis at 1 year<sup>4</sup>.

Bone turnover is a complex process that occurs on a daily basis for physiologic

bone homeostasis; it also occurs in the pathologic setting of fracture-healing. There is a balance of bone formation and resorption performed by osteoblasts and osteoclasts, respectively. Osteoblasts are derived from mononucleated mesenchymal stem cells (MSCs), whereas osteoclasts are derived from multinucleated hematopoietic stem cells. Both cell types have a complex interaction that is primarily regulated by molecules that carry signals between them. We will discuss how the endocannabinoid system plays into this signaling matrix.

### **CB-1 Receptor**

The CB-1 receptor is believed to play a role in bone metabolism through an indirect route by acting on peripheral sympathetic nerves. Stimulation of the CB-1 receptor at these terminals is thought to inhibit osteoblast beta-2 adrenergic receptors, which in turn stimulates osteoblast proliferation, differentiation, and activity<sup>16</sup>. This same decreased inhibition of beta-2 adrenergic receptors has been demonstrated to decrease osteoclast formation via decreased RANKL (receptor activator of nuclear factor kappa-B ligand) signaling<sup>17</sup>. These receptors have also been identified on bone cells in much smaller quantity than CB-2 receptors, suggesting a decreased overall direct effect of CB-1 on bone cells<sup>18</sup>. Studies of CB-1 receptors in genetically manipulated mice have demonstrated ambiguous results. Overall, CB-1 knockout mice developed decreased bone mass<sup>19</sup>. However, these results appeared to be sex-dependent since female mice were noted to have a greater decrease in bone mass when compared with male mice<sup>20</sup>. These results were not noted to have major effects on development; however, they were noted to increase adipogenesis and decrease osteoblastogenesis in adulthood, resulting in decreased bone formation. There was also decreased osteoclast activity noted in these knockout mice. The effective outcome was an initial increase in bone volume, followed by accelerated age-related osteoporosis<sup>21</sup>.

