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SPECIAL EDITORIAL REVIEW

Endocannabinoids in arthritis: current views and perspective

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Abstract

Preclinical and clinical studies using cannabis-based therapy have been shown to provide both analgesia and anti-inflammatory effects, with an overall alleviation of clinical symptoms in animal models of arthritis, highlighting its promising therapeutic application for humans. Despite this, the development of cannabis-based therapeutics remains in its infancy, with further investigation into its efficacy and safety profile in patients still required. This synopsis reviews the various components of the endocannabinoid system in health and disease and their potential as therapeutic targets.

Key words: arthritis, endocannabinoid, inflammation, pain, rheumatic disorders.

INTRODUCTION

Whether smoked, ingested, inhaled or injected, the anxiety-relieving and mood-altering effects of the plant *Cannabis Sativa*, colloquially known as cannabis or marijuana, have been known for over 5000 years.[1,2] The main active ingredients in cannabis have the ability to alter sensory perception, enhance appetite stimulation, induce sedation, evoke elation and euphoria, as well as impair central nervous system (CNS) function related to memory and motor control. In the nineteenth and early twentieth centuries, cannabis derivatives were recommended as muscle relaxants, analgesics and anticonvulsants. However, in the 1940s with increasing global concerns about narcotic addiction, popularity of cannabis and its related drugs as therapeutic agents declined, resulting in the prohibition and further prejudice of these drugs for medical use.[1,3] Recently, there has been a resurgence of interest in cannabis and its natural and synthetic derivatives, the reciprocal endogenous cannabinoid receptor agonists and antagonists, as well as chemically related compounds, for their therapeutic potential. Conditions such as pain, anorexia, emesis, inflammation, epilepsy, multiple sclerosis, neurodegenerative disorders, glaucoma, osteoporosis, schizophrenia, cardiovascular disorders, cancer, obesity and other metabolic syndrome-related disorders, to name just a few, have been the focus of study and exploitation of cannabis-related medicines.[4–6]

The term endocannabinoid appeared in the literature during the mid-1990s following the discovery of the endogenous receptor for the psychoactive constituent, delta 9-tetrahydrocannabinol (Δ^9-THC), a main constituent of marijuana.[7] The identification of Δ^9-THC opened the way to the cloning of the G-protein-coupled receptors, the cannabinoid receptor 1 (CB1) and cannabinoid receptor 2 (CB2), and to the discovery of the important endogenous lipid signalling pathways collectively known as the 'endocannabinoid system'. Endocannabinoid ligands, their receptors, and the enzymes involved in ligand biosynthesis and degradation, constitute the three fundamental components of the endocannabinoid system.[8] The ubiquitous endocannabinoid lipid signalling system has been noted to be relevant in many physiological functions in the body, including the central, peripheral and autonomic nervous systems, endocrine networks and the immune

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system. The investigation and application of endocannabinoids may therefore provide therapeutic potential for a wide range of human pathological conditions, including obesity, CNS diseases, as well as both neuropathic and chronic pain[9,10] as may be found with back pain, fibromyalgia, rheumatoid arthritis (RA) and osteoarthritis (OA).[11,12] This literature review outlines the biochemistry and physiology of the endocannabinoid system and examines the therapeutic potential in the treatment of inflammation and pain associated with arthritis.[10]

ENDOCANNABINOIDS

The endocannabinoid system is regulated by a series of endogenous lipid signalling molecules known as endocannabinoids.[2] To date, six different types of endogenous ligands have been identified within the endocannabinoid system.[8] The three main endogenous ligands (shown in Fig. 1) include anandamide, 2-arachidonoylglycerol (2-AG), and noladin ether.[13–15]

1Anandamide is one of the most widely investigated endocannabinoid ligands and was first isolated from porcine brain. Its structure was described in 1992.[16] Despite exhibiting a similar pharmacological activity to cannabis' main psychoactive constituent Δ9-THC, anandamide's chemical structure is different.[17] Anandamide predominantly binds to the CNS CB1 receptors and has a low affinity binding to peripheral CB2 receptors, acting as a partial agonist.[9] At elevated concentrations, anandamide functions as a full agonist for the transient receptor potential vanilloid (TRPV1), an ion channel responsible for the integration and perception of pain.[18]

