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REVIEW

Clinical Implications for Cannabinoid Use in the Rheumatic Diseases

Potential for Help or Harm?

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Introduction

Cannabinoids as therapeutic agents in traditional medicine are both lauded and maligned. The ubiquitous use in years gone by once made cannabinoids a mainstay of the physician's dispensary, yet the understanding of the pharmacology of these drugs is relatively recent. The physiologic and psychoactive effects of the cannabis, or hemp, plant, cultivated in ancient times for the production of textiles, led to ceremonial, therapeutic, and eventual recreational use, beginning in the Himalayan region of central Asia and with the first recorded medicinal use in China in 2700 BC (1).

In the Western world, 2 paths of scientific study of cannabinoids have been followed. In the earliest studies, 19th century French psychiatrists focused on the effects on mood, whereas British physicians explored the sedative, analgesic, hypnotic, and anticonvulsive properties (1). In the early 20th century, interest in cannabis as a therapeutic agent waned following the introduction of drugs with a more reliable therapeutic profile, such as opiates. With increasing global concerns about narcotic addiction, cannabis was misclassified as a narcotic, similar to heroin, opium, and cocaine, at the Geneva International Convention on Narcotics Control in 1925, which resulted in a ban on cannabis for recreational use in the UK in 1928 and criminalization in the US in 1937 (1,2). Renewed interest in the therapeutic effects of cannabinoids emerged following the identification and cloning of cannabinoid receptors in the late 1980s and 1990 (3–5).

The endocannabinoid system, found throughout the animal kingdom, comprises endogenous ligands, termed endocannabinoids, and receptors. This system has effects on pain mechanisms, immune function, inflammation, and bone health, as has been noted in the laboratory setting. However, formal clinical study has been limited. Therefore, the true efficacy and risk/benefit ratio with regard to the therapeutic effects of cannabinoids, whether derived from the hemp plant *Cannabis sativa* or synthesized from cannabis derivatives, remain controversial (6). The use of cannabinoids as therapeutic agents has mostly remained outside mainstream medicine in modern times and is further prejudiced by the recreational use of marijuana, a drug associated with abuse with a reported usage rate of 4% of the global population (2,3). Because more than 60 alkaloids are present in the plant form, and because there has been increasing identification of endocannabi-

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Dr. Fitzcharles has received consulting fees, speaking fees, and/or honoraria from Eli Lilly, Janssen, Pfizer, and Purdue Pharma (less than $10,000 each) and has provided expert testimony regarding pain related to rheumatic conditions for the plaintiff and the defense in court trials. Dr. McDougall has received consulting fees from Eli Lilly (less than $10,000).

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noids in the animal world and an explosion in the development of synthetocannabinoids, the specific molecules offering clinical benefit require elucidation.

Almost 10% of patients with chronic pain in the US are taking cannabinoids for self-medication purposes, but the purpose of their use in more than one-half of patients has not been disclosed (7). Physicians must therefore be knowledgeable of the physiologic mechanisms, current clinical evidence, and risks associated with cannabinoid use to be able to provide balanced counsel to patients. Because cannabis is illegal in most countries, any recommendation for medicinal use should be made within the law, usually regulated by a "medical exemption authorization." In this selected literature review, we provide an overview of the current status and understanding of cannabinoids and the endocannabinoid system as it pertains to rheumatology practice.

Pain management in the rheumatic diseases

Rheumatologists are increasingly sensitized to the need for effective pain management, with pain being recognized as the most important predictor of psychosocial health in patients with rheumatoid arthritis (RA) (8–10). Because improvements in analgesic treatments are needed, ideally with a mechanism of action different from that of traditional analgesics, cannabinoids may hold potential for pain management and deserve critical appraisal.

At least 3 factors justify additional evaluation of the effects of cannabinoids in rheumatic diseases. First, rheumatic pain is recognized to have both nociceptive and neuropathic components, opening the door to a wider spectrum of treatments (8). Since nociceptive effects are mostly driven by local inflammation, the antiinflammatory properties of cannabinoids may be useful (11,12). Second, joints express the CB_1 and CB_2 receptors, and endocannabinoids act on these receptors to modulate joint pain (13–15). Finally, population studies indicate that arthritis is the reason for medicinal cannabinoid use in up to one-third of subjects (16,17).

Physiology of the cannabinoid system

The effects of cannabinoids are mostly mediated via binding of ligands to receptors, although other actions may occur. The endocannabinoid system consists of 2 G protein–coupled receptors (CB_1 and CB_2) and a recently described putative third receptor, GPR55 (4). Cannabinoid receptors, ubiquitous throughout the mammalian system, were originally termed "cannabinoid" because their signaling was observed to be mediated by the plant product delta-9-tetrahydrocannabinol (Δ^9-THC). Subsequently, the cannabinoid receptor genes were cloned and endogenous eicosanoid molecules, or endocannabinoids, were observed to function as agonists for these receptors (18).

Molecules affecting cannabinoid or related receptors are found in 3 settings: 1) endogenous ligands, or endocannabinoids, that are lipid mediators derived from arachidonic acid; 2) plant derived, termed phytocannabinoids; and 3) synthetic tricyclic terpenes (3,18). Endocannabinoids are produced by breakdown of phospholipids, an integral part of cell membranes, that cascade in a pathway distinct from the inflammatory prostaglandin pathway (19). Endocannabinoids include anandamide, 2-arachidonyl glycerol, noladin, virodhamine, and N-arachidonoyl dopamine. The major eicosanoids (i.e., prostanoids and leukotrienes) are, however, not cannabinoids and bind to different receptors, but interact with endocannabinoids in the inflammatory process (18). Therefore, endogenous ligand–receptor interactions best describe the mechanism for the cannabinoid effects in animals and humans.

