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Cannabinoids in the Management of Musculoskeletal or Rheumatic Diseases

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Abstract The endocannabinoid system impacts pain and inflammation with potential for therapeutic effect on patients with rheumatic diseases. The current treatment options include the herbal product derived from the plant *Cannabis sativa*, as well as pharmaceutical preparations. The legalization of medicinal cannabis (marijuana) in many jurisdictions and widespread public advocacy has propelled an interest in use either by prescription or self-medication. In this review, we examine current evidence for efficacy and adverse effects of any cannabinoid product in rheumatic conditions. The evidence to date is scant and precludes making recommendations for the use of cannabinoid preparations in rheumatology patients. In particular, the risks of herbal cannabis in patients are not well defined. Anecdote and advocacy cannot supersede sound evidence.

Keywords Cannabinoids · Rheumatic disease · Marijuana

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Purpose of Review

Chronic pain is a common symptom in rheumatic conditions. Although acute pain is a necessary protective physiological process, ongoing chronic pain is detrimental to wellbeing. Current chronic pain management strategies are imperfect, prompting a search for more effective treatments to fill this gap. In the absence of cure for any rheumatic disease at this time, pain management must be an integral part of rheumatology care. Furthermore, the changing legal climate regarding marijuana use for medical indications {http://www.ncsl.org/research/health/state-medical-marijuana-laws.aspx} has turned a spotlight on the potential for marijuana use for a host of conditions, including epilepsy, multiple sclerosis, post-traumatic stress disorder and cancer, in addition to disorders causing chronic pain. For this reason, the current interest in the therapeutic potential of cannabinoid molecules has reached celebrity status, catapulted by advocacy and legalization of marijuana, derived from the flax plant *C. sativa*. The endocannabinoid system is recognized as an important modulator of the stress response, including potential for analgesic effects, promoting study to utilize the system for therapeutic effects.

The medicinal and psychoactive properties of *C. sativa* have been known for thousands of years. Symptom relief attributed to herbal cannabis has been claimed for ailments ranging from pain to gastrointestinal, neurological and mood disorders [1, 2]. Musculoskeletal pain is one of the most common reasons for the use, cited by 30–80% persons using herbal cannabis for therapeutic reasons. “Severe arthritis” is cited as a diagnosis for 66% of Canadians with authorization from Health Canada to possess medicinal herbal cannabis [3–6]. Familiarity with marijuana as a recreational drug and recent legalization of marijuana as a recreational product in some jurisdictions, and a medicinal product in many more, has

prompted patients to experiment with self-medication. In this review, we will address the current knowledge and status of cannabinoids with particular attention to the evidence for herbal cannabis as a therapeutic option for rheumatology patients.

Recent Findings from Basic Science

The Function of the Endocannabinoid System

The human organism is protected from physical or emotional harm (stressful events) by a complex and coordinated stress response system, initiated by an immediate autonomic response mediated via the sympathetic nervous system, and followed by a neuroendocrine response mediated by the hypothalamic-pituitary-adrenal axis [7]. This stress response or "fight of flight" has need to be restored to equilibrium, with the endocannabinoid system playing a significant role by increasing levels of cerebral endocannabinoid ligands that contribute to termination of the stress response [8, 9]. This return to homeostasis has potential to be harnessed as a therapy to improve sleep and appetite, and also to reduce pain and inflammation. Found throughout the mammalian kingdom, this system comprises numerous ligands and at least two receptors. The name "cannabinoid" was originally coined as delta-9 tetrahydrocannabinol (Δ^9-THC), a molecule of *C. sativa*, was observed to mediate signalling via receptors. Following cloning of the cannabinoid receptor genes, endogenous molecules termed endocannabinoids were identified as ligands for these receptors with mostly agonistic function and with pertinence to musculoskeletal complaints [10, 11].

