Cannabinoids for the treatment of rheumatic diseases — where do we stand?

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Abstract | As medical use of cannabis is increasingly legalized worldwide, a better understanding of the medical and hazardous effects of this drug is imperative. The pain associated with rheumatic diseases is considered a prevalent indication for medicinal cannabis in various countries. Thus far, preliminary clinical trials have explored the effects of cannabis on rheumatoid arthritis, osteoarthritis and fibromyalgia; preliminary evidence has also found an association between the cannabinoid system and other rheumatic conditions, including systemic sclerosis and juvenile idiopathic arthritis. The potential medicinal effects of cannabis could be attributable to its influence on the immune system, as it exerts an immunomodulatory effect on various immune cells, including T cells, B cells and macrophages. However, the available evidence is not yet sufficient to support the recommendation of cannabinoid treatment for rheumatic diseases.

The tale of Cannabis sativa begins in ancient times, with its cultivation and utilization in everyday life possibly tracing back to 10,000 BC; the first evidence of the medicinal use of cannabis, as an analgesic, dates back to 4,000 BC. Testimonies of cannabis as a remedy for arthritic pain span histories and cultures, from the Chinese emperor Shen Nung, circa 2,700 BC, to the Assyrians in the 9th century BC; in modern medicine, cannabis was mentioned in 1924 in Sajous’s Analytic Cyclopedia of Practical Medicine. However, perceptions of cannabis have since changed, as indicated by an international treaty in 1925 to control the opium and cannabis trade.

Over the past decade, cannabis has re-emerged as a potential medicinal therapy, and its use in this context is increasingly becoming legalized throughout the world. Many of the current medical applications of cannabinoids include rheumatic diseases such as rheumatoid arthritis (RA) and fibromyalgia, prompting the need to evaluate the current evidence for therapeutic use in these conditions and prospective applications.

In this Review, we examine the potential of cannabinoids as a therapeutic option for rheumatic diseases. Whether cannabinoids could be used as medications requires consideration of their mechanisms of action and potential adverse effects as well as a basic understanding of the effects of cannabinoids on the immune system. The question of whether cannabinoids have a place in the treatment of rheumatic diseases also necessitates exploration of the current knowledge of cannabinoids and specific rheumatic diseases.

The endocannabinoid system

The endocannabinoid signalling system comprises cannabinoid receptors, endocannabinoids (the endogenous ligands of cannabinoid receptors) and enzymes that regulate the biosynthesis and inactivation of endocannabinoids. For more than two decades after the isolation of (∆9)-trans-Δ4-tetrahydrocannabinol (THC, the primary psychoactive constituent of cannabis) in the 1960s, the endocannabinoid system remained obscure. A pivotal development was the identification of cannabinoid receptor 1 (CB1) in 1988 [REF.], which was followed by the discovery of the first two endocannabinoids in the 1990s. These two compounds, anandamide (also known as arachidonoyl ethanolamide (AEA)) and 2-arachidonoyl glycerol (2-AG), are currently the most researched endocannabinoids. Other compounds and receptors thought to be part of the endocannabinoid system have since been recognized, such as N-oleylethanolamine and N-palmitoylethanolamine. The enzymes responsible for the biosynthesis and degradation of AEA and 2-AG are important components of the endocannabinoid system. AEA is predominantly synthesized by a process involving N-acyltransferase and N-acyl-phosphatidylethanolamine-hydrolysing phospholipase D, whereas the synthesis of 2-AG relies on diacylglycerol lipase. Both AEA and 2-AG can be degraded by either oxygenation or hydrolysis. Hydrolysis is accomplished via two distinct routes: AEA is degraded by fatty-acid amide hydrolase (FAAH) and 2-AG is degraded by monoacylglycerol lipase.

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Cannabinoids can affect the proliferation, apoptosis and cytokine production of immune cells, acting as possible immune modulators.

Preclinical data suggest that cannabinoids possess therapeutic potential in the following rheumatic diseases: rheumatoid arthritis, osteoarthritis, systemic sclerosis and fibromyalgia.

Clinical data regarding cannabinoid treatment for rheumatic diseases are scarce; therefore, recommendations concerning cannabinoid treatment cannot be made.

Cannabinoid treatment should not be taken lightly; special consideration and advise are required regarding adverse effects and drug interactions.

Cannabinoid receptor 1
CB1 is a G protein-coupled receptor that is known to mediate the psychotropic effects of cannabis. The psychotropic properties of CB1 can be ascribed to the wide distribution of this receptor in the brain, in which it is present at high concentrations in the frontal cortex, basal ganglia and cerebellum and is predominantly expressed on axons and presynaptic terminals. By contrast, expression of CB1 in the brainstem is relatively low, which possibly accounts for the low toxicity of cannabis.