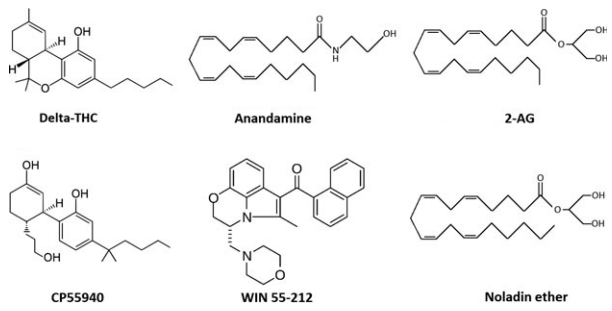

Figure 1 Chemical representation of delta 9-tetrahydrocannabinol (Δ9-THC) and the predominant endocannabinoids anandamide, 2-arachidonoylglycerol (2-AG) and noladin ether reproduced from Ueda.[13] Also shown are structures of two cannabinoid receptor agonists, CP55940 and WIN55212, reproduced from Pertwee.[14]

22-Arachidonoylglycerol (2-AG) 2-AG was first isolated and characterised in 1995 from canine gut and shown to have similar affinity and activity for both the CB1 and CB2 receptors.[19] 2-AG is present in significantly higher concentrations in the CNS when compared to anandamide.

3Noladin ether (2-AG ether) a third endocannabinoid was discovered from porcine brain in 2001.[20] It primarily binds to the CB1 cannabinoid receptor and is responsible for inducing sedation, hypothermia, intestinal immobility and mild anti-nociception in mice.[8]

4Other cannabinoids: a series of other pharmacologically similar cannabinoids N-arachidonoyl dopamine (NADA); O-arachidonoyl-ethanolamine (virodhamine); lysophosphatidylinositol (LPI) and oleoylethanolamide (OEA) have since been isolated or synthesized. NADA was discovered in 2000 and predominantly binds to CB1 receptors with an additional activity to TRPV1.[21,22] NADA is concentrated in the striatum and hippocampus.[2] LPI was recently identified as a potent endocannabinoid ligand for the novel endocannabinoid receptor G protein coupled receptor 55 (GPR55).[23] OEA first discovered in 2002, is known to be a dominant agonist of CB2 receptors, and a partial agonist/antagonist for CB1.[24] OEA and another anandamide analogue palmitoylethanolamide exist at relatively high concentrations in healthy tissues. In inflamed fluid of RA and OA patients the levels of these products are significantly reduced, implying a role during chronic inflammation.[11]

BIOSYNTHESIS, INACTIVATION AND BIO-DEGRADATION OF ENDOCANNABINOIDS

Endocannabinoid biosynthesis

While the predominant endocannabinoids anandamide and 2-AG, are both lipid molecules generated from the breakdown of arachidonic acid,[25] they share very few similarities in their biosynthetic pathways,[26] as shown in Figure 2. Endocannabinoid synthesis is a result of enzymatic cleavage of membrane-bound lipid precursors present in the phospholipid bilayer.[14] Once released, the endocannabinoid ligands diffuse, acting locally as retrograde messengers to regulate the release of multiple presynaptic messengers.[26] Following cellular uptake, the endocannabinoid ligands are quickly transported from the synaptic space and inactivated through subsequent catabolism via specific enzymes within the intracellular environment.[27]