Endocannabinoid Receptors

Cannabinoid receptors are found throughout the organism, with important concentrations present in nervous tissue, immunological cells and bone and joint tissue. There are currently two identified cannabinoid receptors (CB_1 and CB_2), and likely a third, GPR55. These receptors function through G-proteins with effect on the mitogen-activated protein (MAP) kinase pathway and inhibition of adenylyl cyclase activity, activation of potassium channels, and inhibition of voltage-gated sodium channels resulting in suppression of neurotransmitter release at the neuronal synapse [12, 13]. CB_1 receptors, most abundantly expressed not only on GABAergic and glutamatergic nerve terminals but also with effect on serotoninergic, noradrenergic and dopaminergic terminals in the central and peripheral nervous system, have predominantly inhibitory effects [8]. The brain areas that are involved in motor control, memory and cognition are rich in CB_1 receptors. In contrast, CB_2 receptors are mostly located peripherally on immunologic cells and various musculoskeletal cells. The exact function of CB_2 receptors is largely unknown [14••]. The endocannabinoid system involves complex interactions between various ligands, cross reaction with non-cannabinoid receptors and plasticity of response dependent upon local tissue characteristics or the presence of other molecules, such as opioids [15].

Cannabinoid Ligands

Molecules affecting cannabinoid or related receptors are found in three settings: endogenous ligands or endocannabinoids that belong to the class of lipid mediators termed eicosanoids (arachidonic acid derivatives); exogenous plant-derived phytocannabinoids; and synthetic tricyclic terpenes [1, 10].

Endocannabinoids are produced in the postsynaptic membrane "on demand" in response to a stress event. This production of ligand by breakdown of phospholipids, a component of cell membranes, results in a retrograde feedback loop to the pre-synaptic membrane to suppress neurotransmitter release. It is notable that the well-recognized inflammatory prostaglandin pathway also originates with the breakdown of cell membrane phospholipids, but follows an alternate degradation route Fig. 1 [13]. A number of endocannabinoid ligands have been identified, with anandamide and 2-arachidonylglycerol the most commonly studied [10]. The half-life of endocannabinoids is extremely short, with rapid breakdown by endogenous enzyme systems and metabolism of cannabinoids via liver cytochrome P450 (CYP) enzymes and subsequent biliary and intestinal excretion [1]. As cannabinoids are lipophilic, they may remain in lipid tissues for long time periods. Cannabinoid tolerance can occur at the receptor level via receptor internalization or degradation, reduced signalling or reduced protein synthesis.

Plant-derived cannabinoids, the phytocannabinoids, are found in various concentrations in the plant *C. sativa*, which contains over 500 compounds, of which over 100 are

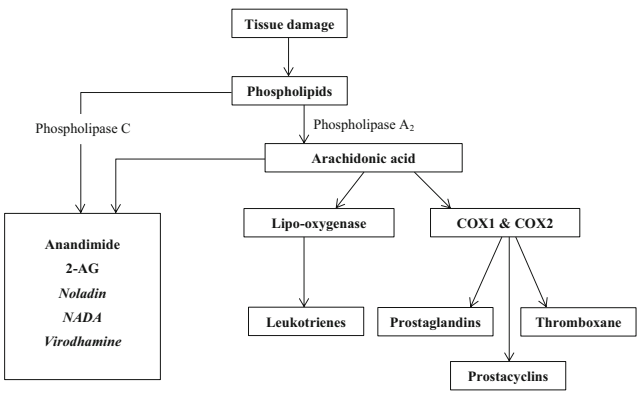

Fig. 1 The ying and yang of phospholipid breakdown: endocannabinoids and proinflammatory molecules

cannabinoids [16••]. The two best studied molecules are Δ^9-THC and cannabidiol (CBD), both found in the leaves and flowers of *C. sativa*, with concentrations varying between strains. Analgesic and psychoactive effects are mainly attributed to Δ^9-THC, whereas CBD, which has less affinity for cannabinoid receptors, has immunologic functions via effect on the transient receptor potential vanilloid channel-1 (TRPV-1) and 5-HT_{1A} receptors, the latter also engaged by endocannabinoids [12]. The various effects of CBD include antioxidant properties and possibly reduction in addictive behaviours in view of ability to modulate neuronal circuits involved in drug addiction [17, 18]. Medicinal herbal cannabis (marijuana), the dried leaves and flowers of *C. sativa* is currently widely advocated as therapy for many ailments and is legal for personal use in Canada and in more than 25 US states, but mostly with limitations for quantity in possession [19].