CB1 is also expressed in a variety of other tissues and organs, including the spinal cord, thyroid gland, adrenal gland, liver, adipose tissue, gastrointestinal tract and reproductive organs, as well as in immune cells. The pattern of CB1 expression is of particular interest in the context of rheumatic diseases as CB1 receptors are found on chondrocytes and osteocytes derived from human joints. Furthermore, evidence suggests that CB1 facilitates the adhesion of fibroblast-like synoviocytes (FLSs) to fibronectin, thus reducing the migratory capacity of these cells and possibly decreasing cartilage destruction.

With regard to the psychoactive properties of CB1, the effects of this receptor on the brain are predominantly facilitated by retrograde signalling (also called retrograde neurotransmission). Signalling is induced by the depolarization of the postsynaptic cell, resulting in the postsynaptic production and release of endocannabinoids, which in turn activate presynaptic CB1 receptors. Overall, CB1 activation exerts an inhibitory effect on the presynaptic cell

Deconstructing CB1 signalling reveals various pathways at the molecular level. Acting via G-protein-coupled proteins, CB1 activation promotes an inhibitory effect on adenylate cyclase, causing a reduction in cellular cAMP levels and, subsequently, a decrease in protein kinase A (PKA) activity. This loss of the inhibitory activity of PKA increases the activity of A-type potassium channels and leads to an overall decrease in cellular potassium levels.

An additional route of CB1 signalling operates via the G protein-coupled receptor subunit βy, by which route mitogen-activated protein kinase and phosphoinositide-3-kinase are activated. Activation of CB1 also induces contrasting effects on various cellular ion channels as it stimulates inward-rectifying potassium channels and inhibits voltage-dependent calcium channels.

Cannabinoid receptor 2
CB2 is also a G protein-coupled receptor and has 44% amino acid similarity with CB1. CB2 functions in a similar manner to CB1 in that it inhibits adenylate cyclase and activates MAPK. Additionally, CB2 activation can cause a transient increase in intracellular calcium levels via phospholipase C.

CB2, which has also been referred to as the peripheral cannabinoid receptor, is primarily known for its expression on immune cells, although evidence shows that CB2 is also expressed on various other cell types, including chondrocytes, osteocytes, fibroblasts, FLSs and dorsal root ganglia. In addition to dorsal root ganglia, CB2 is expressed on microglial cells, yet the extent to which CB2 is expressed in the human nervous system remains controversial. In rodents, evidence of CB2 mRNA was found in the cerebellum, cortex, brainstem, spinal cord and glial cells.

Of note, the Q63R variant of CB2 is associated with several autoimmune diseases such as coeliac disease, immune thrombocytopenic purpura and — of particular interest in the rheumatology field — juvenile idiopathic arthritis.

Other cannabinoid receptors
Although there is a strong consensus that CB1 and CB2 are the two main cannabinoid receptors, the identity of other receptors of the endocannabinoid system is still debated. Several candidates have been suggested in the search for additional cannabinoid receptors.

Transient receptor potential cation channel subfamily V member 1 (TRPV1) is a ligand-activated cation channel and a member of the transient receptor potential superfamily. Regarded mainly as a pain receptor, TRPV1 is activated in response to noxious stimuli such as capsaicin, high temperatures and high proton levels. Accordingly, TRPV1 is mainly expressed on the axon of C-fibre and Aδ sensory neurons, although evidence that TRPV1 is expressed on FLSs and chondrocytes suggests that the role of this receptor extends beyond the nervous system. Several cannabinoid receptors, including AEA, cannabidiol and cannabinergic, have agonistic effects on TRPV1. This suggests an association between TRPV1 and the endocannabinoid system. Furthermore, it is hypothesized that CB1 activation can modulate TRPV1 via dephosphorylation, causing a reduction in TRPV1 activity. This modulation is presumed to cause a reduction in IL-6 secretion from sensitized FLSs, highlighting the potential connection between TRPV1, the endocannabinoid system and rheumatic diseases.

