

Position Statement: A Pragmatic Approach for Medical Cannabis and Patients with Rheumatic Diseases

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ABSTRACT. Objective. Pain is one reason some rheumatology patients may consider use of medical cannabis, a product increasingly perceived as a safe and neglected natural treatment option for many conditions. Legalization of recreational cannabis in Canada will promote access to cannabis. Physicians must therefore provide patients with the best evidence-based information regarding the medicinal effects and harm of cannabis.

Methods. The Canadian Rheumatology Association (CRA) mandated the development of a position statement for medical cannabis and the rheumatology patient. The current literature regarding the effects of medical cannabis for rheumatology patients was assessed, and a pragmatic position statement to facilitate patient care was developed by the Therapeutics Committee of the CRA and approved by the CRA board.

Results. There are no clinical trials of medical cannabis in rheumatology patients. Evidence is insufficient about the benefit of pharmaceutical cannabinoids in fibromyalgia, osteoarthritis, rheumatoid arthritis, and back pain, but there is evidence of a high risk of harm. Extrapolating from other conditions, medical cannabis may provide some symptom relief for some patients. Short-term risks of psychomotor effects can be anticipated, but longterm risks have not been determined and are of concern.

Conclusion. Despite lack of evidence for use of medical cannabis in rheumatology patients, we acknowledge the need to provide empathetic and pragmatic guidance for patient care. This position statement aims to facilitate the dialogue between patients and healthcare professionals in a mutually respectful manner to ensure harm reduction for patients and society. (J Rheumatol First Release January 15 2019; doi:10.3899/jrheum.181120)

Key Indexing Terms:

RHEUMATIC DISEASE

MEDICAL CANNABIS

Persistent pain may cause some rheumatology patients to explore treatment options outside mainstream medicine. Cannabinoids may hold promise for attenuation of pain and inflammation by modulating the endogenous endocannabinoid system¹. The popularized purported benefits of herbal cannabis for many symptoms have catapulted cannabis into the therapeutic arena. Specifically pertinent to rheumatic diseases is the preclinical evidence for effect of cannabinoids

on immunological mechanisms with potential to modulate inflammation and perhaps function as a disease modifier, but with caution to emphasize that these concepts have not been observed in patient populations².

Herbal cannabis, the best-known natural source of cannabinoids, is a genus of flowering plant in the family of *Cannabaceae*, with the species *Cannabis sativa* most commonly used therapeutically. The leaves and flowers contain many molecules, of which Δ^9 -tetrahydrocannabinol (THC) and cannabidiol (CBD) are the most studied. In addition to THC and CBD, herbal cannabis contains many noncannabinoid molecules, with physiologic effects that are largely unknown. Medical cannabis refers to the whole plant or extract thereof, used for medical purposes as dried flowers and leaves or an oil extract, and may be administered by smoking, inhalation through a vaporizer (heating to lower temperatures than smoking), ingestion, or topical applications. Cannabinoids are also available as pharmaceutical-quality preparations, either as plant extracts with specified doses of THC and CBD, or synthesized products acting on cannabinoid receptors.

Medical cannabis has been legally available to Canadians

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since 2001. There are currently about 250,000 users registered with Health Canada, many of whom have musculoskeletal complaints³. In contrast to this prevalent use, rheumatologists are insecure about many aspects of this treatment strategy. In a recent survey, over 80% of Canadian rheumatologist respondents reported being asked at least weekly about medical cannabis, but three-fourths reported limited confidence in their knowledge of cannabinoids, or their ability to effectively advise patients⁴. The need for practical, patient-centered, evidence-based guidance will increase with the legalization of recreational cannabis. In an effort to reconcile these diverse and conflicting opinions, unbiased and empathetic guidance is urgently required.

MATERIALS AND METHODS

This position statement was developed to provide information and practical guidance for Canadian rheumatologists regarding medical cannabis in rheumatology practice, and does not cover pharmaceutical cannabinoid preparations. The target audience is rheumatologists, who will be required to respond to patient requests for advice regarding medical cannabis and to care for patients who may be self-medicating, or who may choose to formally prescribe medical cannabis.