The third group of cannabinoid ligands are those available as pharmaceutical preparations, including synthesized analogues of THC. These preparations have the advantage of delivery of a defined, predictable amount of drug compared to the variable composition of naturally occurring products. Three pharmaceutical products are currently available: dronabinol, a stereoisomer of THC; nabilone, a synthetic analogue of THC and the oromucosal nabiximols spray, a combination of Δ^9-THC and CBD. Dronabinol and nabilone have US Federal Drug Administration (FDA) approval for the treatment of chemotherapy-induced nausea but not for pain relief. In other countries, e.g. Israel and Canada, pharmaceutical cannabinoid preparations have additional indications for cancer pain relief, with Israel also allowing use for pain and spasticity of multiple sclerosis, whereas Canada has a more liberal indication for neuropathic pain and nausea related to human immunodeficiency disease. Therefore, pharmaceutical manipulation of this system holds potential for numerous as yet unexplored conditions including modulation of appetite, mental health disorders, specific neurological disorders and importantly effect on musculoskeletal health [20].

Methods of Administration of Herbal Cannabis

Although cannabis is most commonly smoked as a "joint" weighing 0.5–1 g of dried product, smoking is not recommended by respirologists in view of contamination with toxic hydrocarbons, tar and carbon monoxide [21]. The reason for smoking cannabis is that heating is required to convert the acid precursor to the active molecule THC. Vaporization with less heating is possibly safer, with less production of toxic hydrocarbons. The plasma concentration achieved by smoking cannabis can be extremely variable and is dependent on the concentration of THC in the herbal product as well as the method of smoking (frequency and depth of inhalation, holding time and inhalation volume) [21, 22]. Even when medicinal herbal cannabis is available, patients still mostly access cannabis "on the street", with concentrations of THC in illicit marijuana having progressively increased worldwide [23]. With multiple factors influencing the bioavailability of THC, estimation of dosing of the herbal product is imprecise [24]. Although peak plasma level of THC is attained within a few minutes of inhalation, there is a time lag for effects on pain and cognition [25]. In contrast, the oral administration of cannabis has a delayed onset of effect with lower peak plasma levels and more protracted pharmacologic effects, but with erratic gastrointestinal absorption and first-pass liver metabolism [25]. This more delayed effect related to oral administration may also be a factor in harmful delayed psychoactive effects [21]. Therefore, the ideal route of administration for herbal cannabis remains controversial.

Adverse Effects of Cannabinoids

1. Psychomotor effects

   Cannabinoids have immediate psychomotor effects that may persist for up to 5 h after consumption and with increased effects for increased doses, with reduced reaction time, difficulty with selective attention, and impairment of short-term memory and motor control [26]. The effect on cognition may however persist for days following use with impact on learning and retention of new information. In line with acute psychomotor effects, acute cannabis consumption is a risk for motor vehicle accidents, with risk doubled for serious injury or fatality following acute cannabis use according to a meta-analysis of nine studies with report of 49,000 subjects [27•]. Cannabis is also the most frequently identified illicit drug, found in 0.5 to 7.6% of seriously injured drivers, in a survey carried out six European countries [28]. Patients should be warned that driving ability or activities requiring alertness or coordination may be impaired for up to 24 h following consumption of herbal cannabis [29]. This safety risk may be further compounded in the presence of other medications with psychoactive properties.
2. Cardiovascular effects

   The acute cardiovascular effects of tachycardia and hypotension could compromise cardiovascular status in those with underlying heart disease and be a risk for cardiovascular events [30]. Acute cannabis use was suggested to have a temporal relationship to an increased risk of myocardial infarction and to reduce the exercise capacity of those with angina pectoris [31]. The French AddictoVigilance Network identified 35 vascular events spontaneously reported between 2006 and 2010 attributable to cannabis use, with 26% resulting in death [32]. Although these numbers are small, this report highlights

the poorly recognized risk of cardiovascular events associated with cannabis use.