G protein-coupled receptor 55 (GPR55) is referred to by some researchers as a candidate ‘CB3’ receptor. GPR55 was first discovered as an orphan G protein-coupled receptor, with evidence of its expression in the central nervous, immune and gastrointestinal systems as well as in articular surface tissues. The association between GPR55 and the endocannabinoid system is controversial owing to conflicting data regarding the ability of cannabinoids to activate or antagonize GPR55.
Peroxisome proliferator-activated receptor-α (PPARα) is a fatty-acid-activated transcription factor. Predominately expressed on skeletal muscles with some degree of hepatic expression, PPARα is the designated site of action for fibrates (fibric acid derivatives used in the treatment of hypercholesterolaemia). Aside from muscular and hepatic expression, PPARα is expressed on human chondrocytes and osteocytes. An association between PPARα and the endocannabinoid system is corroborated by evidence that PPARα is stimulated by the ‘entourage effect’ which emphasizes the benefits of cannabis use over the use of synthetic cannabinoids. Other cannabis components that might contribute to the entourage effect by acting in synergy with THC are the terpenoids and flavonoids. Terpenoids, which share a common precursor with the phytocannabinoids, give cannabis its distinctive aroma but are also known to induce medicinal effects attributed to anti-inflammatory properties as well as modulatory effects on THC.

Cannabinoids

More than 100 phytocannabinoids have been isolated from *C. sativa*, of which THC and cannabidiol have predominantly been explored and are already being employed in medical therapy. Whereas Δ⁹-THC is considered to be the prominent psychoactive component of *C. sativa*, owing to its high affinity and partial agonist effect on CB1, cannabidiol is the major non-psychoactive phytocannabinoid component of *C. sativa* and is characterized by a relatively low affinity for cannabinoid receptors. Cannabidiol seems to act as a partial CB1 antagonist and a weak inverse CB2 agonist, although some data suggest that cannabidiol can activate CB1 and CB2 indirectly by increasing AEA and 2-AG levels. The combination of THC and cannabidiol is thought to have a synergistic effect in which other phytocannabinoids possibly participate. This synergism gave rise to the theory of the ‘entourage effect’, which emphasizes the benefits of cannabis use over the use of synthetic cannabinoids. Other cannabis components that might contribute to the entourage effect by acting in synergy with THC are the terpenoids and flavonoids. Terpenoids, which share a common precursor with the phytocannabinoids, give cannabis its distinctive aroma but are also known to induce medicinal effects attributed to anti-inflammatory properties as well as modulatory effects on THC.

Adverse effects of cannabinoids

The use of cannabinoids is associated with a range of adverse effects. The toxicity of cannabinoids made the headlines in 2017 with news of a ‘zombie’ outbreak spreading fear in New York. Although adverse events

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*Fig. 1: Endocannabinoid signalling via cannabinoid receptor 1.* **a** Activation of the postsynaptic cell triggers the production and release of endocannabinoids (primarily anandamide and 2-arachidonoyl glycerol) into the synaptic gap. Subsequently, presynaptic cannabinoid receptor 1 is activated, exerting an inhibitory effect on the presynaptic cell. Synthesis and degradation of 2-AG are carried out by diacylglycerol lipase (DAGL) and monoacylglycerol lipase (MAGL), respectively. AEA is synthesized by the enzyme fatty acid amide hydrolase (FAAH). The activity of A-type potassium channels is increased following the reduction in inhibitory PKA activity. Pathway 2: the cannabinoid receptor 1 (CB1) interacts with several main possible pathways. Pathway 1: acting via G proteins, activated CB1 inhibits adenylate cyclase, leading to a decrease in cAMP levels and consequently reducing protein kinase A (PKA) activity. Pathway 3: CB1 activation can also lead to stimulation of inward-rectifying potassium channels whilst inhibiting calcium ion channels. Although CB1 agonists cause inhibition of L-type calcium channels, it is unclear if this inhibition is via the G protein-coupled receptor.
Box 1 | Cannabinoid receptor ligands

**Endocannabinoids**
- 2-Arachidonoyl glycerol (2-AG) — endogenous agonist of cannabinoid receptor 1 (CB1) and CB2
- Anandamide (also known as arachidonoyl ethanolamide (AEA)) — endogenous agonist of CB1 and CB2

**Phytocannabinoids**
- (−)-trans-Δ⁹-Tetrahydrocannabinol (THC) — the primary psychoactive constituent of cannabis
- Cannabidiol — the major non-psychoactive phytocannabinoid component of cannabis