The 2 best-known exogenous cannabinoids are Δ^9-THC and cannabidiol (CBD), both found in the plant *Cannabis sativa*, which contains at least 66 different cannabinoid molecules (2). The Δ^9-THC form has pain-relieving and psychoactive properties, whereas CBD, with influence on immunologic functions and limited affinity for cannabinoid receptors, acts mainly via the transient receptor potential vanilloid channel 1 (TRPV-1) and 5-HT_{1A} receptors (2). CBD enhances the signaling properties of adenosine and anandamide, has antioxidant effects, has less psychoactive properties, and possibly has a reduced addiction potential (2,20). Cannabinoids have also been synthesized as analogs of, mostly, THC, with the advantage that defined amounts can be administered and tested in a more controlled setting when compared to the variable composition of naturally occurring products.

Cannabinoid receptors are concentrated in nervous system tissue, immune cells, and bone and joint tissue. This system is not a simple on/off receptor effect. A complex response mechanism exists in interactions between the endogenous and exogenous ligands, in cross-reactions with noncannabinoid receptors, and in the plasticity of response, which is dependent on local tissue characteristics or the presence of other molecules, such as opioids (21).

Cannabinoid receptors are negatively coupled with adenylate cyclase via G proteins, and positively

coupled to MAP kinase. Moreover, cannabinoid receptors also regulate activities of calcium and potassium channels (19). CB_1 receptors, mostly associated with neural tissue, have pain-modulating effects extending from the primary afferent neuron to the spinal cord and central pain centers (5). They are also found in brain areas that subserve motor control, memory, and cognition. In contrast, CB_2 receptors are mostly located peripherally on immune cells such as chondrocytes and osteoclasts, and in musculoskeletal tissue, but also play a role in the central nervous system (22). The exact function of the CB_2 receptors on bone, cartilage, and immune cells still requires clarification. In summary, cannabinoids are best understood to have effects on pain, motor control, and cognition mediated via nervous system tissue, whereas there is less knowledge of the effects on the musculoskeletal and immune systems.

Cannabinoids are metabolized in the liver via hepatic cytochrome P450 (CYP) enzymes, with initial hydroxylation and conversion to glucuronides, followed by biliary and intestinal tract excretion (3). They are lipophilic molecules, and therefore can be deposited for prolonged periods of time in the tissues. Cannabinoid tolerance is mediated via a number of mechanisms, including internalization or degradation of receptors, reduced receptor signaling, or reduced receptor protein synthesis.

Effects of cannabinoids

Pain. Modulation of pain is the most-recognized therapeutic effect of cannabinoids, supported by studies in animal arthritis models and in patients with arthritis. Evidence for an effect in joint tissue came from the observation that local administration of the CB_1 receptor agonist arachidonyl-2-chloroethylamide (ACEA) increased synovial blood flow (23). Thereafter, CB_2 agonists were shown to alter joint vasoreactivity, confirming the presence of both receptor subtypes in the joints. Schuelert and McDougall were the first to report that ACEA could inhibit the hypersensitivity of joint nociceptors in a rat model of osteoarthritis (OA) (14). In contrast, the CB_2 receptor agonist GW405833 inhibited nociceptor activity in control rat joints, but produced a paradoxical sensitization of joint afferents in rats with knee OA (13).

These preclinical studies demonstrated that the neuromodulatory effects of peripherally administered synthetocannabinoids occurred via TRPV-1 ion channels, suggesting that interactions are taking place between the endocannabinoid and endovanilloid systems. Endocannabinoids such as anandamide are rapidly broken down by fatty acid amide hydrolase (FAAH), such that the half-life of anandamide is short. Treatment of rats with OA with the FAAH inhibitor URB597 has been shown to reduce joint mechanosensitivity and pain behavior, providing further evidence for an endocannabinoid system in the joints (15). Synovial fluid from patients with OA or RA, but not normal control synovial fluid, contained anandamide and 2-arachidonyl glycerol, confirming that endocannabinoid synthesis occurs following tissue injury (24). These studies provide evidence that the endocannabinoid system is activated locally in response to nociceptive stimuli in the arthritis state, and functions as an endogenous pain modulator.

Rheumatic pain is both nociceptive and neuropathic. Following joint injury, nerves innervating the healing joint have a truncated appearance similar to that seen in models of peripheral neuropathy (25). Furthermore, these nerves contain high levels of algogenic neurotransmitters, such as substance P and calcitonin gene–related peptide (25,26). It follows that agents controlling neuropathic pain could be adjuncts in the reduction of musculoskeletal pain. Animals with peripheral neuropathy demonstrate elevated cannabinoid receptor expression in both the central and peripheral nervous systems (27–29). Administration of nonselective cannabinoid agonists has been shown to reduce neuropathic pain in surgical models of nerve injury (30–32) as well as in rats with diabetic neuropathy (33,34).