3. Respiratory effects

   Smoking of cannabis remains the most common method of administration. Inhaled cannabis is a respiratory irritant causing chronic respiratory disease that is additive with cigarette smoking, with reduced expiratory flow rates related to the quantity of cannabis use in early adult life [33]. Evidence for risk for lung cancer has been debated especially due to confounding for cigarette smoking [33–35]. A recent pooled analysis of over 2000 lung cancer cases showed an overall OR for all lung cancers for habitual versus non-habitual or never users as 0.96 (95% CI 0.66–1.38), and an OR of 1.73 (95% CI 0.75–4.00) for adenocarcinoma [36]. The use of cannabis on at least 50 occasions doubled the risk for lung cancer over a 40-year period for Swedish military conscripts aged between 18 and 20 years at study onset (hazard ratio 2.12, 95% CI 1.08–4.14) [35]. This increased risk persisted when controlled for tobacco and alcohol use and socioeconomic status.

4. Psychological and mental health effects

   The acute psychological and psychiatric effects of cannabis may vary amongst individuals, and can be influenced by the specific compound. Although generally causing relaxation for most, some may develop euphoria or anxiety, have lapses in judgement and experience acute withdrawal effects. Paranoia or psychosis is especially related to the higher concentration of THC in some strains of herbal cannabis. Immediate psychiatric effects include acute anxiety and agitation, suicidal ideation and acute psychosis [37, 38].

The long-term effects on mood are less clear, but with indications that depression is more prevalent in current cannabis users [38, 39]. Chronic cannabis use is associated with 1.4 times higher odds for depression for 8000 US adults, although causality is not established [39]. Evidence reviewed here suggests that cannabis does not in itself causes psychosis, but rather that both early and heavy use of cannabis are more likely in individuals with a vulnerability to psychosis [40]. In those with a current diagnosis of schizophrenia, cannabis was associated with increased symptoms of mental disturbance [41]. Withdrawal and dependence related to cannabis have been demonstrated in animal studies and are emerging as identifiable risks in humans [42–44]. Withdrawal signs include the physical effect of weight loss and the psychological effects of cravings, anger, aggression, sleep disturbance, hunger, tremors, restlessness and irritability [45].

Cannabis is associated with dependence, defined as a physiological response resulting in withdrawal symptoms when a drug is discontinued, and addiction defined as continued and uncontrolled use of a substance despite negative health and psychosocial consequences. This is especially true in the context of an adverse psychosocial setting and is mediated via the rewarding effects of CB_1 receptors, and dopamine release in the mesolymbic-dopamine reward pathway [44]. Over a 3-year period, the cumulative incidence of cannabis dependence was 37.2% (95% CI 30.7–43.8%) for young recreational users [46•]. Nine percent of all users develop dependence, with this number increasing to 17% for onset of use in adolescence, and climbing to between 25 and 50% for the daily users [47, 48]. In a study using high-resolution MRI brain scans, marijuana use at least once a week by young people was associated with structural changes that included increased gray matter density, increased volume and shape differences in mostly the left nucleus accumbens, a key region involved in addiction, even when controlled for age, sex, alcohol and cigarette use [49•].