**Herbal cannabis and synthetic cannabinoids**
- Nabiximols — natural THC and cannabidiol extracted from cannabis
- Nabilone — synthetic cannabinoid resembling THC
- Dronabinol — synthetic THC
- JWH-015 — CB2 agonist
- JWH-133 — CB2 agonist
- HU-308 — CB2 agonist
- WIN 55,212-2 mesylate — CB1 and CB2 agonist
- SR141716A — CB1 antagonist
- VCE-004.8 — Peroxisome proliferator-activated receptor-γ (PPARY) and CB2 agonist
- GP1a — CB2 agonist
- O-1966 — CB2 agonist
- Ajulemic acid — derivate of a non-psychoactive THC metabolite

such as mass intoxication might act as a deterrent against the medicinal use of cannabinoids, a distinction must be made between recreational and medicinal cannabinoid compounds. Most cannabinoids share similarities, but synthetic cannabinoids abused for recreational purposes tend to be highly potent — potentially as much as 85 times more potent than THC⁴⁰. However, most of the available data regarding the adverse effects of cannabinoids do not make this distinction as they relate to all cannabinoids regardless of composition and dosage. Another issue of debate is the possibility of inherent differences between medicinal users and recreational users, which might contribute some confounding factors. In light of the paucity of data, the discussion in this section does not make a clear distinction between synthetic cannabinoids and phytocannabinoids.

A systematic review of adverse events related to medicinal use of cannabinoids in randomized controlled trials (RCTs; 4,779 events in total) revealed a higher rate of non-serious adverse effects among participants exposed to cannabinoids than in controls (rate ratio 1.86), whereas the incidence of serious adverse events did not differ between the two groups⁴¹. Common adverse effects of cannabinoids include dizziness, nausea, dry mouth, tachycardia and agitation; rare adverse effects include major complications such as cardiovascular events, acute kidney injury, seizures and psychiatric presentations⁴¹,⁴². A committee sponsored by the US government, comprising 16 experts from a wide range of fields including cannabinoids, neurodevelopment, addiction, paediatrics and public health, produced a report in 2017 that addresses the major and common adverse effects associated with consumption of cannabis and cannabinoids. The committee formulated a number of conclusions that were then classified on the basis of the supporting evidence ranging from conclusive to no or insufficient evidence⁴³. As this report encompasses most of the current data regarding the adverse effects of cannabinoids, in this section we briefly address the committee’s conclusions as well as subsequently published complementary research.

**Effects on the nervous system**

Extensive research has explored the effect of cannabinoids on the nervous system. Many adverse effects have been attributed to consumption of cannabinoids, yet only moderate-grade evidence accumulated thus far indicates that cannabis consumption can cause acute impairment of learning, attention and memory⁴⁴. Evidence regarding the long-term effects of cannabinoid consumption on the nervous system are less conclusive as only limited evidence suggests that learning, attention and memory abilities are diminished after sustained periods of abstinence from cannabis⁴⁵. Deficits in memory were also exhibited in a study published in 2017 of 5,115 volunteers followed over 25 years, which demonstrated an association between lifelong cannabis consumption and poor performance in tests of cognitive abilities examining verbal memory, processing speed and executive function⁴⁶.

The effects of cannabinoids on the brain have also been examined through the use of imaging. Two systematic reviews published in 2013 concluded that chronic cannabis consumption can result in anatomical changes in the brain⁴⁷,⁴⁸. In one of these systematic reviews, an examination of 43 imaging studies led to the conclusion that chronic cannabis use can alter the structure of the cerebellum, medial temporal cortex and frontal cortex⁴⁹. In accordance with these findings, the second systematic review concluded that chronic cannabis consumption might lead to a reduction in hippocampal size⁵⁰. Cannabinoids seem to have divergent effects on the nervous system depending on the age of the user. It is postulated that cannabis exerts a different, possibly more hazardous effect on adolescents than on adults because of the plasticity and ongoing development of the brain during adolescence⁵¹. Compared with adult cannabis users, individuals who start to use cannabis during adolescence perform poorly in cognitive tests, exhibiting deficiencies in memory, attention, inhibition and verbal fluency⁵²,⁵³. Furthermore, cannabis consumption during adolescence has been associated with a decline in IQ score, possibly accounting for a drop of as many as 8 points⁵⁴,⁵⁵. Cannabis use during adolescence has also been associated with poor academic achievement and educational outcomes, although the evidence for these effects is limited⁵⁶. This subject is controversial, with cause and effect being unclear, as suggested by a study published in 2017 that compared the IQ scores of 1,989 twins at the ages of 5, 12 and 18 years⁵⁷. Interestingly, in this co-twin control study, cannabis users had a lower IQ score prior to cannabis consumption and did...
not experience a substantial decline in IQ over time compared with non-users50.