The particular cannabinoid receptor subtype responsible for analgesia in neuropathic pain is controversial. Both the CB_1 and CB_2 receptors have been implicated in modulation of inflammatory and neuropathic pain (21). The antinociceptive effects, particularly with regard to CB_2 receptor agonists, may be enhanced by coactivation of the opioid system (21). Pain responses in CB_1-knockout mice were found to be similar to those in wild-type control animals, suggesting that this particular cannabinoid receptor is unnecessary for reducing neuropathic pain (35). Conversely, a model in which CB_1 receptors were deleted from the peripheral nerves, but retained centrally, exhibited reduced analgesia in response to systemic and peripheral administration of cannabinoids (36). Thus, the results of that study highlighted the importance of peripheral CB_1 receptors in modulating neuropathic pain, an effect possibly applicable to arthritis pain.

Immune system. Cannabinoids exert both immunosuppressive and antiinflammatory actions, and these effects are mediated via the CB_2 receptor. Postulated

mechanisms include effects on apoptosis, inflammatory cell proliferation and trafficking, cytokine production, and regulatory T cells (37,38). Ajulemic acid, a synthetic cannabinoid, increases production of an eicosanoid with antiinflammatory properties in fibroblast-like synovial cells, reduces production of interleukin-6 in human monocyte-derived macrophages, induces apoptosis in human lymphocytes, and suppresses fibroblast metalloproteinase production (39). CBD has both antiinflammatory and antioxidative properties (40). In animal models of inflammation, CBD reduced cell-mediated joint destruction in an RA model, and reduced plasma levels of proinflammatory cytokines in a mouse model of diabetes (41,42).

The role of the endocannabinoid system in modulation of fibrotic conditions is intriguing. Contrary to the expected antiinflammatory effect usually attributable to activation of the endocannabinoid system, the CB_1 receptor has recently been shown to promote an inflammatory response. In a mouse model of scleroderma, activation of the CB_1 receptor facilitated leukocyte infiltration, resulting in secondary fibroblast activation, whereas inactivation of this receptor resulted in reduced lymphocyte-related profibrotic effects (43). Whether these effects extend to the management of human disease, such as in patients with scleroderma, remains to be seen. Although most evidence points to a composite antiinflammatory effect of cannabinoids on many immune cells, there is emerging evidence to indicate that, in certain settings, cannabinoids may be proinflammatory.

Bone metabolism. Cannabinoid receptors and ligands have effects on bone metabolism that are still in the early stages of understanding. Studies in mice indicate that defects of both the CB_1 and CB_2 receptors can result in age-related osteoporosis, although it is likely that different mechanisms will influence the bone remodeling process (44). Ajulemic acid has been shown to suppress osteoclast formation in a dose-dependent manner in osteoclast cultures (45). These effects may eventually play a role in conditions associated with excessive osteoclast function, such as osteoporosis, and in the regional osteoporotic effects of RA (44).

Sleep. *Cannabis sativa* has been used as a sedative agent since ancient times. The effects of both short-term and long-term use of cannabinoids on sleep have been studied, as have the effects of withdrawal after prolonged use (46,47). Short-term administration of THC causes reduced latency of sleep onset, increased slow-wave sleep, and reduced rapid eye movement (REM) sleep. The effects of long-term use of marijuana on sleep are less clear, with some evidence that the sleep-promoting effects are attenuated over time. There is more evidence to support adverse effects on sleep following the withdrawal of cannabinoids after long-term use, as shown by changes on polysomnography indicating a reduction in total sleep time, sleep efficiency, and REM sleep, an increase in "wake after sleep onset," and periodic limb movements (47). Subjects report considerable subjective sleep difficulties and strange dreams following the discontinuation of cannabinoids, but with improvement following reintroduction. A recent study in sleep laboratories indicated that Δ^9-THC has sedative effects, whereas CBD has mild activating effects; a combination of both molecules in nabixomol (commercially available as Sativex) has demonstrated subjective sleep improvement in clinical trials of mostly neuropathic pain conditions (48).

Cannabinoids as a therapy

Cannabinoids are available as the natural product from the leaves and flowers of the plant *Cannabis sativa*, mostly accessed illegally and without control regarding content or dosing, or as a prescribed pharmacologic medication that is composed of either natural molecules or synthesized molecules. Current formulations are administered in pill form, as oromucosal spray, or by inhalation. The transdermal route of administration for cannabinoids, which have lipophylic properties, is currently being explored in animal studies.

The most commonly used form of cannabinoid is *Cannabis sativa*, which is either smoked or ingested. Pharmacologic concerns regarding smoked cannabis arise from variable concentrations of the substance in the natural product, variable pharmacokinetics, and risks of smoke inhalation. There are 3 pharmacologic cannabinoid preparations available. Dronabinol (Marinol), a stereoisomer of THC, and nabilone (Cesamet), a synthetic analog of THC but with less psychoactive effects, are oral agents. Nabixomol, an oromucosal spray, is a combination of Δ^9-THC and CBD and is postulated to have less psychoactive effects than that attributed to CBD alone, and may also contribute antiinflammatory and analgesic effects (49). The potential for abuse of pharmacologic preparations of dronabinol and nabilone is reported to be low (2). Although there is ample evidence to indicate that cannabis can be abused when used for recreational purposes, the frequency of abuse when cannabis is used for therapeutic purposes is unknown and requires further study.