This document was developed by the Therapeutics Committee and the Canadian Rheumatology Association (CRA). According to CRA policies, position statements are designed as an immediate response to an emerging or controversial topic, adhering to the standards of evidence-based literature to support statements⁵.

The relevant literature was reviewed with special attention to the position paper by the European Pain Federation, as well as a recent clinical practice guideline published for Canadian family physicians^{6,7}. This latter guideline assessed use of all cannabinoids for various complaints and appended summaries of provincial regulatory requirements. Using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) methodology, the results of 4 systematic reviews were used to support statements⁸. This guideline was rated as high quality according to the Appraisal of Guidelines Research and Evaluation (AGREE)-II instrument by 2 independent reviewers (GH, MAF). Relevant statements and supporting evidence pertinent to rheumatic diseases from all publications were reviewed, and a draft document was developed by the present authors; this document was circulated to members of the Therapeutics Committee of the CRA as well as an external expert, and was revised in an iterative fashion based on feedback. The final document was reviewed and approved by the CRA board, in accordance with CRA policy.

RESULTS

The recent Canadian guideline for prescribing medical cannabinoids in primary care addressed the use of cannabinoids for pain associated with rheumatologic conditions⁶. There were no randomized trials of medical cannabis in rheumatic diseases^{6,9}. Additionally, there was insufficient evidence for the benefit of pharmaceutical preparations for fibromyalgia, osteoarthritis, rheumatoid arthritis, and back pain, but there was evidence of a high risk of harm^{10,11}. In evaluating the harm of medical cannabis reported for pain in conditions other than rheumatic complaints, there was a high rate of short-term harm, and the amount of longterm harm was unknown. On the basis of the lack of evidence for benefit, and the increased harm, the guideline group made a strong recommendation against cannabinoids in general

(including pharmaceutical preparations) for rheumatic pain. Further, in patients in whom cannabinoids were being considered, there was a strong recommendation against medical cannabis (particularly smoked) over pharmaceutical cannabinoids. There is a high risk of bias in studies of smoked cannabis, with unknown longterm consequences.

DISCUSSION

The reality of medical cannabis use in Canada. In accordance with the lack of evidence for the effect of medical cannabis in rheumatic diseases, the simplistic response, as endorsed by others, is to recommend against use pending more evidence⁶. The reality is that patients are requesting information, may be considering use, or may be currently self-medicating. Physicians may also have personal biases regarding medical cannabis, either positive or negative. Further, the Canadian legalization of recreational cannabis allows freer access to cannabis by patients. Rheumatologists therefore have an obligation to provide competent advice.

Physicians should understand the reason for consideration of medical cannabis: relief of pain, sleep difficulties, or mood disorders; poor effect of current treatments; perception of a natural treatment; and encouragement by friends or family members to use. Another prevailing argument is that medical cannabis is safer than traditional analgesic drugs (i.e., opioids)¹². Almost one-fifth of rheumatology patients are currently using opioids, although not guideline-recommended for rheumatic pain^{13,14}. Considering fatalities associated with opioids and absence of respiratory suppression by cannabinoids, medical cannabis may be a safer choice. Inserted into this context must be the extensive media coverage of medical cannabis, almost always favorable, and the constantly associated anecdotes of outstanding effect. Subtle marketing strategies buoyed by financial interests cannot be sufficiently emphasized. In this highly charged climate, rheumatologists must maintain an empathetic therapeutic relationship with their patients, avoid personal biases, and ensure harm reduction for both patients and society.

Position statement from the CRA for medical cannabis in rheumatology patients. Given the lack of evidence for medical cannabis for rheumatic complaints, but faced with escalating access among patients, the CRA suggests the following overarching principles (Table 1). Patients should be informed that medical cannabis is not an alternative to standard care for any rheumatic disease and that evidence for the effect in rheumatic diseases is lacking. Short-term adverse events including immediate psychomotor effects, dizziness, appetite changes, effect on mood, and the rare serious side effects of disorientation and psychosis are high, and longterm risks are not yet known. Rheumatologists should adhere to current treatment standards and guidelines for rheumatic disease management and should maintain an empathetic therapeutic relationship with their patients, avoid personal biases, and ensure harm reduction for both patients and society.