**Effects on mental health**
One of the main concerns regarding cannabis consumption is that it could trigger psychosis or schizophrenia. Indeed, a substantial body of evidence supports the association between cannabinoids and the development of psychosis and schizophrenia43. Other mental health disorders are less strongly associated with the use of cannabinoids. Moderate-quality evidence suggests that cannabinoid use slightly increases the risk of depressive disorders43. A moderate level of evidence also suggests an increased incidence of suicidal ideation, suicide attempts, suicide completion and social anxiety among cannabinoid users43. Contrary to these findings, cannabinoid use is only weakly associated with the development of bipolar disorder, anxiety disorders (apart from social anxiety) and increased symptoms of anxiety43.

**Addiction**
An important factor that should be considered before medicinal cannabis is prescribed is the potential addictive effect of cannabinoids. Although cannabinoids are commonly considered to be non-addictive, epidemiological studies indicate that 9% of adult users will develop cannabinoid dependence41. A moderate level of evidence also suggests an increased incidence of suicidal ideation, suicide attempts, suicide completion and social anxiety among cannabinoid users43. Contrary to these findings, cannabinoid use is only weakly associated with the development of bipolar disorder, anxiety disorders (apart from social anxiety) and increased symptoms of anxiety43.

**Effects on the cardiovascular system**
Acute myocardial infarction and ischaemic stroke are some of the adverse effects of cannabinoid consumption. The association between cannabis use and these cardiovascular events is supported by only limited evidence. Furthermore, the available data are insufficient to either corroborate or discredit the association between chronic cannabis consumption and an increased risk of acute myocardial infarction43. A more frequent cardiovascular adverse effect than myocardial infarction is tachycardia, one of the most prevalent adverse effects of synthetic cannabinoid use43.

**Effects on the respiratory system**
The development of respiratory symptoms following cannabis consumption mostly relates to cannabis smoking. Substantial evidence supports an association between long-term cannabis smoking and respiratory symptoms such as wheezing and morning phlegm as well as frequent episodes of chronic bronchitis. Interestingly, a moderate level of evidence suggests that cessation of cannabis smoking improves respiratory symptoms. In addition, although...
smoking is widely associated with lung cancer, current data do not support a statistical association between cannabis smoking and lung cancer. Of special concern is the risk of cannabis poisoning due to an accidental overdose in children, which can lead to respiratory distress.

**Effects of prenatal exposure**

Data regarding the consequences of prenatal exposure to cannabinoids are fairly scarce, and the analysis of such data is hampered by various confounders such as the use of multiple drugs. Moreover, differences (such as motivation to engage in behaviours associated with a healthy lifestyle, access to healthcare and education regarding illegal drug use) between women who choose to use or not to use cannabinoids during pregnancy might account for later outcomes such as child delinquency or substance abuse. Hence, the currently available data are insufficient to conclude whether a relationship exists between prenatal cannabis exposure and future outcomes in the offspring. Only limited evidence links prenatal cannabis use with anaemia in the mother and with the placement of newborn babies in intensive care units. However, substantial evidence does corroborate an association between cannabinoid consumption during pregnancy and low birthweight in newborn babies.

A study published in 2016 addressed the late outcomes of prenatal cannabis exposure from a different approach by using imaging modalities. In the study, functional MRI was used to compare neurophysiological functioning in 16 young adults exposed to cannabinoids in utero and 15 young adults with no prenatal cannabinoid exposure. The imaging results demonstrated a difference in blood flow between the two groups during the performance of tasks related to executive function, although task performance was similar in both groups.

**Effects on mortality**

No or insufficient data are available to support or refute the association between cannabis and death due to overdose. Evidence is also lacking with regard to any association between cannabis use and all-cause mortality.

Although they do not reflect statistically significant findings, the results of a phase I study testing the safety of BIA 10–2474 (a reversible inhibitor of FAAH) should be addressed. In January 2016, six healthy volunteers started treatment with BIA 10–2474 at a dose of 50 mg per day, and two others received placebo. By day 5 of the trial, one volunteer in the treatment group presented with symptoms of blurred vision and was admitted to the emergency department; his condition deteriorated until he was declared brain dead on day 9. In the treatment group, five individuals developed an acute neurological syndrome, the experiment was halted at day 6. This acute syndrome presented with various symptoms, including anterograde amnesia, limb ataxia, dysarthria and altered consciousness. The remaining symptomatic participants improved over time (up to 55 days follow-up), but some had residual morbidity. This tragic course of events highlights that although cannabinoid research has come a long way in the past few decades, we remain far from understanding the endocannabinoid system and the potential hazards associated with synthetic cannabinoid use.