In addition to acting in isolation, cannabinoids

are known to interact with other analgesic pathways to modulate nociception and pain processing. Cannabinoids and opioids act synergistically to inhibit pain via independent, but physiologically related, pathways. The antinociceptive effects of morphine can be enhanced by coadministration of Δ^9-THC, which activates δ- and κ-opioid receptors (50). Molecular studies have determined that μ-opioid receptors can form heterodimers with CB_1 receptors, with the functional consequence of this interaction being a MAP kinase–dependent effect (51). The synergism between the cannabinoid and opioid systems has implications for pain treatment, as doses of opioids could potentially be reduced when combined with cannabinoids. These synergistic effects apply to both the positive therapeutic effects and the negative adverse effects of these agents when used in clinical practice. Whether this synergy will translate into a clinically meaningful effect requires examination.

Cannabinoids have effects on the cyclooxygenase system. A synergistic effect was observed when aspirin was combined with an inactive dose of the nonselective cannabinoid HU210 in a pain behavioral test in rats (52). In contrast, prolonged administration of Δ^9-THC was shown to abrogate the effect of selected nonsteroidal antiinflammatory drugs in a mouse model of visceral nociception (53). The combination of cannabinoid and an antiinflammatory agent therefore has less evidence for consistent synergy.

Cannabinoids in rheumatic disease management

Information regarding the use of cannabinoids for management of pain in rheumatic conditions is available from preclinical science, population surveys, anecdotal reports, and the results of only 3 formal clinical trials, 2 of which were in patients with fibromyalgia (FM) and 1 in patients with RA (16,17,54–57). Although FM has traditionally been managed by rheumatologists, this condition is neurologically based, with evidence indicating dysregulation of pain processing rather than a true musculoskeletal process. Anecdotal reports of the effects of cannabinoids in rheumatic conditions are open to reporting bias, but indicate a modest attenuation of pain, with patients reporting feeling "distanced" from the pain. Even in this setting of limited evidence for efficacy, treatment of rheumatic pain is a common reason given for medicinal cannabinoid use.

Musculoskeletal pain was reported by >80% of 139 subjects who accessed medicinal cannabis in a regional pain clinic in Washington, with back pain and OA identified as specific symptoms (58). Arthritis was the reason given for cannabinoid use among one-third of the subjects in 2 chronic pain population surveys, 1 from the UK (n = 3,000) and 1 from Australia (n = 128), with two-thirds of subjects having reported considerable improvement after use (16,17). A concerning observation with regard to the findings of both studies was the overlap with recreational cannabinoid use in more than one-third of the patients, as well as their reported use of cannabinoids to self-medicate for depression (16,17). These 2 surveys provide only a limited view of the scope of patient-driven cannabis use, but due to the limitations noted in both studies, conclusions regarding the effectiveness or safety of cannabis remain questionable.

Cannabinoids in RA have been studied in a single randomized, controlled trial of moderate quality, according to a recent systematic review (55,59). Fifty-eight patients with RA were treated with the oromucosal spray nabixomol or placebo over a 5-week period, resulting in significant improvement in pain and sleep in the active-drug group. No serious adverse events were identified, and there were no treatment-related withdrawals, although dizziness, dry mouth, and nausea were reported. This study suggests a possible therapeutic role for cannabinoids in inflammatory rheumatic diseases.

FM could conceivably be a condition responsive to cannabinoids, in view of its neurologic basis and associated symptoms of sleep disturbance and anxiety. In a study of 9 patients with FM, orally administered Δ^9-THC reduced electrically induced pain as well as the extent of pain on daily self-report, but did not attenuate axon-induced flare, with 5 of the 9 subjects withdrawing due to treatment-related side effects (60). Two small randomized, controlled trials have examined the use of nabilone in FM (56,57). In the first study, involving 40 patients with FM of 6 weeks' duration, nabilone was associated with statistically significant improvements in pain and function, as measured by the Fibromyalgia Impact Questionnaire (FIQ) (57). This study was rated to be of moderate quality in 2 recent systematic reviews (59,61). Although significant improvement was achieved, the modest effects of a 2-point reduction in pain and 12-point reduction in the FIQ score raise the question as to whether these effects are truly clinically meaningful.

Drowsiness was reported by almost one-half of the patients treated with nabilone, a side effect with important safety consequences. In a randomized, double-blind, active-control, equivalency crossover study of nabilone and amitriptyline, which addressed sleep

disturbance in 31 patients with FM, both agents performed equally in terms of improving sleep quality, but without any effect on pain or quality of life, and with more adverse effects in the cannabinoid treatment group (56). This study was conducted over a period of 6 weeks, with each subject receiving each drug for a 2-week period (with a 2-week washout period). In an uncontrolled study, reductions in pain scores were observed 2 hours after treatment with herbal cannabis in 28 patients with FM, but with no impact on function as measured by the 36-item Short-Form Health Survey or the FIQ (62). Therefore, on the strength of evidence, cannabinoid use in FM remains of questionable value.