Studies of the Physiological Cannabinoid Effects Pertaining to Rheumatic Diseases

Endocannabinoids are present in human OA and IA joints, but not normal controls, suggesting synthesis following tissue injury or inflammation [50]. This on-demand synthesis is analogous to the upregulation of the endogenous opioid system in the setting of inflammation [51]. Joints affected by inflammatory arthritis (IA) and osteoarthritis (OA) express cannabinoid receptors in the synovium and have endocannabinoids in the synovial fluid, in contrast to normal volunteers [50]. In a Wistar rat model, with OA induced by intraarticular knee injection of sodium monoiodoacetate, manipulation of the CB_1 receptor, either activation or blockade, affected nociceptive transmission in the primary afferent nerve, with a more pronounced effect in the OA affected joints compared to saline controls [52]. These findings suggest that cannabinoid activity is generally upregulated in this animal model of OA. In a murine model of collagen-induced arthritis, administration of a CB_2 receptor agonist attenuated the inflammatory response and decreased joint destruction, holding potential for impacting synovitis in IA [53]. The complexity of the endocannabinoid system has been demonstrated by a paradoxical response when an agonist to the CB_2 receptor caused inhibition of nociceptor activity in control joints, but sensitization of OA joint afferents in the Wistar rat OA model [54]. Less is known about the immunological effects of the cannabinoid system mediated via the CB_2 receptor with postulated effects that include modulation of apoptosis, inflammatory cell proliferation and trafficking, cytokine production and regulation of T cells [55].

Recent Findings Regarding Cannabinoid Treatments in Rheumatic Diseases

The evidence for use of any cannabinoid in rheumatic diseases is sparse. Barriers to research have included the lack of

availability of legally registered marijuana manufacturers able to provide researchers with marijuana for research purposes. It was not until August 11, 2016, that the US Drug Enforcement Agency announced that it would expand the number of registered facilities beyond the single current location at the University of Mississippi {https://www.dea.gov/divisions/hq/2016/hq081116.shtml}. However, marijuana remains classified by DEA as a schedule I drug under the Controlled Substance Act, the most restricted class of pharmaceuticals which also includes heroin and LSD.

Authors of three recent systematic reviews concluded that current evidence is insufficient to allow for recommendation for any cannabinoid preparation for rheumatology patients [56, 57, 58••]. The cannabinoids tested were nabilone (two studies with fibromyalgia (FM), one study with spinal pain), an oromucosal spray with THC/CBD, nabiximols (one study with rheumatoid arthritis (RA)) and a fatty acid amide hydrolase (FAAH) inhibitor (one study with OA).

In the first review of four short-term studies comprising 203 patients (58 RA, 71 FM and 74 OA), cannabinoids had a statistically significant effect on pain in two, sleep in two, and improved health-related quality of life [HRQoL) in one, with the OA study terminated due to futility [56, 59–62]. For the study of nabiximols in 58 RA patients with study duration of 5 weeks, a nonstandard primary outcome measurement of improved morning pain on movement was used, but measurement of pain intensity was unchanged [59]. Similarly, the clinically meaningful effect for nabilone on the two studies of 71 FM patients, with study duration of 6 and 8 weeks, is debatable [60, 61]. Although reported as significant, a 1.43-cm change in pain from baseline (on the 10-cm visual analogue scale) and a 10.76 point change for the fibromyalgia impact questionnaire (FIQ), are of questionable clinical effect [60]. The second review included an additional study of nabilone in 30 patients with spinal pain, conducted in a single center in Austria, with a cross-over design of 4 weeks for each treatment period and a 5-week washout period, with similar findings of high risk for bias and inconsistent findings of superiority of cannabinoids over controls [57]. The third review analysed the two trials with nabilone in FM and concluded that there is no convincing, unbiased, high-quality evidence that nabilone is of value in treating people with FM, with low-tolerability noted. Very low quality evidence indicated better effects of nabilone on sleep compared to amitriptyline, but without significant differences between the two drugs for pain, mood and HRQoL [58••]. The systematic searches failed to find any RCT of dronabinol or medical cannabis in rheumatic diseases. Considerable limitations for these studies included small sample size, short study duration, heterogeneous medical conditions and products and absence of any study of herbal cannabis.