**Interactions with other drugs**

The implementation of therapy with cannabinoids must take into account possible interactions with other drugs (Fig. 3). Cannabis is presumed to induce CYP1A2 and to act as a substrate of CYP3A4, CYP2C9 and CYP2C19 (REFS 56–58). Thus far, clinical research has explored interactions of cannabinoids with antipyrine, clobazam, indinavir, theophylline, chlorpromazine, ethanol and several opioids (59–60). The interaction between cannabis and ethanol is of particular importance owing to the association between cannabis use and alcohol abuse (which is supported by moderate-grade evidence) (61). The combination of cannabis and ethanol was shown to increase plasma THC concentration. Interactions with other drugs are also postulated to be mediated by a common mechanism of CYP degradation.

Two case reports call for special attention owing to the prevalence of the drugs used and the nature of the adverse effects. In one case, a 41-year-old man experienced an acute myocardial infarction 12 hours after consuming sildenafil and cannabis simultaneously. In the second case, a 56-year-old man presented with an upper gastrointestinal bleed. Although the patient in the second case had received warfarin over the past 10 years, his international normalized ratio (INR) was extremely high (10.41–11.5) in two separate incidents. Further questioning revealed that the patient used cannabis at the time of both incidents. After cessation of cannabis use, the patient’s INR remained in the range 1.08–4.4 for a period of 9 months. These two cases illustrate that cannabinoids should not be taken lightly, and physicians who choose to prescribe cannabinoids should do so with caution.

**Effects at the cellular level**

Cannabinoids exert different effects on various cells. Because inflammation is a key feature in many rheumatic diseases, characterization of the effects of cannabinoids on immune cells is essential to the assessment of the potential use of cannabinoids for the treatment of rheumatic diseases. CB2 is widely distributed on immune cells; therefore, cannabinoids are presumed to possess immunomodulatory traits. Here, we focus on the main immunomodulatory effects of cannabinoids, including cytokine production and cell apoptosis, proliferation and differentiation. Cells other than immune cells also participate in the progression of rheumatic diseases. Hence, fibroblasts, chondrocytes and synovial cells will also be addressed. The effects of cannabinoids on immune and other cells are detailed in Table 1.

**Cannabinoids and rheumatic diseases**

**Rheumatoid arthritis**

**Disease-modifying attributes**. RA is one of the most prevalent autoimmune diseases and is one of the main causes of disability worldwide, causing pain, joint malformation and joint destruction. Preliminary evidence suggests that cannabinoids have a role in the future treatment of RA. In one study, protein and mRNA expression of AEA, 2-AG, CB1 and CB2 were found in synovial tissue obtained from 13 patients with RA undergoing arthroplasty, whereas synovial tissue obtained from healthy volunteers was negative for AEA and 2-AG. Additionally, stimulation of RA
patient FLs with the synthetic cannabinoid HU-210 (an agonist of CB1 and CB2) resulted in phosphorylation of extracellular-signal-regulated kinase 1 (ERK1) and ERK2, which was blocked by exposure of the cells to the CB1 antagonist SR141716 (REF. 65). Although the exact role of the cannabinoid system in RA is not yet clear, these experiments suggest a role for cannabinoids in the treatment of RA. In a separate study of synovial tissue from patients with RA, production of IL-6 and IL-8 by stimulated synovial cells was attenuated by low concentrations of WIN 55,212-2 mesylate, and CB2-dependent inhibition of IL-6 and IL-8 production was achieved at high concentrations of WIN 55,212-2 mesylate. These results are supported by a variety of experimental studies, both in vivo and in vitro. Using a murine model of collagen-induced arthritis (CIA), three different groups have achieved clinical improvement in CIA mice following treatment with various cannabinoids. Overall, exposure to cannabidiol or the CB2 agonists JWH-133 or HU-308 reduced arthritis severity, inflammatory cell infiltration, bone destruction, production of auto-antibodies type II IgG1, IFNγ production and TNF release67–69.

Pain management. The use of cannabinoids for the treatment of pain associated with RA has been assessed in only one clinical trial. In this RCT, 58 patients with RA were allocated to receive either nabiximols or placebo. Compared with placebo, patients treated with nabiximols exhibited decreased pain, both when moving and at rest, along with improved sleep quality70.