Table 1. Overarching principles for medical cannabis in rheumatology patients.

1. Medical cannabis is not an alternative to standard care for any rheumatic disease, and rheumatologists should adhere to current treatment standards and guidelines for rheumatic disease management.
2. There are no published studies of the effects of medical cannabis in patients with rheumatic diseases, and the few studies examining cannabinoid pharmaceutical products report limited benefits and high risk of adverse events.
3. Medical cannabis should not be used in rheumatology patients under the age of 25 years.
4. It is acknowledged that rheumatic disease patients may seek advice regarding use of medical cannabis, may currently be self-medicating with medical cannabis, or may request a prescription for medical cannabis.
5. Common reasons that patients may consider use of medical cannabis are for pain relief and/or sleep promotion.
6. Current treatment strategies for pain relief and sleep promotion including non-pharmacologic treatments must be tried before consideration of use of medical cannabis.
7. Medical cannabis may provide symptom relief for some patients with rheumatic diseases.
8. Short-term adverse events (including immediate psychomotor effects, dizziness, appetite changes, and effect on mood, and the rare serious side effects of disorientation and psychosis) are frequent with the use of medical cannabis and are likely to be similar to those reported for other disease populations.
9. The longterm risks associated with medical cannabis use in patients with rheumatic diseases are unknown.
10. Despite a patient's understanding of the lack of any scientific evidence to support a benefit, and the increased risk of harm, some patients may prefer a trial of medical cannabis over other options, including opioids.
11. Rheumatologists must endeavor to maintain an empathetic therapeutic relationship with their patients, avoid personal biases, and ensure harm reduction for both patients and society.
12. There is an urgent need for further research regarding the effects of medical cannabis in rheumatic diseases.

Putting principles into practice. Treatment principles to reduce harm are outlined in Table 2. In line with good medical practice, physicians must adhere to standard of care when prescribing medical cannabis¹⁵. Beginning with a clear understanding of the symptoms requiring treatment, attention should be given to previous treatment trials, including nonpharmacologic measures. Standard therapeutic options should be accessed prior to consideration of medical cannabis.

A prescription should only be provided by a physician who is fully knowledgeable of the patient and is responsible for patient care. Cannabis should not be prescribed following online consultation or by those who project themselves as “cannabis experts” focusing only on prescription of cannabis without attention to global patient care. A formal distance consultation requested by, and in collaboration with, the treating physician may be considered for patients in distant

locations. The medical encounter must include documentation of the medical condition, reason for medical cannabis consideration, associated comorbidities, current medications, and previous treatment trials. A psychosocial history must include an assessment of mental health status, including past or present psychosis or substance use disorder. A treatment trial with a pharmaceutical product before consideration of medical cannabis, although recommended, is often not a practical consideration owing to difficulties with access and cost.

Following consideration of potential benefits versus harm, and when a decision is made to initiate a treatment trial, the prescribing physician must assume responsibility for followup. The goals of treatment should be clearly specified and be realistic [e.g., a 30% symptom relief (pain, sleep, and mood problems) and/or individually defined relevant improvement of daily functioning]. Some physicians may choose to complete a written treatment contract. Followup should be within 4–8 weeks to evaluate efficacy and side effects. Treatment should be initiated slowly, beginning with a nighttime dose, and not exceeding 3 g/day, the maximum average dose reported by medical cannabis users¹⁶. Cannabis should be obtained legally from a registered grower following submission of a prescription with known molecular content of THC and CBD, and patients and physicians must adhere to the legal requirements in their geographic region. Some authors have suggested a maximum of 9% THC concentration¹⁷. The treatment trial for a period of about 4–12 weeks may result in discontinuation of the product if ineffective or if there are unwanted side effects.

Cannabis should not be smoked because of the toxic products of combustion. Inhalation through a vaporizer is preferred because less intensive heating reduces release of toxic combustion products. Inhaled cannabis, through a vaporizer, will give effects within a few minutes, with effects

Table 2. Treatment principles to reduce harm.

