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Cannabis and joints: scientific evidence for the alleviation of osteoarthritis pain by cannabinoids

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Cannabis has been used for millennia to treat a multitude of medical conditions including chronic pain. Osteoarthritis (OA) pain is one of the most common types of pain and patients often turn to medical cannabis to manage their symptoms. While the majority of these reports are anecdotal, there is a growing body of scientific evidence which supports the analgesic potential of cannabinoids to treat OA pain. OA pain manifests as a combination of inflammatory, nociceptive, and neuropathic pain, each requiring modality-specific analgesics. The body's innate endocannabinoid system (ECS) has been shown to ameliorate all of these pain subtypes. This review summarizes the components of the ECS and details the latest research pertaining to plant-based and man-made cannabinoids for the treatment of OA pain. Recent pre-clinical evidence supporting a role for the ECS to control OA pain is described as well as current clinical evidence of the efficacy of cannabinoids for treating OA pain in mixed patient populations.

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Introduction

Osteoarthritis (OA) is the most common type of musculoskeletal disease and its principal symptom is pain which may be persistent or intermittent [1,2]. The source of OA pain is obscure, but is thought to be driven by acute inflammatory flares, abnormal mechanical loading of damaged joint tissues, and in some patients, nerve damage [1–3]. Thus, OA patients present with a mix of inflammatory, nociceptive, and neuropathic pain which suggests that a blend of different analgesics may be required for effective treatment [2,3]. Commonly used pharmacotherapies for OA pain are non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, opioids, and the selective serotonin-noradrenaline reuptake inhibitor (SNRI) duloxetine [3]. As many as 60% of OA patients are unsatisfied with their current pain management reflecting the need for a better understanding of OA pain mechanisms and propitious analgesics [4]. Current treatment options are not optimal for all patients and long-term use of some drugs has the potential for serious unwanted side-effects [4,5]. For example, long-term use of NSAIDs for mild-moderate pain increases the risk of serious gastrointestinal and cardiovascular events [4,5]. Opioids which are prescribed for moderate-severe OA pain may cause nausea, constipation, and hazardous cardiorespiratory depression in vulnerable populations [5]. Duloxetine, which is effective for neuropathic-like OA pain, can cause nausea, constipation, dizziness, headaches, high blood pressure, and heart palpitations [5,6]. The development of new analgesics that are efficacious and have minimal side effects with chronic use are sorely needed for OA patients. Ongoing research is pointing towards one of the body's natural analgesic systems, the endocannabinoid system (ECS), as a viable target for new OA therapies [1,7,8••,9,10••].

The first reported use of cannabis for pain control can be dated back to 2737 B.C. when it was utilized in traditional Chinese medicine. In 1850, cannabis was first listed in the United States pharmacopeia and by 1935 there were 28 different cannabis-containing compounds available to be used as analgesics [11,12•,13]. This boom in medical cannabis use and research came to a screeching halt in 1937 when self-appointed commissioner of the Federal Bureau of Narcotics, Harry J. Anslinger, introduced the Cannabis Tax Act which made it too expensive to prescribe and investigate cannabis in the US. In 1941, cannabis was removed from the formulary and later scheduled as a controlled substance in the United States and Canada [12•]. The identification of the ECS in the 1990s and changing legal and social views have reinvigorated research into the potential analgesic benefit of cannabis and its naturally occurring constituents (phytocannabinoids), man-made synthetocannabinoids, and the body's endogenous endocannabinoids [11,12•]. This review focuses on the current evidence for use of medical cannabis, cannabinoids and modulators of the ECS for the alleviation of OA pain.

Cannabinoid receptors and the endocannabinoid system

The ECS is an endogenous signalling system consisting of receptors, constitutive ligands and their signal-

terminating enzymes. The most widely investigated receptors are the G protein-coupled cannabinoid receptors 1 and 2 (CB1 and CB2) [14]. CB1 is expressed widely in the 'pain pathway' on peripheral neurons as well as in the spinal cord and pain processing centres in the brain [11,14,15]. CB2 is also expressed in the central and peripheral nervous systems (CNS and PNS) and found largely, but not exclusively, on immune cells including macrophages, mast cells, and glial cells where it regulates inflammatory responses [11,14]. The endocannabinoids anandamide (AEA) and 2-arachidonoylglycerol (2-AG) act as endogenous ligands for CB1 and CB2 receptors [12•,14]. AEA has been implicated as a regulator of nociceptive transmission via partial activation of CB1 and CB2 receptors as well as acting as an agonist at transient receptor potential vanilloid 1 (TRPV1) ion channels expressed on primary afferent nociceptors [7,14]. Alternatively, 2-AG is a full agonist at both CB1 and CB2 receptors and is synthesized in high amounts in the CNS [14]. The signalling capacity of AEA and 2-AG is limited due to their rapid hydrolysis by the endogenous enzymes fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL) [8••,12•,14]. Figure 1 depicts the elements of the joint ECS and the loci within the pain pathway where cannabinoids can exert their analgesic effects.