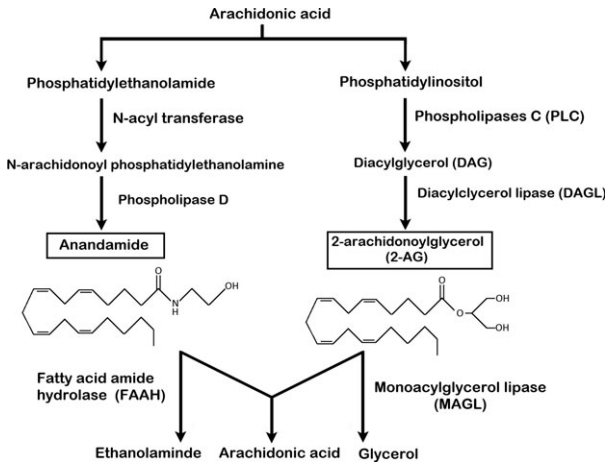

Figure 2 Main pathways for the biosynthesis and degradation of the two main endocannabinoids, anandamide and 2-arachidonoylglycerol (2-AG), reproduced from Castillo.[26]

Degradation of endocannabinoids

As with all other endogenous mediators produced during a physiological or pathological response, endocannabinoids require an efficient mechanism for their biodegradation and rapid removal from their target site.[25] For the termination of the endocannabinoid signalling, the endocannabinoids are first subject to removal from the synaptic cleft via facilitated transport mechanism and then subsequent catabolism via specific enzymes within the intracellular environment.[11] These intracellular enzymes are unique to each endocannabinoid and include fatty acid amide hydrolase (FAAH), the principal enzyme of endocannabinoid hydrolysis for anandamide and monoacyl glycerol lipase (MAGL) for 2-AG shown in Figure 2.

CANNABINOID RECEPTORS

There are two predominant endocannabinoid receptors, CB1 and CB2.[15] Both the CB1 and CB2 receptors are G proteins coupled to seven trans-membrane domain receptors which are negatively coupled with adenylate cyclase via G proteins, and positively coupled to mitogen-activated protein kinase. Due to this, the endocannabinoid receptors are able to regulate suppression of adenylate cyclase as well as the activities of the calcium and potassium channels resulting in the suppression of neurotransmitter release at the neural synapse.[16,28] While both are G-protein coupled receptors, amino acid sequencing reveals the two receptors share little sequence homology, with only 44% identity shared at the protein level and 68% in the transmembrane domains which are thought to contain the binding sites for endocannabinoids.[29] The unique distinction between CB1 and CB2 receptors are due to splice variants in their primary structural homology, differences in their signal transduction mechanisms, pharmacological characteristic distribution in biological tissue, and selective sensitivity to certain potent agonists and antagonists displaying a marked affinity for either the CB1 or CB2 receptor.[30,31]

CB1

The CB1 receptors were first discovered in 1990[7] and are abundantly expressed in the mammalian nervous system.[32] CB1 receptors are densely expressed in several areas of the brain and supra-spinal regions involved with nociceptive transmission. While CB1 receptors can be located on postsynaptic neurons, the majority are located on presynaptic neurons in anticipation of retrograde signalling,[33] shown diagrammatically in Figure 3. In retrograde signalling, a neurotransmitter is released from the postsynaptic neuron to be detected by a receptor on the presynaptic neuron. The presence of CB1 on presynaptic neurons allows for the regulation and inhibition of neurotransmitter release. This allows for a negative feedback mechanism to develop between the anterograde and retrograde signalling pathways mediated by the endocannabinoid system. CB1-mediated suppression of neurotransmitter release in nerve terminals has been associated with the characteristic effects of cannabis, including analgesia, feeling of wellbeing, catalepsy and depression of motor activity.[14]

CB2

The CB2 receptor was identified in 1993.[29] Unlike CB1, the CB2 receptor is almost exclusively expressed outside the CNS, and predominately found in peripheral immune and hematopoietic cells.[15,30] CB2 receptors mediate cannabinoid-induced immunosuppression and anti-inflammatory effects by modulating cytokine release and immune cell migration.[14] Due to its wide expression on the peripheral immune cells, CB2 receptors represent a potential target in inflammatory pain processing. Direct evidence of CB2 medicated anti-nociceptive effects was first reported in 1999 using the selective CB2 agonist, HU-308, which produced a marked decrease in pain behavior in rats receiving hindpaw injections of dilute formalin.[34] CB2 receptor agonists contribute to antinociception in models of both inflammatory and nociceptive pain by inhibiting the release of pro-inflammatory factors by non-neural cells which