On closer scrutiny of the reported rheumatic disease studies, the marginal positive effects of cannabinoids could mostly be outweighed by adverse events. Adverse events related to cannabinoid treatments were common, but although not serious, were sufficiently troubling to impact wellbeing. At least, a third of subjects reported side effects with not only quasi-neurological effects of dizziness, drowsiness and effect on cognition most common but also gastrointestinal effects of dry mouth, nausea and constipation. The frequency of side effects prompted Skrabek et al. to suggest that a gradual introduction and titration of nabilone should be considered for future studies [60]. In the studies of nabilone, more participants dropped out due to adverse events in the active versus the control groups [58••]. Therefore, the evidence for effects of cannabinoids in rheumatic diseases is currently so poor that physicians will have to look to studies in other conditions to glean some information in order to counsel patients.

Another systematic review and meta-analysis of cannabis and cannabinoid drugs examined in various conditions, including eight chronic pain trials of which three were for rheumatic pain (2 FM, 1 RA), concluded that most studies showed improvement in symptoms, but with no evidence on the effects of marijuana (herbal cannabis) in rheumatic pain [63•]. No long-term studies were identified, even when searches were extended to lower levels of evidence. In an accompanying editorial titled “Medical Marijuana. Is the Cart before the Horse?”, D’Souza and Ranganathan have cautioned against widespread use of medical marijuana until high-quality evidence is available to guide the healthcare community, especially as marijuana is not a life-saving intervention [64••]. In a study designed specifically to examine adverse events related to cannabis use for 431 patients with chronic non-cancer pain, medical cannabis users were at increased risk of non-serious adverse events (adjusted incidence ratio = 1.72, 95% CI = 1.42–2.13), leading the authors to conclude that quality-controlled herbal cannabis, when used by patients with experience of cannabis use, appears to have a reasonable safety profile [65]. The rate of serious adverse events (SAEs) for both groups was extremely high and recorded as 22.6 vs. 27.45 events/100 patient years for the cannabis vs. control group. With more than half patients in each group receiving opioid therapy, this high rate of SAEs confirms the known risks of opioid therapy and places medicinal cannabis risk equivalent to opioids.

For these reasons, there is currently insufficient evidence to recommend cannabinoid treatments and medicinal herbal cannabis, in particular for rheumatic conditions [66].

The Current Reality and Future of Cannabinoid Use in Rheumatic Diseases

Boyed by the legalization of herbal cannabis for both recreational as well as medicinal use in many jurisdictions worldwide, healthcare professionals must be knowledgeable of risks associated with use in order to effectively advise patients for

the protection of the individual and society. Legalization of a product projects an image of safety but with increasing concerns that herbal cannabis is not innocuous. This is especially true as producers (even those for medicinal use) are cultivating strains of *C. sativa* with progressively increased concentrations of the psychoactive molecule Δ^9-THC. Furthermore, public advocacy and financial incentives will continue to propel use by patients in a runaway train mode, with physicians required to function more as health educators, rather than as effective prescribers. The risks associated with use can be categorized as the immediate effects on cognition, psychomotor function, cardiovascular system and mood, and the consequences of chronic use on mental ability, pulmonary function, cancer risk and drug dependence [67]. Interactions of cannabinoids with other medications that are being used therapeutically are also mostly unknown.