Osteoarthritis

Disease-modifying attributes. Osteoarthritis (OA) is regarded as the most prevalent chronic degenerative joint disease overall and is the most commonly diagnosed rheumatic disease among cannabis users71,72. Although OA is highly prevalent, the treatment of this disease is mainly focused on analgesia as no disease-modifying treatment has yet been discovered73. The endocannabinoid system has been implicated as a potential target for OA therapy on the basis of evidence that suggests that this system is involved in OA. Both CB1 and CB2 are expressed in osteoarthritic synovia65. Additionally, synovial fluid derived from patients with OA contains 2-AG and AEA, whereas these endocannabinoids were not detected in the synovia of healthy volunteers65. Consistent with these findings, CB1 and CB2 are expressed in chondrocytes from patients with OA71. The prospect of cannabinoid therapy for OA was further affirmed by the results of a 2015 study. In a model of surgically induced OA (by destabilization of the medial meniscus), mice treated with the CB2 agonist HU-308 presented with milder disease than vehicle-treated mice74. Correspondingly, CB2-deficient mice exhibited a more severe form of OA than wild-type mice74.
Various mechanisms have been proposed for the possible therapeutic effects of cannabinoids in OA. The activity of a disintegrin and metalloproteinase with thrombospondin motifs 4 (ADAMTS4), a suspected participant in cartilage breakdown, was reduced following exposure of OA chondrocytes to WIN 55,212-2 mesylate 

Pain management. Remarkably, although current treatments for OA rely mainly on analgesia, only one clinical trial has explored the efficacy of cannabinoids in the management of osteoarthritis pain. In this RCT, 74 patients with OA received one of two main interventions, each of which was assessed in relation to crossover treatment with placebo: PF-04457845, an inhibitor of FAAH, or naproxen, an NSAID. However, the trial was discontinued owing to futility. Despite a stated reduction in FAAH activity of >96%, PF-04457845 treatment had no effect on pain compared with placebo whilst naproxen reduced pain scores.

Systemic sclerosis

Systemic sclerosis (SSc; also known as scleroderma) is an autoimmune disease characterized by fibrosis, extracellular matrix deposition and vasculopathy. Visceral involvement in SSc leads to high mortality, with an estimated 10-year survival from diagnosis of 62.5%. Different pathways are being explored for the treatment of SSc, one of which is the endocannabinoid system.

In contrast to these results, levels of 2-AG, as well as expression of the genes encoding CB1 and CB2, were higher in plasma derived from patients with OA than from healthy individuals. Furthermore, among patients with OA, levels of 2-AG correlated positively with knee pain and with hospital anxiety and depression scale scores and correlated negatively with memory performance and 36-Item Short-Form Survey (SF-36) scores. Consistent with these findings, local injection of the FAAH inhibitor URB597 reduced noxious afferent firing rate by 56% in a murine model of OA, and similar results were achieved in a guinea pig model of OA.

2-AG, 2-arachidonoyl glycerol; AEA, anandamide (also known as arachidonyl ethanolamide); AJA, ajulemic acid; CB1, cannabinoid receptor 1; CB2, cannabinoid receptor 2; FLS, fibroblast-like synoviocyte; MMP3, matrix metalloproteinase 3; NF-κB, nuclear factor-κB; NO, nitric oxide; OA, osteoarthritis; PGE1, prostaglandin E1; RA, rheumatoid arthritis; SSc, systemic sclerosis; TH1, (−)trans-Δ9-tetrahydrocannabinol; Treg, regulatory T cell.
content and myofibroblasts in response to bleomycin (which induces skin fibrosis in a murine model of SSc)\textsuperscript{81}. In contrast to CB1, CB2 might protect against SSc. CB2-deficient mice injected with bleomycin exhibited increased dermal thickness and higher leukocyte counts in skin lesions, whereas in wild-type mice, treatment with the CB2 agonist JWH-133 reduced leukocyte infiltration and dermal thickening\textsuperscript{82}. Similar results were achieved in mice treated with VCE-004.8, a dual agonist of PPARγ and CB2: VCE-004.8 reduced dermal thickness, collagen accumulation in blood vessels, skin macrophage infiltration and mast cell degranulation\textsuperscript{83}.

In a different murine model, using a hypochlorite to induce fibrosis, JHW-133 prevented the development of skin and lung fibrosis and reduced levels of anti-DNATopoisomerase antibodies and fibroblast proliferation\textsuperscript{84}. Studies of wound repair also provide data supporting the role of CB2 as a potentially key modulator of fibrogenesis. Wounded mice treated with the CB2 agonist GP1a demonstrated reduced fibroblast accumulation, fibroblast-to-myofibroblast transformation, collagen deposition and levels of transforming growth factor-β1 (TGFβ1), IL-6, TNF and vascular endothelial growth factor (VEGF)\textsuperscript{85,86}.