Two recent systematic reviews have examined the effect of cannabinoids for the treatment of chronic non–cancer-related pain, which mostly included patients with neurologic pain (59,61). The reviews each evaluated 18 studies, mostly graded as being of moderate quality, and 11 of the studies were reported in both reviews. Cannabinoids were superior to placebo for analgesic effect in chronic pain, with some studies showing improvement in sleep (59,61). Any therapeutic effect must, however, be balanced with adverse effects. The numbers needed to harm were calculated to be between 5 and 8 for events affecting motor function, altered perception, and altered cognition. This narrow therapeutic window associated with currently available cannabinoid treatments calls for the development of new cannabinoid molecules or manipulation of the endocannabinoid system (12). Since there are considerable limitations in the existing studies, including small sample sizes, short duration, and effect sizes noted to be modest at best, any conclusions remain tenuous, and therefore larger, well-controlled clinical trials are needed.

Risks associated with cannabinoid use

Risks related to cannabinoids can occur in both the short term and the long term, with unanswered questions regarding equivalency of risk between herbal cannabis and pharmacologic preparations. Medicinal cannabinoids are associated with more adverse events as compared with placebo, when studied in short-term trials. The most commonly reported effects include dizziness, disorientation, euphoria, drowsiness, and an impact on cognition (63).

In contrast, the long-term risks of therapeutic cannabinoid use are unknown. Elucidation of the long-term risks of recreational cannabis use may give some direction for patient care, but direct extrapolation is not appropriate. Questions remain regarding drug interactions, effects on psychological health and associations with mental illness, development of dependence and addiction, long-term effects on memory and cognition, and effects of smoked cannabinoids on respiratory health (64).

Any current knowledge of the effects of cannabinoid use on psychological health stems from studies of younger adult recreational users, in whom there have been reported associations with depression, suicidality, anxiety, and exacerbation or precipitation of schizophrenia. Swedish military conscripts who had reported use of cannabis at least 50 times had a relative risk of 6.7 for the development of schizophrenia (65). Similarly, patients with schizophrenia who had taken cannabis had more symptoms of mental disturbance (65). The link between recreational cannabis and symptoms of depression, suicidal ideation, and anxiety is increasingly appreciated (64). Other than for Sativex, which has been associated with depression, suicidal ideation, hallucinations, and paranoia in 5% of patients in the short term, there is no information with regard to the effects of medicinal cannabinoids on mental health, especially in the long term (2).

Dependence, abuse, or gateway to other drug abuse remains a concern for any use of cannabinoids. Effects related to psychological dependence on cannabis are similar to those related to alcohol, whereas the physical effects are less prominent (64). Physiologic withdrawal results in anxiety, sleep disturbance, and abdominal complaints, and is dopamine mediated, whereas dependence, mediated via the mesolimbic–dopamine reward pathway and occurring in 8% of recreational marijuana users, is defined as a preoccupation with the need to acquire the substance (64,66,67). When potential for abuse was tested using standard measures for drug discrimination and liking, dronabinol and nabixomol, especially in higher doses for the latter, were different from placebo in terms of evidence of modest abuse potential (68).

Abuse, as in diversion, has not been formally observed for either of the oral preparations, dronabinol or nabilone, or the oromucosal preparation nabixomol (2). Substance abuse and intentional misinforming of health care providers are reported characteristics that have become increasingly more common in patients with chronic pain. Fishbain and colleagues found discrepancies in the frequency of substance abuse according to patient self-report and that revealed by urine drug screening among ~50% of 274 patients with chronic pain; in fact, those authors observed that 8% of patients tested positive for illicit drugs and 6% tested positive for

cannabis on the urine test (69). Although prevalence estimates for cannabis use in the general population may appear similar to those in the study by Fishbain et al, population estimates tend to record a positive response for even a single exposure in a particular year. Substance abuse and/or dependence associated with opioid therapy was reported in one-tenth of a cohort of 801 patients with chronic pain in whom degenerative arthritis, low back pain, and FM were identified as common diagnoses (70).

When cannabis is smoked, chronic inflammatory changes occur in the respiratory mucosa, an effect independent of cigarette use (71). Reduced expiratory flow rate, indicative of early chronic obstructive pulmonary disease, is also associated with the quantity of cannabis smoked in early adult life (71). An earlier study, however, suggested that these effects were most evident with heavy marijuana use, rather than customary social use (72). Similarly, increased periodontal disease was associated with increased cannabis exposure (73). Risks of development of cancers of the airway are less clear and confounded by concomitant cigarette smoking, but with increasing evidence for an additive effect, with cannabis use resulting in a 3-fold increased risk of upper aerodigestive tract cancers (74).

Conclusion

Although use of cannabinoids and a clear understanding of the endocannabinoid system may be pertinent to the mechanisms and management of the rheumatic diseases, there remains limited evidence to support the therapeutic use of cannabinoids to date, and unanswered questions remain with regard to their true clinical efficacy and long-term risks. The ubiquitous distribution of cannabinoid receptors throughout the body, coupled with the known effects of cannabinoids on inflammation, pain, and even joint damage, should prompt further study in the rheumatic diseases. Indeed, preclinical studies look promising, with future protocols perhaps involving peripherally restricted cannabinoids or agents that boost endocannabinoid tone.