Prior to starting medical herbal cannabis
Treatment goals and objectives should be realistic and clearly specified.
An assessment for substance use disorder must be documented.
Patients should be well informed about the adverse effects associated with cannabis use.
Drug preparations, route of administration, and dosing
Inhalation through a vaporizer has a rapid therapeutic effect, whereas oral ingestion has a slower but more sustained effect. Both routes of administration are preferred over smoked cannabis.
Cannabis with a low THC content (maximum 9%) and higher CBD content is preferable.
Total daily dose should not exceed 3 g.
The drug can be used regularly or on demand.
Assessment of side effects and efficacy
Followup 4–8 weeks after initiating the drug
Followup every 3 months thereafter

THC: Δ^9 -tetrahydrocannabinol; CBD: cannabidiol.

lasting up to a few hours, although the psychoactive and motor effects may last for over 24 h¹⁶. The effects of ingested cannabis will occur more slowly and be more prolonged, and may be the preferred method of administration for a treatment regimen. Although there is no evidence to support the therapeutic effect of various concentrations of THC and CBD in the herbal product, cannabis with a low THC content and higher CBD content is preferable because there will be fewer and less severe THC-induced psychoactive effects. Studies to date have reported on THC content up to 12.5%, but with a high rate of adverse events at this concentration¹⁸.

The ideal dosing schedule for medical cannabis is unknown, with no dose-finding studies to examine optimal daily amount or specific molecular concentrations of THC and CBD⁶. Some patients may choose “on-demand” use rather than regular use, but there is no evidence to support this method. It is conceivable that ingested cannabis could provide a more sustained effect, and that on-demand inhalation could be used as a breakthrough measure. However, on-demand use could lead to progressive increased use and misuse.

Patients reporting benefit should be followed at least every 3 months, with assessment of efficacy as well as need for continued treatment. Medical cannabis is ideally not a lifetime treatment, and at each visit justification for continued treatment must be documented. Physicians may choose to request a urine drug screen for patients taking continuous cannabis treatment as a caution to ensure that cannabis is not being used as a concomitant recreational product, or that the prescribed cannabis is not being diverted if there is reimbursement for the medical product.

Risks applicable to all rheumatic disease patients using medical cannabis. The risks associated with medical cannabis have not been specifically examined in patients with rheumatic diseases. Extrapolation from risks reported for other medical conditions as well as from recreational users is currently the only reasonable means to help inform clinical care.

1. Smoking of herbal cannabis

Cannabis should not be smoked. Inhalation of combustible products carries a risk of bronchial irritation¹⁹. Attenuation of the protective respiratory tract mucosa will promote entry of foreign antigens that have immunological effects that influence the expression of inflammatory arthritis²⁰. Similar to the smoking of cigarettes, smoked cannabis may adversely affect rheumatic diseases, but remains to be examined. The risk for lung cancer and smoked cannabis remains unclear²¹.

2. Psychomotor effects

Psychomotor function is affected by cannabis in young recreational users for up to 5 h after use²². This effect may be prolonged for as long as 24 h when cannabis is ingested. Driving after cannabis use is a risk for a collision, with risk increased with dose of cannabis and further increased when combined with alcohol²³. In a metaanalysis of 9 studies

(49,411 subjects), Asbridge and colleagues reported a pooled motor vehicle collision risk of 1.92 (95% CI 1.35–2.73, $p = 0.0003$)²⁴. Therefore, in line with recommendations of Health Canada, patients using medical cannabis should be warned not to drive or operate machinery for at least 24 h after consumption, with possible effects prolonged in the presence of other agents affecting psychomotor function such as tranquilizers, antidepressants, anti-epileptic drugs, and opioids¹⁶. Self-report that a patient experiences no psychomotor effects is not sufficient reason to ignore this risk and requires formal evaluation (e.g., a formal test of driving ability).

3. Risks of addiction

Cannabis is an addictive substance²⁵. Regular recreational cannabis use is associated with a risk of addiction estimated to be about 9% for all users, but with increased rates for younger age of onset of use, regular daily use, and likely increased concentration of THC. Addiction risk is not known for medical cannabis use but is unlikely to be different from that observed for recreational users. It is prudent to reflect on the evolution of the 1980s concept that opioid treatment for chronic pain would not be associated with addiction; that concept is now completely overturned²⁶.