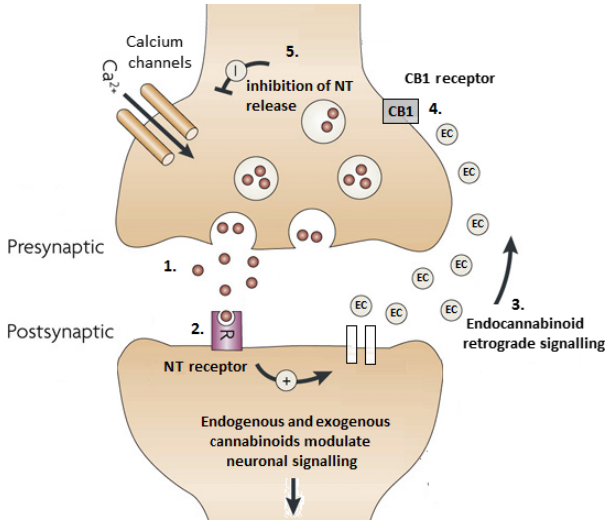

Figure 3 Overview of the endocannabinoid-mediated synaptic signalling. (1) Action potential generated causes cytoplasmic vesicles to fuse with presynaptic membrane and release NTs. (2) Binding of neurotransmitter on post-synaptic membrane receptors causes Ca^{2+} accumulation, depolarization of the membrane and activation of calcium-dependent enzymes responsible for the biosynthesis of endocannabinoids. (3) Endocannabinoid retrograde transport. (4) Cannabinoid receptor 1 (CB1) receptor activation and the activating of target signaling pathways reduce neurotransmitter release. Reproduced from Honoré.[33] NT, neurotransmitter; EC, endocannabinoid ligands [Colour figure can be viewed at wileyonlinelibrary.com]

sensitize neighboring nociceptive neuron terminals.[35] Activation of peripheral CB2 receptors therefore generates an antinociceptive response in situations of inflammatory hyperalgesia and neuropathic pain by acting locally on peripheral immune cells in the periphery and microglia in the CNS.[36,37] Although originally described as being restricted to immune cells, evidence for CB2 expression in primary sensory neurons and in nerve fibers in human synovium and digit skin has been reported.[38]

TRPV1

TRPV1s are ionotropic cannabinoid receptors responsible for the integration of noxious stimuli.[39] While primarily expressed on sensory Aδ and C-fibers, TRPV1s are also located on peripheral cells and sensory neurones abundantly expressed in arthritis synovial tissue. This receptor is a calcium permeable non-selective, ligand gated, cation channel belonging to the transient receptor vanilloid family, which is sensitive to capsaicin and related analogues. The TRPV1s are thought to be involved in 'cross talk'[40] between the endocannabinoid system and endovanilloid system by existence of endogenous cannabinoids, anandamide, virodhamine and LPI,[18] responsible for the activation of both endovanilloid receptors and CB1/CB2 receptors under several pathological and physiological conditions.[32]

THERAPEUTIC POTENTIAL OF ENDOCANNABINOIDS IN ARTHRITIS

The discovery of the endocannabinoid-mediated retrograde synaptic signalling pathway has opened up a new era for cannabinoid research and evaluation for their therapeutic use. A sizeable number of clinical and preclinical studies have confirmed the potential of the cannabinoid system in providing a number of promising therapeutic benefits for patients with chronic inflammatory disease.[41–44] Furthermore, increasing evidence demonstrates an active participation of the endocannabinoid system in the pathophysiology of joint pain associated with OA.[11,44]