Well-controlled clinical studies in the rheumatic diseases are lacking, and much of the reported therapeutic use has been based on anecdotal reports and advocacy. Unfortunately, the tainted image of cannabinoids, which stems from worldwide recreational use of marijuana, has negatively influenced stakeholders at all levels when medicinal use of cannabinoids is under consideration, and thus evidence-based therapeutic evaluation has stalled. Clearly, an agent with such diverse effects could potentially hold great promise for symptom management in the rheumatic disorders. At this time, however, there is insufficient evidence available to support a recommendation for the use of cannabinoids in the management of pain in the rheumatic diseases.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Fitzcharles had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

REFERENCES

1. Kalant H. Medicinal use of cannabis: history and current status. Pain Res Manag 2001;6:80–91.
2. Robson P. Abuse potential and psychoactive effects of δ-9-tetrahydrocannabinol and cannabidiol oromucosal spray (Sativex), a new cannabinoid medicine. Expert Opin Drug Saf 2011;10:675–85.
3. Pertwee RG. Cannabinoid pharmacology: the first 66 years. Br J Pharmacol 2006;147 Suppl 1:S163–71.
4. Howlett AC. A short guide to the nomenclature of seven-transmembrane spanning receptors for lipid mediators. Life Sci 2005;77:1522–30.
5. Pertwee RG. Cannabinoid receptors and pain. Prog Neurobiol 2001;63:569–611.
6. Campbell FA, Tramer MR, Carroll D, Reynolds DJ, Moore RA, McQuay HJ. Are cannabinoids an effective and safe treatment option in the management of pain? A qualitative systematic review. BMJ 2001;323:13–6.
7. Bronstein K, Dhaliwal J, Leider H. Rates of inappropriate drug use in the chronic pain population: an update. J Pain 2011;12:P5.
8. Goldenberg DL, Clauw DJ, Fitzcharles MA. New concepts in pain research and pain management of the rheumatic diseases. Semin Arthritis Rheum 2011;41:319–34.
9. Fitzcharles MA, Almahrezi A, Shir Y. Pain: understanding and challenges for the rheumatologist [review]. Arthritis Rheum 2005;52:3685–92.
10. Courvoisier DS, Agoritsas T, Glauser J, Michaud K, Wolfe F, Cantoni E, et al, on behalf of the Swiss Clinical Quality Management Program for Rheumatoid and the National Data Bank for Rheumatic Diseases. Pain as an important predictor of psychosocial health in patients with rheumatoid arthritis. Arthritis Care Res (Hoboken) 2012;64:190–6.
11. Greineisen WE, Turner H. Immunoactive effects of cannabinoids: considerations for the therapeutic use of cannabinoid receptor agonists and antagonists. Int Immunopharmacol 2010;10:547–55.
12. Karst M, Wippermann S, Ahrens J. Role of cannabinoids in the treatment of pain and (painful) spasticity. Drugs 2010;70:2409–38.
13. Schuelert N, Zhang C, Mogg AJ, Broad LM, Hepburn DL, Nisenbaum ES, et al. Paradoxical effects of the cannabinoid CB_2 receptor agonist GW405833 on rat osteoarthritic knee joint pain. Osteoarthritis Cartilage 2010;18:1536–43.
14. Schuelert N, McDougall JJ. Cannabinoid-mediated antinociception is enhanced in rat osteoarthritic knees. Arthritis Rheum 2008;58:145–53.
15. Schuelert N, Johnson MP, Oskins JL, Jassal K, Chambers MG, McDougall JJ. Local application of the endocannabinoid hydrolysis inhibitor URB597 reduces nociception in spontaneous and chemically induced models of osteoarthritis. Pain 2011;152:975–81.