Phytocannabiniods and synthetocannabiniods

Plant-based and man-made cannabinoids can be used to mimic the actions of the body's endocannabinoids. The cannabis plant currently has 537 known constituents, 107 of which are cannabinoids [12•]. The two most studied phytocannabinoids are Δ-^{9} tetrahydrocannabinol (THC) and cannabidiol (CBD). THC is a major component of cannabis and is used clinically to treat pain, nausea, and anorexia [11,12•]. It also has psychoactive properties which can cause euphoria, relaxation and heightened sensory perception [12•]. Synthetic THC and its analogues have been developed and are prescribed for a variety of indications. Dronabinol and nabilone are synthetic forms of THC which are used to treat chemotherapy-induced vomiting and anorexia associated with HIV/AIDS. Nabiximols are a combination of THC and CBD in a 1:1 ratio. These sublingual sprays have been approved for use in multiple sclerosis-induced neuropathic pain and advanced cancer pain.

Pre-clinical research on the endocannabinoid system and OA pain

Pre-clinical studies have revealed that the ECS plays an integral role in OA pathogenesis, joint neuropathy and pain control. In rodents, CB1 and CB2 receptors have been localised in synovial tissue where they are expressed on nerve terminals [13,15]. Local administration of cannabinomimetics has been found to cause synovial hyperaemia via activation of CB receptors and TRPV1 ion channels [16,17]. In the monosodium iodoacetate (MIA) model of OA, an activated ECS is present in the joints of rats where it has been found to regulate joint pain and inflammation [7,10••,15].

Modulating CB1, CB2, or FAAH enzymes has been found to be anti-nociceptive in animals [7,8••,10••,18]. Arachidonyl-2-chloroethylamide (ACEA), a synthetic CB1 receptor agonist, decreased firing of joint nociceptors by 62% in the MIA model [7]. Similarly, the CB2 receptor agonist A-796260 decreased pain behaviour in the same model [18]. Targeting the CB2 receptor with GW405833 surprisingly had pro-nociceptive effects, where local administration increased joint nociceptive firing in OA animals but not control animals [15]. These paradoxical findings were attributed to opening of ligand-gated TRPV1 ion channels within the joint [15]. The FAAH inhibitor URB597 has been found to produce an analgesic and anti-inflammatory effect when given acutely during the early phases of OA development [8••]. This prophylactic treatment with URB597 also prevented the end-stage development of nerve damage and neuropathic pain in these OA mice [8••]. Recently, a similar anti-nociceptive and neuroprotective effect has been discovered with the use of the phytocannabinoid CBD. When administered locally in end-stage OA, CBD dose-dependently decreased the firing of joint nociceptors and attenuated pain behaviour and joint inflammation [10••]. Prophylactic use of CBD, which blocked the acute inflammatory flare associated with the MIA model, prevented the subsequent development of chronic joint pain and nerve damage [10••]. These pre-clinical studies provide a strong scientific basis for the clinical evaluation of the ECS in OA patients.

Clinical research on cannabinoids and OA pain

The presence and function of the ECS has been studied in OA patients in which synovial tissues were found to express both CB1 and CB2 receptors, and synovial fluid contained both AEA and 2-AG. Notably, both AEA and 2-AG were absent in synovial fluid extracted from healthy volunteers [9]. There are few published clinical studies evaluating ECS modulators in arthritis patients which is probably due to a lack of understanding by clinicians of cannabinoid-based treatments [19]. In 2012, the results of a randomized clinical trial of a potent FAAH inhibitor, PF-04457845, in OA patients indicated no significant difference compared to placebo [20]. PF-04457845 was found to increase AEA in these subjects, but in contrast to animal studies, this did not produce an analgesic effect [20]. The reasons for this lack of analgesia may be related to possible off-target effects of PF-04457845 such as TRPV1 activation or the formation of cyclooxygenase-2-dependent prostanoids [21]. Currently, there are a handful of ongoing trials in which the analgesic effects of cannabinoids are being explored. The 'Cannabinoid