Endocannabinoids and joint inflammation

Inflammatory joint disease results in the generation of pro-inflammatory cytokines (interferon [IFN]-γ, interleukin [IL]-12, IL-15, IL-17, IL-18), chemokines, chemical mediators such as nitric oxide synthetase (NOS)-2, cyclooxygenase-2 (COX-2), matrix metalloproteinases (MMPs) and various other metabolic by-products of arachidonic acid leading to the production and release of endocannabinoids.[45,46] Overall, the preclinical and clinical data support the potentially effective anti-inflammatory properties of endocannabinoids and agonists targeting CB2 receptors.[47–50] The absence of psychotropic effects and low toxicity, favor the development of endocannabinoids as novel anti-inflammatory agents for the treatment of RA and OA.[47–50] Pre-clinical studies[47–50] examining endocannabinoid anti-inflammatory effects on arthritis are summarized in Table 1.

It has been well documented that anandamide and 2-AG endocannabinoid levels are stimulated under inflammatory conditions.[45] In a more recent study, Lowin *et al.*[51] showed that cannabinoid receptors, CB1 and CB2, and endocannabinoids, anandamide and 2-AG produced by fibroblast-like synoviocytes (FLS), are present in higher concentrations in synovium of patients with RA and OA disease compared to normal volunteers, suggesting a functional role of the endocannabinoid receptor system in the pathological effects noted in arthritic patients.

Zurier *et al.*[52] demonstrated that a synthetic cannabinoid 1′1′-dimethylheptyl-THC-11 oic acid (ajulamic

Table 1 Pre-clinical studies examining cannabinoid anti-inflammatory effects on arthritis.

Drug	Preclinical model/cell line	Outcome of mechanism	Reference
Cannabidiol	Murine collagen-induced arthritis in mice	Decreased production of cell-mediated immunity IFN-γ, TNF-α and reduced arthritis	47
Ajulamic acid	PBMC and synovial fluid monocytes (*in vitro*)	Decreased production of IL-1β	48
	Adjuvant-induced arthritis in rats (*in vivo*)	Decreased joint inflammation, prostaglandin production and decreased granulocyte influx	17
HU-320	CIA in mice	Decreased production of TNF-α and cell mediated immunity. Decreased arthritis	49
WIN55212–2; CP55940	Rheumatoid FLS cells	Significant reduction of IL-6 and IL-8 secretion from FLS. Reduced cartilage degradation.	49,50

IFN, interferon; TNF, tumor necrosis factor; PBMC, peripheral blood mononuclear cells; IL, interleukin; CIA, collagen–induced arthritis; HU-320, Hebrew University-320; FLS, fibroblast-like synoviocytes.

acid, AjA), a nonpsychoactive anti-inflammatory agent with an endocannabinoid template structure, was a potent anti-inflammatory in animal models of joint tissue injury and that *in vitro* it was able to suppress both COX-2, and 5 lipoxygenase activity of cells in tissue cultures.[53] AjA has a pharmacological profile similar to that of non-steroidal anti-inflammatory drugs (NSAIDs). Oral administration of low-dose AjA suppressed joint inflammation and tissue injury in adjuvant-induced arthritis.[53] Rats treated with AjA demonstrated mild synovitis in the tibiotarsal joints at the end of the treatment when compared to the control group, which exhibited moderate to severe changes. This activity was presumed to be initiated through peripheral CB1 receptor activation.[17] However, since AjA has weak CB1 and CB2 receptor activity, the anti-inflammatory effects may be partly owing to the activation of other receptors belonging to the TRPV family. George *et al.*[54] demonstrated that AjA can suppress the release of cytokine IL-1β from peripheral blood and synovial fluid monocytes and prevent bone degradation of rats with AjA by inhibition of osteoclastogenesis, osteoclast formation (in mononuclear precursor cells) and apoptosis in mature osteoclast-like cells.