16. Swift W, Gates P, Dillon P. Survey of Australians using cannabis for medical purposes. Harm Reduct J 2005;2:18.
17. Ware MA, Adams H, Guy GW. The medicinal use of cannabis in the UK: results of a nationwide survey. Int J Clin Pract 2005;59: 291–5.
18. Howlett AC. Cannabinoid receptor signaling. Handb Exp Pharmacol 2005:53–79.
19. Cravatt BF, Lichtman AH. The endogenous cannabinoid system and its role in nociceptive behavior. J Neurobiol 2004;61:149–60.
20. Mechoulam R, Parker LA, Gallily R. Cannabidiol: an overview of some pharmacological aspects. J Clin Pharmacol 2002;42:11–9S.
21. Anand P, Whiteside G, Fowler CJ, Hohmann AG. Targeting CB_2 receptors and the endocannabinoid system for the treatment of pain. Brain Res Rev 2009;60:255–66.
22. Croxford JL, Yamamura T. Cannabinoids and the immune system: potential for the treatment of inflammatory diseases? J Neuroimmunol 2005;166:3–18.
23. Baker CL, McDougall JJ. The cannabinomimetic arachidonyl-2-chloroethylamide (ACEA) acts on capsaicin-sensitive TRPV1 receptors but not cannabinoid receptors in rat joints. Br J Pharmacol 2004;142:1361–7.
24. Richardson D, Pearson RG, Kurian N, Latif ML, Garle MJ, Barrett DA, et al. Characterisation of the cannabinoid receptor system in synovial tissue and fluid in patients with osteoarthritis and rheumatoid arthritis. Arthritis Res Ther 2008;10:R43.
25. McDougall JJ, Bray RC, Sharkey KA. Morphological and immunohistochemical examination of nerves in normal and injured collateral ligaments of rat, rabbit, and human knee joints. Anat Rec 1997;248:29–39.
26. McDougall JJ, Yeung G, Leonard CA, Bray RC. A role for calcitonin gene-related peptide in rabbit knee joint ligament healing. Can J Physiol Pharmacol 2000;78:535–40.
27. Wotherspoon G, Fox A, McIntyre P, Colley S, Bevan S, Winter J. Peripheral nerve injury induces cannabinoid receptor 2 protein expression in rat sensory neurons. Neuroscience 2005;135:235–45.
28. Siegling A, Hofmann HA, Denzer D, Mauler F, De Vry J. Cannabinoid CB_1 receptor upregulation in a rat model of chronic neuropathic pain. Eur J Pharmacol 2001;415:R5–7.
29. Lim G, Sung B, Ji RR, Mao J. Upregulation of spinal cannabinoid-1-receptors following nerve injury enhances the effects of Win 55,212-2 on neuropathic pain behaviors in rats. Pain 2003;105: 275–83.
30. Scott DA, Wright CE, Angus JA. Evidence that CB-1 and CB-2 cannabinoid receptors mediate antinociception in neuropathic pain in the rat. Pain 2004;109:124–31.
31. Herzberg U, Eliav E, Bennett GJ, Kopin IJ. The analgesic effects of R^+-WIN 55,212-2 mesylate, a high affinity cannabinoid agonist, in a rat model of neuropathic pain. Neurosci Lett 1997;221: 157–60.
32. Bridges D, Ahmad K, Rice AS. The synthetic cannabinoid WIN55,212-2 attenuates hyperalgesia and allodynia in a rat model of neuropathic pain. Br J Pharmacol 2001;133:586–94.
33. Ulugol A, Karadag HC, Ipci Y, Tamer M, Dokmeci I. The effect of WIN 55,212-2, a cannabinoid agonist, on tactile allodynia in diabetic rats. Neurosci Lett 2004;371:167–70.
34. Dogrul A, Gul H, Yildiz O, Bilgin F, Guzeldemir ME. Cannabinoids blocks tactile allodynia in diabetic mice without attenuation of its antinociceptive effect. Neurosci Lett 2004;368:82–6.
35. Castane A, Celerier E, Martin M, Ledent C, Parmentier M, Maldonado R, et al. Development and expression of neuropathic pain in CB1 knockout mice. Neuropharmacology 2006;50:111–22.
36. Agarwal N, Pacher P, Tegeder I, Amaya F, Constantin CE, Brenner GJ, et al. Cannabinoids mediate analgesia largely via peripheral type 1 cannabinoid receptors in nociceptors. Nat Neurosci 2007;10:870–9.
37. Rieder SA, Chauhan A, Singh U, Nagarkatti M, Nagarkatti P. Cannabinoid-induced apoptosis in immune cells as a pathway to immunosuppression. Immunobiology 2010;215:598–605.
38. Klein TW, Newton CA, Friedman H. Cannabinoids and the immune system. Pain Res Manag 2001;6:95–101.
39. Bidinger B, Torres R, Rossetti RG, Brown L, Beltre R, Burstein S, et al. Ajulemic acid, a nonpsychoactive cannabinoid acid, induces apoptosis in human T lymphocytes. Clin Immunol 2003;108: 95–102.
40. Zuardi AW. Cannabidiol: from an inactive cannabinoid to a drug with wide spectrum of action. Rev Bras Psiquiatr 2008;30:271–80.
41. Weiss L, Zeira M, Reich S, Har-Noy M, Mechoulam R, Slavin S, et al. Cannabidiol lowers incidence of diabetes in non-obese diabetic mice. Autoimmunity 2006;39:143–51.
42. Malfait AM, Gallily R, Sumariwalla PF, Malik AS, Andreakos E, Mechoulam R, et al. The nonpsychoactive cannabis constituent cannabidiol is an oral anti-arthritic therapeutic in murine collagen-induced arthritis. Proc Natl Acad Sci U S A 2000;97:9561–6.
43. Marquart S, Zerr P, Akhmetshina A, Palumbo K, Reich N, Tomcik M, et al. Inactivation of the cannabinoid receptor CB1 prevents leukocyte infiltration and experimental fibrosis. Arthritis Rheum 2010;62:3467–76.
44. Idris AI, Ralston SH. Cannabinoids and bone: friend or foe? Calcif Tissue Int 2010;87:285–97.
45. George KL, Saltman LH, Stein GS, Lian JB, Zurier RB. Ajulemic acid, a nonpsychoactive cannabinoid acid, suppresses osteoclastogenesis in mononuclear precursor cells and induces apoptosis in mature osteoclast-like cells. J Cell Physiol 2008;214:714–20.
46. Schierenbeck T, Riemann D, Berger M, Hornyak M. Effect of illicit recreational drugs upon sleep: cocaine, ecstasy and marijuana. Sleep Med Rev 2008;12:381–9.
47. Bolla KI, Lesage SR, Gamaldo CE, Neubauer DN, Funderburk FR, Cadet JL, et al. Sleep disturbance in heavy marijuana users. Sleep 2008;31:901–8.
48. Russo EB, Guy GW, Robson PJ. Cannabis, pain, and sleep: lessons from therapeutic clinical trials of Sativex, a cannabis-based medicine. Chem Biodivers 2007;4:1729–43.
49. Russo E, Guy GW. A tale of two cannabinoids: the therapeutic rationale for combining tetrahydrocannabinol and cannabidiol. Med Hypotheses 2006;66:234–46.
50. Pugh G Jr, Smith PB, Dombrowski DS, Welch SP. The role of endogenous opioids in enhancing the antinociception produced by the combination of Δ9-tetrahydrocannabinol and morphine in the spinal cord. J Pharmacol Exp Ther 1996;279:608–16.
51. Rios C, Gomes I, Devi LA. μ opioid and CB1 cannabinoid receptor interactions: reciprocal inhibition of receptor signaling and neuritogenesis. Br J Pharmacol 2006;148:387–95.
52. Ruggieri V, Vitale G, Filaferro M, Frigeri C, Pini LA, Sandrini M. The antinociceptive effect of acetylsalicylic acid is differently affected by a CB_1 agonist or antagonist and involves the serotonergic system in rats. Life Sci 2010;86:510–7.
53. Anikwue R, Huffman JW, Martin ZL, Welch SP. Decrease in efficacy and potency of nonsteroidal anti-inflammatory drugs by chronic Δ^9-tetrahydrocannabinol administration. J Pharmacol Exp Ther 2002;303:340–6.
54. Ware MA, Gamsa A, Persson J, Fitzcharles MA. Cannabis for chronic pain: case series and implications for clinicians. Pain Res Manag 2002;7:95–9.
55. Blake DR, Robson P, Ho M, Jubb RW, McCabe CS. Preliminary assessment of the efficacy, tolerability and safety of a cannabis-based medicine (Sativex) in the treatment of pain caused by rheumatoid arthritis. Rheumatology (Oxford) 2006;45:50–2.
56. Ware MA, Fitzcharles MA, Joseph L, Shir Y. The effects of nabilone on sleep in fibromyalgia: results of a randomized controlled trial. Anesth Analg 2010;110:604–10.
57. Skrabek RQ, Galimova L, Ethans K, Perry D. Nabilone for the treatment of pain in fibromyalgia. J Pain 2008;9:164–73.
58. Aggarwal SK, Carter GT, Sullivan MD, ZumBrunnen C, Morrill