4. Interactions of cannabinoids with other medications

Information regarding interactions of herbal cannabis and other drugs is limited. It can be anticipated that the psychomotor effects of drugs, such as tranquilizers, antidepressants, anticonvulsants, and also alcohol, will be augmented with cannabis and should be avoided or used with caution. In a study of smoked cannabis in patients with chronic pain, with almost two-thirds of the subjects treated concomitantly with opioids, the rate of serious adverse events was over 20 per 100 patient-years, an alarmingly high rate that is greater than many rheumatology drug treatments¹⁸.

Contraindications and cautions for medical cannabis use. Attention should be given to the use of medical cannabis for certain patient populations (Table 3).

Table 3. Contraindications and cautions for medical cannabis.

Populations in which medical cannabis should not be used
Rheumatology patients under the age of 25 years
Patients with allergic reactions to cannabinoid products
Women who are pregnant or breastfeeding
Patients with a history of a psychotic illness, substance abuse disorder, previous suicide attempts, or suicidal ideation
Populations in which medical cannabis should be used with caution
Elderly patients
Patients with unstable mental health disease
Patients with a history of current moderate or severe cardiovascular or pulmonary disease
Patients working in settings requiring high levels of concentration, optimal executive functioning, and alertness
Patients receiving concomitant therapy with sedative-hypnotics or other psychoactive drugs

1. Young persons

Herbal cannabis should not be used by patients under the age of 25 years, in line with the Canadian Paediatric Association^{17,27}. Brain development continues until the early 20s, with the cannabinoid system playing a critical role²⁸. Cannabis use at a young age adversely affects psychosocial development, academic and social attainment, and is a risk for mental health disease^{29,30}. There are no studies examining the above effects related to various concentrations of THC and CBD in the herbal product, although concentration of THC in street cannabis has increased exponentially in the last 2 decades, from 3% to a current 25–30%^{31,32}. Young patients self-medicating with a recreationally acquired product should be cautioned about this increased concentration of THC and the associated increased risk of cognitive and psychoactive effects. Microbial contamination of the street product is also a risk for patients who may be immunocompromised.

2. Pregnant and lactating women

Cannabis should be avoided in women during pregnancy and lactation. The endocannabinoid system is critical in normal brain development, although effect on the human fetus is unclear. THC crosses the placenta in rat studies, with appreciable levels measured in the pups, and associated transient and permanent behavioral effects³³. There is transfer of cannabinoids into breast milk, with cannabinoid metabolites excreted by both animal and human offspring³⁴.

3. Those hypersensitive to cannabis

Allergic sensitization with the development of specific immunoglobulin E can occur through inhalation, oral ingestion, or cutaneous contact with cannabis. Depending on the route of exposure, hypersensitivity reactions can vary widely and range from mild cutaneous or respiratory symptoms to angioedema and anaphylaxis³⁵. Because of the potential for life-threatening reactions, strict avoidance measures should be enforced for patients with suspected or confirmed cannabis allergy³⁶.

4. Older persons

Medical cannabis has had limited study in the elderly. In an Israeli study of patients over 65 years, with one-third of the original 2736 persons followed for 6 months, there was reduction of pain and discontinuation or reduction of opioid doses in 18%³⁷. The potential risks associated with medical cannabis in the elderly include effects on cognitive function and motor coordination, risk of confusion, and falls and injury. Psychomotor impairment is well described in young recreational users, but although not evaluated in the elderly, is likely to be at least similar but probably more pronounced²². Impairments in reaction time, selective attention, short-term memory, and motor control will critically affect the well-being of older persons. Additional potential risks not yet examined are the effects of drug interactions and comorbid illnesses, especially cardiac and pulmonary diseases. Drug interactions can reasonably be expected to be compounded by cannabis, especially those

affecting cognition, motor control, or mood. Therefore, extreme caution should be exercised when an elderly patient anticipates use of medical cannabis.

5. The working patient

Cannabis has psychoactive properties and affects motor function; therefore, competence in the work environment is critical. Higher concentrations of THC are associated with greater effect on cognition and psychomotor activity, although even a low concentration may have appreciable effects for some²². Patient self-report of competence is unreliable. In the absence of any formal standard of testing, patients should be informed that cognitive function will likely be impaired, although perhaps not perceptibly, and that any use of cannabinoids should be avoided in settings requiring concentration, optimal executive functioning, and alertness. This is particularly true for settings where impairment of cognition may pose a threat to others.