Skin pathology in animal models is similar to the pathology from patients with diffuse cutaneous SSc (dcSSc). Analysis of biopsy-obtained human skin indicated overexpression of CB1 and CB2 in fibroblasts from patients with dcSSc as compared with fibroblasts from healthy samples\textsuperscript{87}. Furthermore, treatment of fibroblasts with WIN 55,212-2 mesylate decreased extracellular matrix disposition, myofibroblast differentiation and resistance to apoptosis\textsuperscript{88}.

**Fibromyalgia**

Fibromyalgia is a chronic pain syndrome characterized by diffuse pain, fatigue and sleep disturbance and by tenderness at a number of specific sites (tender points)\textsuperscript{89}. In the absence of a known pathophysiology or suitable treatment, cannabis, which is commonly utilized for its analgesic properties, is a natural candidate for the treatment of fibromyalgia. Hence, medicinal use of cannabis for fibromyalgia is approved in several countries\textsuperscript{89–92}.

To date, all clinical trials exploring the effectiveness of cannabinoids as a therapy for fibromyalgia have used nabiflone. Two RCTs were included in a Cochrane review addressing this matter\textsuperscript{93}. Both studies showed promising results, with one trial demonstrating that nabiflone effectively reduced anxiety, pain and Fibromyalgia Impact Questionnaire (FIQ) scores\textsuperscript{94} and the other trial showing that nabiflone was superior to amitriptyline in resolving sleep disturbance, although with no improvement in quality of life, mood or pain\textsuperscript{95}. However, small sample sizes and the short duration of each experiment preclude unbiased conclusions. Hence, the main conclusion of the Cochrane review did not support cannabinoid treatment for fibromyalgia\textsuperscript{93}. By contrast, a US government-sponsored committee concluded that there is currently moderate-grade evidence supporting the effectiveness of cannabinoids for the treatment of fibromyalgia\textsuperscript{94}.

In addition, an observational study that did not meet the inclusion criteria for the Cochrane review also put medicinal cannabis to the test\textsuperscript{95}. The study population included 28 patients with fibromyalgia who were cannabis users and 28 patients with fibromyalgia who were not. Evaluating their symptoms before and after self-administration of cannabis, the cannabis users reported reductions in pain and stiffness and an increase in relaxation accompanied by a rise in somnolence, in feelings of well-being and in the SF-36 mental health component score 2 hours after consumption of cannabis. No improvements were observed in other SF-36 components, in the FIQ score or in the Pittsburgh Sleep Quality Index\textsuperscript{96}.

**Conclusions**

Medical cannabis presents the physician with a challenge in the face of demands from patients. About 75% of surveyed rheumatologists report that they lack confidence regarding treatment with cannabinoids and thus refrain from recommending it\textsuperscript{97}. Physicians must take into account possible adverse effects, with particular consideration of interactions with other drugs and the risk of addiction, owing to the chronicity and unique characteristics of rheumatic diseases. The potential benefits of cannabinoid therapy must be weighed against these risks. Cannabinoids have various effects on immune cells, resulting in an overall anti-inflammatory effect. The immunomodulatory properties of cannabinoids are substantiated by studies in animal models of RA and SSc, but other rheumatic diseases, such as systemic lupus erythematosus, are yet to be explored. Surprisingly, although cannabis consumption is highly prevalent and preliminary laboratory findings support cannabinoid therapy in rheumatic diseases, clinical trials in this setting are scarce. To date, clinical trials have been conducted in RA, OA and fibromyalgia, but small sample sizes and inconsistency in the findings prevent the formulation of conclusions and recommendations. Furthermore, a gap seems to exist between the encouraging results achieved in animal models and the inconclusive results of clinical studies. This contradiction, such as in the clinical trial of the FAAH inhibitor PF-04457845 (REF.\textsuperscript{77}), might raise the question of whether the usual animal models are suitable for research into cannabinoids and whether the effects attributed to cannabis arise from the entourage effect. Regardless of promising preclinical findings, the current clinical data simply do not suffice for conclusions to be drawn; therefore, clinicians should not routinely recommend cannabinoids for the treatment of rheumatic diseases. However, in adults with rheumatic diseases, especially in those with fibromyalgia, cannabinoid treatment could be considered in specific cases. The increasing legalization of medicinal cannabis emphasizes the need for further research, which should include large-scale clinical trials. In addition, in light of promising preclinical results, research should be extended to other rheumatic diseases.

In conclusion, although still far from being quantified and standardized therapies, cannabinoids have potential in the management of rheumatic diseases. As sufficient evidence is currently lacking, further research is paramount before cannabis can gain a place in the medicine cabinet.


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