### **CB-2 Receptor**

Compared with the CB-1 receptor, the CB-2 receptor is more common within

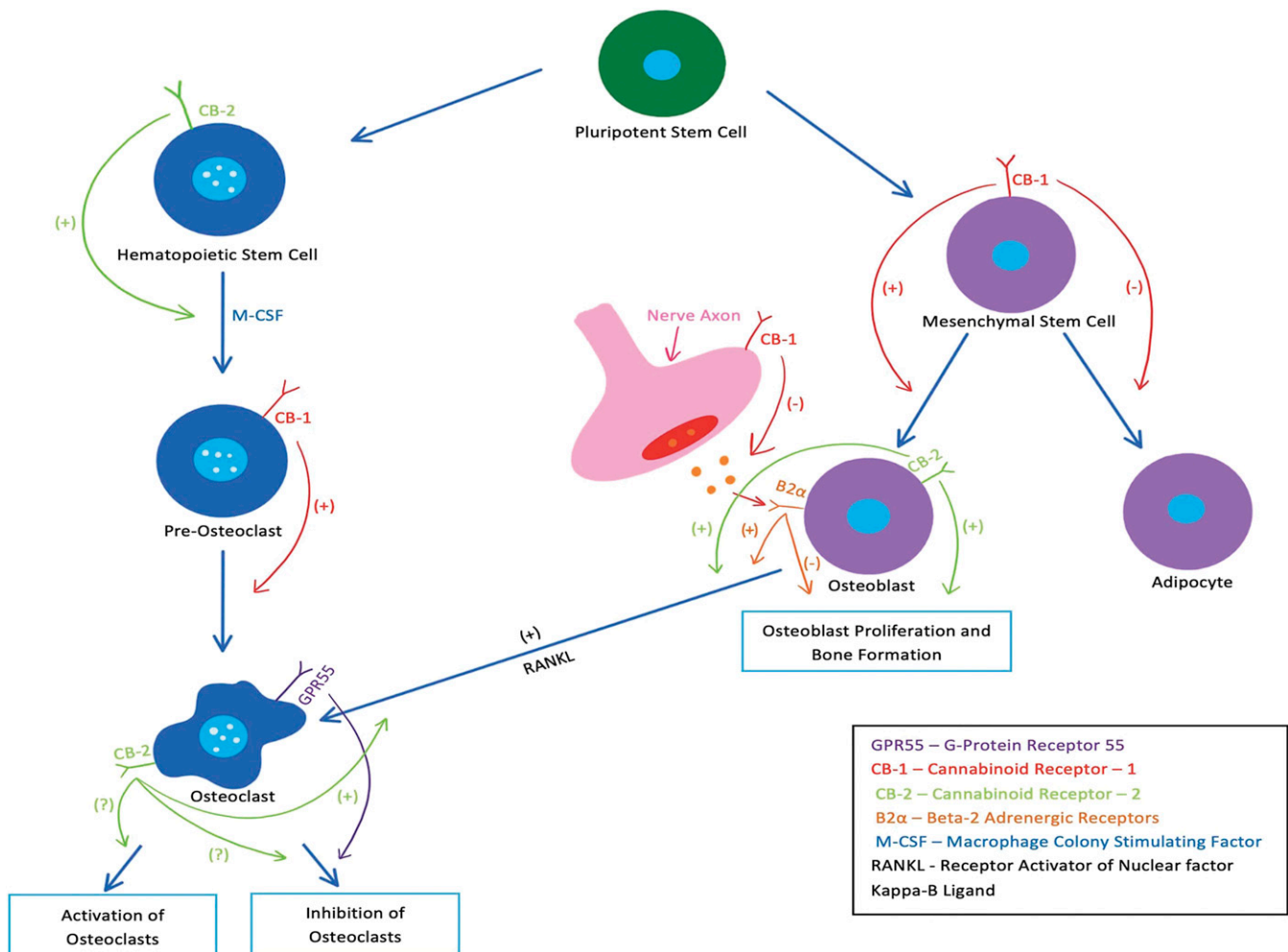


Fig. 1

The effects of the cannabinoid receptors (CB-1, CB-2, and GPR55) throughout osteoclast and osteoblast cell lines with cannabinoid receptor-mediated actions and effects on bone metabolism. (+) represents activation, or a positive effect; (-) represents inhibition, or a negative effect; and (?) represents an unknown or debated effect.

bone cells and is often expressed under bone remodeling<sup>22</sup>. Stimulation of CB-2 has been shown to increase osteogenic factors, including RUNX2, bone sialoprotein, osteopontin, alkaline phosphatase, and osteocalcin<sup>23</sup>. Studies of genetically manipulated mice have demonstrated increased osteoporosis, with a lower osteoblast-to-osteoclast ratio, when compared to those without the knockout mutation<sup>24</sup>. This suggests that CB-2 stimulation increases osteoblast mitogenesis<sup>25</sup>. Currently, the effect of the CB-2 receptor on osteoclasts is indeterminate. Some studies involving CB-2 receptor activation have demonstrated a positive effect on bone mass, with the mechanism believed to be decreasing activation of osteoclasts and downregulation of RANKL<sup>26</sup>. However, this has been dis-

puted because selective antagonists have shown inhibition of osteoclast formation in other *in vitro* studies<sup>7</sup>. Another study demonstrated that agonism of CB-2 leads to an increased RANKL-to-osteoprotegerin ratio as well as increased macrophage-colony stimulating factor (M-CSF), leading to increased osteogenesis<sup>22</sup>.

*GPR55*

GPR55 is a third cannabinoid receptor that has been identified throughout the body, primarily within the CNS but also condensed within osteoblasts and osteoclasts<sup>24</sup>. Greater density was found within osteoclasts, and it was noted that stimulation of GPR55 decreases osteoclast formation<sup>7</sup>. GPR55 knockout mice had increased trabecular bone mass

and increased cartilage remnants at the growth plate<sup>24</sup>. There was no demonstrated impact on osteoblast function<sup>24</sup>. Figure 1 provides a visual representation of the roles of CB-1, CB-2, and GPR55; these effects are summarized in Table I.

## Natural Endocannabinoid Agonists

The 2 main chemical constituents of cannabis are  $\Delta 9$ -THC and CBD, each of which plays a role in bone homeostasis and fracture-healing.  $\Delta 9$ -THC is a partial agonist of CB-1 and CB-2 receptors, with a higher affinity for CB-1 in the CNS<sup>27</sup>. However, it is also believed that  $\Delta 9$ -THC has a negative effect on MSC differentiation, with  $\Delta 9$ -THC decreasing MSC viability because of decreased metabolism and affecting osteocyte

TABLE 1 Effects of CB-1, CB-2, and GPR55 on Bone Formation and Bone Resorption

Receptor	Bone Formation	Bone Resorption
CB-1	The primary effect is through stimulation of osteoblast formation and activity indirectly through peripheral nervous system beta-2 adrenergic receptors <sup>16</sup> and, less importantly, through direct osteoblast stimulation <sup>18</sup> .	Inhibits RANKL stimulation through peripheral nervous system beta-2 adrenergic receptors <sup>17</sup> .
CB-2	Stimulates osteoblast formation and bone formation directly as it is located in high quantities on osteoblasts <sup>22</sup> ; stimulates other osteogenic factors <sup>23</sup> .	Currently unknown due to conflicting studies <sup>7,22,26</sup> .
GPR55	No effect has been established <sup>19,24</sup> .	Inhibits osteoclast formation and activity directly <sup>7</sup> .