Similarly, Sumariwalla *et al.*[49] demonstrated that systemic administration of Hebrew University-320 (HU-320), a putative endocannabinoid metabolite, had significant therapeutic potency in ameliorating disease progression in a collagen-induced arthritis mouse model. These effects were attributed to the suppression of cellular immune responses, resulting in decreased production and release of tumor necrosis factor (TNF)-α, reactive oxygen intermediates and IFN-γ from synovial cells isolated from the arthritic knee joints of affected mice. Protection of the joints against severe damage was also noted as a clinical improvement in treated animals, demonstrating the immunosuppressive and anti-inflammatory properties of HU-320 in the absence of adverse psychotropic effects.

Together, these data suggest that endocannabinoids have anti-arthritic properties due in part to the preservation of cartilage matrix integrity through their ability to inhibit NO production and metalloproteinase activation, inhibition of the release of reactive oxygen species immunosuppression, especially of the Th1 immune response, and an anti-inflammatory action by way of reducing TNF-α and other cytokines in the synovium. These features thereby provide hope of useful application in the therapeutic management of arthritic disorders.[55]

Endocannabinoids in inflammatory joint pain

Increasing evidence from both pre-clinical and clinical studies support the therapeutic application of cannabinoids in the treatment of chronic pain. Preclinical studies have evaluated the therapeutic potential of cannabinoids in models of both RA and OA and to date, patients with chronic arthritic and musculoskeletal pain represent the most prevalent users of medicinal cannabis.[44]

Nociceptive arthritic pain is primarily derived from localized inflammation.[11] The presence of elevated anandamide, 2-AG and their synthetic precursor concentrations in synovial fluid of RA and OA patients indicates the potential for endocannabinoids to act locally in response to noxious stimuli to suppress nociceptive inflammatory responses.[11] Administration of cannabinoid agonists, WIN55212 and CP55940, is shown to reduce inflammatory IL-6 and IL-8 production by FLS cells, ameliorating acute inflammation and associated pain in arthritic joints.[56] These anti-inflammatory effects are limited by the rapid cellular uptake

and degradation of endocannabinoid metabolites[35] but can be overcome through the inhibition of the catabolic enzyme FAAH allowing longer physiological effects.[57] *In-vivo* studies by Krustev *et al.*[58] reported that FAAH inhibition by URB597 can elevate tissue concentration of anandamide by inhibiting local endocannabinoid degradation and dampen inflammatory pain in rodent models of OA. Similarly, URB597 suppressed inflammatory hyperaemia, as well as microvascular leukocyte rolling and adherence in a mouse model of acute arthritis,[59] highlighting the anti-inflammatory and analgesic capacity of endocannabinoids, and the modulation of the efficacy through metabolism inhibition.

Electrophysiological studies in models of spontaneous and chemically induced arthritis have demonstrated that the facilitated nociceptive responses of peripheral nerves are attenuated in the presence of cannabinoid receptor agonists.[60] Exogenously administered anandamide and CB1 agonist arachidonyl-2-chloroethylamide (ACEA) have been shown to significantly reduce the firing rate of afferent nerve fibers. This effect is attenuated by the administration of the CB1 antagonist AM251. Similarly, the selective CB2 agonist, JWH-133, inhibited acute nociceptive responses in neuropathic rats, while systemic administration of another CB2 receptor agonist, A-796260, reversed decreases in grip strength, a surrogate measure of pain, in the monosodium iodoacetate (MIA) models of RA pain.[61] From this, it is suggested that both CB1 and CB2 receptors exhibit synergistic action in cannabinoid-mediated anti-nociception in RA rat knee joint.[60] The peripheral localization of CB1 on joint primary afferents and CB2 in the synovium have the potential as a promising target for arthritic pain by reducing joint nociceptor propensity to emit action potentials.

In clinical use, endocannabinoids and synthetic cannabinoids have been shown to exert synergistic antinociceptive effects when combined with two common NSAIDs; indomethacin and flurbiprofen, in the pharmacotherapy of pain.[38,62] More recently, the analgesic activity of commonly used paracetamol was prevented by the blockade of cannabinoid CB1 receptors in rats,[63] while *in vitro* data have suggested the action of some general anaesthetic drugs, such as propofol,[64] involve interplay with the endocannabinoid system.