The Societal Perspective

Acceptance of herbal cannabis as a recreational product has fostered a perception of safety, and physicians will be providing care for patients who may be self-medicating with herbal cannabis or may request medical guidance regarding potential use of this agent. In this context, it is of great concern that physicians generally lack confidence in their knowledge of cannabinoids and in their competence to effectively advise patients on the use of medicinal cannabinoids [68•, 69]. In a survey of family physicians in Colorado, only 19% thought that physicians should recommend medical marijuana, with 92% reporting need for more education [68•]. Similarly, two thirds of Canadian rheumatologists expressed poor confidence in their knowledge of cannabinoid medical use, with 70% stating that there is currently no role for herbal cannabis in the treatment of rheumatic complaints [69]. The sanctioning use of herbal cannabis for therapeutic reasons is currently provided by a small numbers of physicians for the majority of patients [68•].

As different jurisdictions worldwide have unique laws governing cannabis use for either recreational or medical purposes, patients and physicians must to be knowledgeable of current regulations that apply, particularly regarding possession, safety when driving and in the workplace and differing regulations in case of travel. There is also a risk for potential litigation in the setting of an adverse event following prescription of medicinal marijuana, as cannabis is not an approved therapy by drug regulatory authorities and physicians will be held accountable for their actions.

Guidance for the Rheumatologist Regarding Medicinal Cannabis Use

An informed and empathetic care requires knowledge of the best available evidence, an objective to reduce symptoms and maintain function, while ensuring that the individual and society are protected from harm. The clinical encounter with a patient requesting information about medicinal cannabis should be conducted without personal bias and should provide the patient with up to date information on known benefits and risks, while maintaining a good therapeutic alliance [70]. The patient should be informed that the endocannabinoid system is an important player in human health and that there is active ongoing research in this field. Furthermore, available non-pharmacologic and pharmacologic strategies to treat rheumatic pain should be explored, and a pharmaceutical cannabinoid preparation should be tried prior to recommendation for the use of herbal cannabis. There should be a clear statement that any cannabinoid treatment for rheumatic disease symptoms constitutes off-label use. Finally, a prescribing physician must have a bona fide relationship with the patient, with existing mutual trust that might extend to a signed informed consent document. A checklist to facilitate decision making is shown in Table 1.

The College of Family Physicians of Canada (CFPC) published preliminary guidance on authorizing dried cannabis for chronic pain or anxiety in 2014 [71]. Amongst the CFPC's recommendations are the following: authorizations should only be considered for patients with neuropathic pain with failed response to standard treatments and not as a therapy for anxiety or insomnia; monitoring for misuse or abuse should occur; communication with responsible health providers should occur regularly; the recommended inhaled dose of dried cannabis should be in the range of 100–700 mg a day with THC content not exceeding 9% and physicians should follow the regulations of their provincial medical regulators. To date, no other professional organization worldwide has published guidelines for the use of medical marijuana, although 25 states and the District of Columbia have approved and currently

Table 1 Key steps in clinical assessment regarding medical cannabis use

Comprehensive clinical assessment
Current and past medical history
Current and past mental health history
Psychosocial and work history
Specific questions
Which specific symptoms require treatment
Previous treatment trials
Current use opioids or other psychoactive medications
Recreational cannabis use, current or past
Substance abuse, current or past
Family history of mental health disorder.
Previous encounter with the law, particularly regarding cannabis
Assessment of addiction risk
Goals for treatment and expectation of outcome, including work status

regulate its medical use, with specific requirements pertaining to individual states.

Conclusion

While for some conditions, cannabinoids have been shown to be effective, with best evidence for spasticity in multiple sclerosis, high-quality evidence for the effect of any cannabinoid preparation for rheumatic diseases is lacking. With patients currently self-medicating with cannabis, and numbers likely to increase, a sound knowledge of cannabinoids pertaining to health and disease is imperative. Familiarity with recreational cannabis and the prevalent public perception of safety of the herbal product likely contributes to prevalent use, but absence of evidence precludes any recommendation for routine use in rheumatology care. With the knowledge that the endocannabinoid system plays an important role in health, we hope that pharmacologic manipulation of the endocannabinoid system will be further explored and strongly recommend further research of cannabinoids in general.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published and were in compliance with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

This article does not contain any studies with human or animal subjects performed by any of the authors.

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