differentiation due to its agonist-induced blockade that affects osteocyte differentiation<sup>28</sup>. Additionally,  $\Delta^9$ -THC is a strong inducer of caspase-3, which leads to osteocyte cell death via activation of the intrinsic proapoptotic mitochondrial signaling pathway<sup>29</sup>. CBD is a GPR55 and CB-2 antagonist, with a far lower affinity for CB-1 than  $\Delta^9$ -THC. Currently, studies have not demonstrated substantial effects on bone homeostasis. Isolated CBD has been shown to increase bone-fracture mechanical properties through the enhancement of osteoblastic expression of lysyl hydroxylase 1, a collagen cross-linking enzyme, as well as stimulating MSC migration and osteogenic differentiation<sup>30</sup>. While recent preclinical data have demonstrated promising effects of CBD on bone-healing and bone metabolism, clinical studies have been insufficient and inconclusive. This is believed to be due to the enhanced production of a collagen cross-linking enzyme (PLOD1) from osteoblasts, which increases bone-bridging across the fracture defects<sup>16,31,32</sup>. Heath et al. compared time to union between cannabis users and nonusers in 339 pediatric orthopaedic fracture patients and found a significantly longer time to union in cannabis users (159 days) compared with nonusers (80 days)<sup>33</sup>.

The effects on bone quality are of rising concern in those who are  $\geq 65$  years of age and partaking increasingly in marijuana use<sup>3</sup>. Sophocleous et al. evaluated 200 adults and concluded that heavy cannabis users had lower bone mineral density and increased fracture risk compared with nonusers<sup>5</sup>. A larger study by Bourne et al. demonstrated no association

between a history of cannabis use and decreased bone mineral density<sup>6</sup>. It should be noted that there is a paucity of information of the effects of cannabinoids on osteocyte function and osteocalcin production. Additionally, the previously published articles were unable to account for all of the confounding variables (e.g., chronic medication use) and how this may have affected the study outcome variables.

Two of the other most researched endogenous endocannabinoids are anandamide and 2-arachidonoylglycerol. Anandamide has been shown to have partial efficacy as an agonist and acts similarly to  $\Delta^9$ -THC; 2-arachidonoylglycerol has been found in increased levels in patients with traumatic brain injury, a patient population known to exhibit increased bone formation<sup>34,35</sup>. Further investigation is needed into the role that these compounds play, if any, in the processes of bone homeostasis and healing in patients with traumatic brain injury.

### Wound-Healing

The endocannabinoid system is present throughout the skin and subcutaneous tissues. Its anti-inflammatory effects may assist with wound-healing<sup>36</sup>. With the commercial distribution of marijuana on the rise, public interest in these anti-inflammatory and wound-healing effects has risen. Although some degree of inflammation is believed to assist with healing due to increased vascular supply, excessive inflammation has been demonstrated to inhibit wound-healing<sup>37</sup>. In vitro trials have shown that CB-2 agonism results in decreased infiltration by neutrophils and macrophages, as well as decreased

levels of IL-1, IL-6, TNF- $\alpha$ , and transforming growth factor (TGF)- $\beta$ <sup>36</sup>. A study on topical CBD application in mice showed increased proliferation of keratinocytes and increased re-epithelialization speed<sup>36,38</sup>. One clinical study showed improvements in subjective measures, including wound appearance and symptom relief, in those using topical CBD oil. Importantly, that study involved only 20 patients, and their wounds were due to chronic conditions, including psoriasis and atopic dermatitis, and superficial scars after trauma rather than traumatic or surgical scars<sup>39</sup>.

### Total Joint Arthroplasty

Because the elderly population that is more likely to receive joint arthroplasty is increasing their cannabis use, the effects of cannabis in patients who undergo total joint arthroplasty are also under review<sup>3</sup>. Cannabis smoke has been demonstrated to decrease radiographic bone-healing around titanium implants in rat models<sup>22</sup>.

Several clinical articles have evaluated cannabis use in patients who have undergone total joint replacement. A large retrospective study that included >2.7 million total knee arthroplasty (TKA) procedures from the Medicare database compared substance use and rates of revision. A higher revision rate was found in cannabis users (12.8%) than in nonusers (9.1%), with a higher prevalence of revision due to infection<sup>8</sup>. However, the study did not account for several confounding factors, demographic information was limited, and quantity of use was not considered. Another retrospective study by Jennings

et al. evaluated patients who underwent TKA and found no differences in the rate of revision. They also found no differences in outcomes after TKA, including length of stay, 1-year range of motion, and Knee Society scores<sup>9</sup>. However, the study had a much smaller patient size and was based on self-reporting; there were only 71 cannabis users. In another retrospective cohort study evaluating patients who underwent TKA, there were higher rates of deep venous thrombosis and pulmonary embolism in cannabis users<sup>10</sup>.