Current work and future direction

While evidence suggests the therapeutic potential of cannabis-based medicines in the treatment of arthritis and chronic musculoskeletal pain syndromes, barriers to research including insufficient legally registered marijuana manufacturers and limited clinical trials have restricted its progress into the therapeutic field. Authors of three recent reviews concluded that current evidence is insufficient to allow for recommendation for any cannabinoid preparation for use by rheumatology patients.[65–67] Concerns regarding the endocannabinoid-based adverse effects such as reduced reaction time, impaired motor control, difficulty with attention, tachycardia, hypotension, acute anxiety and agitation, although not severe, were common and 'sufficiently troubling to impact on wellbeing'.[65] Other more severe adverse effects such as acute psychosis were noted in some patients.[65]

In the study by Blake *et al.*[68] the effect of nabiximols (phytocannabinoids extracted from cannabis and supplied as an oromucosal spray) was compared to placebo in a double-blind randomized trial of 58 patients with RA. Over a 5-week period, improvements in pain, sleep quality and Disease Activity Score in 28 joints were observed. Although adverse events in the active treatment group were not serious, they were common, with dizziness in 26%, dry mouth in 13%, light-headedness in 11%, and nausea and falls in 6%, and less frequent reports of constipation, arthritis pain and headache.[68] Similarly, in studies examining the endocannabinoid-based drug, nabilone, on pain outcomes in fibromyalgia, the statistically significant effects were outweighed when side effects were taken into consideration.[69]

PF-04457845, a potent and selective inhibitor of FAAH, showed both analgesic and anti-inflammatory effects in animal studies comparable to naproxen.[70] However, when compared to naproxen as an active comparator of OA pain in humans, no difference between the FAAH-1 and placebo was noted.[70] In favor of the study, the FAAH-1 demonstrated a well-tolerated safety profile.

While benefits of pharmaceutically prepared cannabinoid treatments vary across animal species and population groups, they appear to have clinical benefits warranting the need for further investigation. Our increased understanding of the endocannabinoid system and novel scientific research into the therapeutic use of endocannabinoids in the treatment of disease remains a promising avenue of contemporary importance.

CONCLUSION

The physician should have an open mind to the use of endocannabinoids in musculoskeletal conditions and

the advice given to a patient requesting information for the off-label use of cannabis, based on existing evidence, and latest information on benefits and side-effect risks, rather than anecdotal evidence or personal bias. There are various guidelines published in different countries that may be helpful.[71–73] In Australia, the Australian Government passed legislation allowing the prescription of non-smokable, medical grade cannabis products for painful and chronic conditions.[74] In response, the Australian Rheumatology Association has issued a position statement on the use of medical cannabis for musculoskeletal pain stating 'there should be evidence for efficacy and safety from high-quality randomised controlled trials (RCTs) before any potential intervention for chronic musculoskeletal pain (or other musculoskeletal diseases or symptoms) is adopted into clinical practice'.[75]

Despite the cautionary tone, advancements in our understanding of the endocannabinoid system and cannabinoid pharmacology have highlighted the potential of new pharmacological entities. While current cannabinoid therapy has offered particular promise in the treatment of certain inflammatory conditions including multiple sclerosis[41] and as well as chronic pain models, research in the use of cannabinoids for rheumatic diseases is limited and the evaluation of medicinal cannabis in humans remains in its infancy.[44,65–68] Further investigation on the function of the endocannabinoid system and its role in rheumatic disease is required to provide a solid foundation and allow the evolution and refinement of cannabis-based medicine. Comprehensive evaluations through well-controlled randomized trials are also required to clarify the true clinical efficacy and long-term risks associated with cannabinoid therapy. Despite being in early stages, the endocannabinoid system holds promise as a novel drug class for rheumatic disease treatment.

COMPETING INTERESTS

There are no competing interests or conflicts of interest.

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