6. Those with comorbid illness

a. Mental health disease

Cannabis should generally be avoided in persons with a history of mental health disease, with an absolute contraindication for persons with a personal or family history of a psychotic illness, a history of substance abuse disorder, previous suicide attempts, or suicidal ideation³⁸. According to the comprehensive publication on the health effects of cannabis and cannabinoids by The National Academies of Sciences, Engineering, and Medicine, there is an absence of evidence to support or refute cannabis-induced changes in the course of depressive disorders, but moderate evidence for increased suicidal ideation, suicide attempts, and suicide completion³⁸. For anxiety, there is limited evidence of an association of daily cannabis use and development of any type of anxiety disorder, except social anxiety, and limited evidence for increased symptoms of anxiety in those with a previous anxiety state³⁸. Therefore in this context of uncertainty, it is prudent to be cautious when counseling patients with mental health disorders on the use of cannabis, and in a case of uncertainty, referral for psychiatric evaluation should be considered. Therefore, the CRA suggests a relative contraindication in persons with mental health disorders including anxiety and depression, with a warning that mood disorders may be aggravated by cannabis. Although cannabis is mostly anxiolytic, paradoxically anxiety may be increased and depressive symptoms aggravated. Although cannabis is widely advocated for effect on posttraumatic stress disorder, the current evidence is limited to anecdotes, case reports, and observational studies³⁹. Clinical judgment should be used to assess the risk of medical cannabis in current recreational users. There should be an assessment of addiction risk and severity of symptoms requiring treatment, and as much as possible, distinction made between recreational and medicinal use. If medical cannabis is used, treatment should ideally be in collaboration with a psychiatrist.

b. Cardiovascular disease and pulmonary disease

Cannabis should not be used in patients with moderate or severe cardiovascular or pulmonary disease^{40,41}. Because cannabis increases heart rate, blood pressure, and myocardial oxygen demand, use may aggravate stable angina or trigger myocardial infarction. Daily cannabis use increases the annual risk of myocardial infarction from 1.5% to 3% per year. Cardiovascular events, including sudden cardiac death, vascular events (coronary, cerebral, and peripheral), and arrhythmias are increasingly reported in young recreational users without other risk factors, suggesting that older persons with preexisting disease are at even greater risk⁴². Smoked cannabis is associated with chronic bronchitis symptoms, but case-controlled studies have not identified an association with lung cancer⁴⁰.

Much remains unknown regarding medical cannabis use in rheumatic diseases, including true efficacy as well as risks (Table 4). Rheumatologists can play an important role in (1) ensuring patients are educated regarding what is currently known concerning potential risks versus benefits of medical cannabis, and (2) providing patient-centered counseling for those who are taking or planning to take cannabis, with a goal toward harm reduction. Whether medical cannabis will finally emerge as a standard treatment option for our patients remains to be seen.

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Table 4. Key points associated with use of medical cannabis.

Medical cannabis is defined as the leaves and flowers of the plant family *Cannabaceae*.

Cannabis comprises many molecules, of which Δ^9 -tetrahydrocannabinol (THC) and cannabidiol (CBD) are the most studied for therapeutic effect.

THC is associated with psychoactive effects whereas CBD is likely to have pain- and inflammatory-modulating effects.

Herbal cannabis has THC content varying from < 1% to 24% and CBD content from < 1% to 13%.

There are no studies examining the efficacy of whole plant herbal cannabis (i.e., medical cannabis) in patients with rheumatic disease.

Studies examining cannabinoid pharmaceutical products reveal limited benefits and high risk of adverse events.

Patients considering use of medical cannabis should be warned not to drive or operate machinery for at least 24 h after consumption.

Patients should be warned that their function may be compromised when working in settings requiring high levels of concentration, optimal executive functioning, and alertness.

Regular recreational cannabis use is associated with a risk of addiction, but this risk has not been assessed in medical cannabis users.

Concomitant use of medical cannabis and tranquilizers, antidepressants, anticonvulsants, or alcohol should be avoided.

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