R, Mayer JD. Characteristics of patients with chronic pain accessing treatment with medical cannabis in Washington State. J Opioid Manag 2009;5:257–86.
59. Lynch ME, Campbell F. Cannabinoids for treatment of chronic non-cancer pain: a systematic review of randomized trials. Br J Clin Pharmacol 2011;72:735–44.
60. Schley M, Legler A, Skopp G, Schmelz M, Konrad C, Rukwied R. Delta-9-THC based monotherapy in fibromyalgia patients on experimentally induced pain, axon reflex flare, and pain relief. Curr Med Res Opin 2006;22:1269–76.
61. Martin-Sanchez E, Furukawa TA, Taylor J, Martin JL. Systematic review and meta-analysis of cannabis treatment for chronic pain. Pain Med 2009;10:1353–68.
62. Fiz J, Duran M, Capella D, Carbonell J, Farre M. Cannabis use in patients with fibromyalgia: effect on symptoms relief and health-related quality of life. PLoS One 2011;6:e18440.
63. Wang T, Collet JP, Shapiro S, Ware MA. Adverse effects of medical cannabinoids: a systematic review. CMAJ 2008;178: 1669–78.
64. Kalant H. Adverse effects of cannabis on health: an update of the literature since 1996. Prog Neuropsychopharmacol Biol Psychiatry 2004;28:849–63.
65. Zammit S, Allebeck P, Andreasson S, Lundberg I, Lewis G. Self reported cannabis use as a risk factor for schizophrenia in Swedish conscripts of 1969: historical cohort study [published errata appears in BMJ 2002;325:435.1]. BMJ 2002;325:1199.
66. Nordstrom BR, Levin FR. Treatment of cannabis use disorders: a review of the literature. Am J Addict 2007;16:331–42.
67. Budney AJ, Moore BA, Vandrey RG, Hughes JR. The time course and significance of cannabis withdrawal. J Abnorm Psychol 2003; 112:393–402.
68. Schoedel KA, Chen N, Hillard A, White L, Stott C, Russo E, et al. A randomized, double-blind, placebo-controlled, crossover study to evaluate the subjective abuse potential and cognitive effects of nabixomol oromucosal spray in subjects with a history of recreational cannabis use. Hum Psychopharmacol 2011;26:224–36.
69. Fishbain DA, Cutler RB, Rosomoff HL, Rosomoff RS. Validity of self-reported drug use in chronic pain patients. Clin J Pain 1999;15:184–91.
70. Fleming MF, Balousek SL, Klessig CL, Mundt MP, Brown DD. Substance use disorders in a primary care sample receiving daily opioid therapy. J Pain 2007;8:573–82.
71. Taylor DR, Fergusson DM, Milne BJ, Horwood LJ, Moffitt TE, Sears MR, et al. A longitudinal study of the effects of tobacco and cannabis exposure on lung function in young adults. Addiction 2002;97:1055–61.
72. Tashkin DP, Shapiro BJ, Lee YE, Harper CE. Subacute effects of heavy marihuana smoking on pulmonary function in healthy men. N Engl J Med 1976;294:125–9.
73. Thomson WM, Poulton R, Broadbent JM, Moffitt TE, Caspi A, Beck JD, et al. Cannabis smoking and periodontal disease among young adults. JAMA 2008;299:525–31.
74. Zhang ZF, Morgenstern H, Spitz MR, Tashkin DP, Yu GP, Marshall JR, et al. Marijuana use and increased risk of squamous cell carcinoma of the head and neck. Cancer Epidemiol Biomarkers Prev 1999;8:1071–8.