### Operative Complications

Marijuana also has been noted to have effects on many other systems in the body; therefore, its use should be considered when evaluating patients prior to surgical intervention. This is especially true with the respiratory and cardiovascular systems. Noted respiratory effects of cannabis use include increased airway edema with associated bronchial endothelial damage and lung inflammation with obstruction and reduced outcomes on pulmonary function testing<sup>40</sup>. There is also a suspected decreased respiratory immune response with inhalation of cannabis products<sup>41</sup>.

Tachycardia is a well-documented effect of cannabis use due to stimulation of the adrenergic system, as demonstrated in multiple studies<sup>42</sup>. A tachycardic response has been demonstrated to be dose-dependent based on the duration and degree of ingestion of cannabis products<sup>42</sup>. There is a 5-fold increased risk of myocardial infarction within an hour of cannabis use in the general population<sup>43</sup>. Another study comparing >2.5 million individuals with acute myocardial infarction showed that the overall risk was 8% greater in cannabis users<sup>44</sup>.

The effects of cannabis use on platelet activity are inconclusive. Various *in vitro* studies have demonstrated inhibitory effects on platelet activation, while other studies have demonstrated a procoagulant effect<sup>10</sup>. As discussed previously, increased rates of deep venous thromboembolism and pulmonary embolism after total joint replacement surgeries have been noted<sup>10</sup>.

### Pain Management

Chronic pain from various orthopaedic conditions is important to acknowledge. There are a number of nonoperative measures that are used to treat these conditions and many comparisons of their efficacy have been made. Due to the large number of possible interventions, it is important to evaluate and compare their efficacy. Given the opioid crisis, there has been an increased focus on nonopioid pain interventions in recent years. Cannabis has been identified as a possible substance that can be used during treatment because its interactions with CB-1 and CB-2 are thought to have antinociceptive properties.

Thus far, results have been ambiguous regarding the effect of cannabis on pain reduction. A study on acute pain management by Salottolo et al. included individuals who were involved in motor vehicle collisions who presented to trauma centers. They compared patients who used marijuana for pain control versus those who did not and the effect of marijuana use on concomitant opioid use. They found that individuals who were previous marijuana users required increased opioid analgesic medications for pain control and had higher pain scores (4.9 versus 4.2) throughout their hospital stay<sup>45</sup>. Chronic pain management studies have also had varying results. One study surveyed individuals with chronic pain due to cancer, arthritis, and multiple sclerosis. Cannabis use was linked to increased productivity and ability to exercise, specifically in those with arthritis<sup>46</sup>. A prospective study by Haroutounian et al. showed a significant reduction in chronic pain and decreased use of opiates in cannabis users<sup>47</sup>. However, these studies noted limitations in control over their patient populations as well as adverse events such as psychiatric disturbances of paranoia, anxiety, gastrointestinal distress, and elevated liver function tests.

### Perioperative Concerns

People who use cannabis preoperatively have been shown to require higher levels of anesthetic and postoperative pain medications<sup>48</sup>. Cannabis users have reported higher levels of pain following orthopaedic

surgery and require increased levels of opioid pain medication after surgery<sup>49,50</sup>. Chronic cannabis users are at risk for developing hyperemesis as part of their withdrawal symptoms, which could be a postoperative concern for inpatients who are unable to use cannabis<sup>51</sup>. For these reasons, some have advocated standardized preoperative testing for cannabis use<sup>52,53</sup>.

### Overview

With the increasing use of cannabis products among almost all populations in the U.S., further evaluation of their effects is needed. We have identified the endocannabinoid system that is intimately related to these effects as well as many other compounds that may contribute to the effects; although substantial progress has been made to understand this system, additional studies are needed. Specifically, more research is needed to determine how the endocannabinoid system affects bone. Currently, 3 primary receptors, CB-1, CB-2, and GPR55, that have a role in bone homeostasis and fracture-healing relating to the endocannabinoid system have been identified. While the exact mechanisms for how they interact need further elucidation, agonism of these receptors appears to be protective with regard to bone homeostasis. However, this has not been shown in fracture-healing, where cannabis use appears to be detrimental. Current evidence suggests a possible advantage to cessation of marijuana use in the setting of a fracture to avoid these detrimental effects on bone-healing (including delayed bone-healing). Additional research needs to be completed with respect to the effects of cannabinoids on healing, especially in complex situations (including aseptic loosening, malunion, and nonunion), but also regarding outpatient surgical procedures such as rotator cuff surgery. Other possible effects of topical compounds on wound-healing show promise at this time, but further clinical research needs to be performed prior to recommendation.

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