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The Dilemma of Medical Marijuana use by Rheumatology Patients

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1. Introduction

"Severe pain" is the most common reason for medicinal herbal cannabis use, with arthritis and musculoskeletal pain cited as the most prevalent specific medical condition [1, 2]. Eighty percent of marijuana users in a United States pain clinic report use for myofascial pain, whereas up to one third of persons in population studies in the United Kingdom and Australia reported use for treatment of arthritis pain (1-3). Similarly "severe arthritis" is the diagnosis for 65% of Canadians authorized to possess cannabis for medicinal purposes as of June 2013 (4). Medical marijuana has however never been recommended by any rheumatology group worldwide for symptom relief in rheumatic conditions. As the health care professionals best placed to advise on issues of rheumatic diseases, rheumatologists must have a voice in the current debate concerning medical marijuana, hereafter identified as herbal cannabis.

Advocacy for access to cannabinoid treatments has led to a societal groundswell with regulatory bodies around the globe considering the legalization of herbal cannabis for medicinal use. Currently, herbal cannabis is legalized in twenty states in the US for medicinal use. Physicians will therefore be caring for patients who may be self-medicating with herbal cannabis or may request medical advice about cannabis. In order to responsibly advise patients on any medical issue, and in particular herbal cannabis, it is essential that the health care professional has a competent knowledge of the subject based on sound scientific study. In this review we will examine the current evidence for dosing and administration, efficacy and risks of herbal cannabis in rheumatic pain management, and thereby address practical issues confronting rheumatologists whose patients request advice. We will confine our comments to herbal cannabis as it pertains to rheumatic conditions, acknowledging that evidence and information may differ for other conditions. We will not enter into the debate addressing the legalization of recreational herbal cannabis.

2. Herbal Cannabis

Prior to present day pharmacology, healers and patients sought relief from pain and suffering by using natural products. The plant *Cannabis sativa,* commonly known as marijuana, has been used for pain relief for millennia, with additional effects on appetite, sleep, and mood, but with psychoactive properties leading to recreational use (5). The analgesic effects of herbal cannabis, derived from the dried leaves and flowers, have been most studied in neuropathic pain conditions.

Cannabis sativa contains over 450 compounds, with at least 70 classified as phytocannabinoids, two of which have particular medical interest (6). The acid precursor of delta-9-tetrahydrocannabinol (Δ^9-THC), transformed by heat into THC, has psychoactive and pain relieving properties. The second molecule is cannabidiol, with lesser affinity for the cannabinoid receptors and the potential to counteract the negative effects of THC on memory, mood and cognition. Cannabinoid molecules interact with at least two receptors of the human endocannabinoid system to induce physiological effects (7, 8).

Herbal cannabis may be ingested or inhaled, with the latter route preferred by users due to onset of action within a few minutes. Smoking of cannabis is however not medically recommended

due to the potential respiratory tract dangers of noxious compounds such as polycyclic aromatic hydrocarbons, tar and carbon monoxide. Furthermore, plasma concentrations of THC achieved by smoking a "joint", containing between 0.5-1.0 grams of dried substance, are extremely variable, with blood levels varying between 7-100ng/mL. Finally, blood levels are influenced by the plant concentration of THC, variable THC delivered in the smoke, and characteristics of the smoking method (frequency of inhalation, hold time and inhalation volume) (9, 10). There is also discordance between the measured THC plasma peak and the maximum subjective psychoactive effects which occur an hour later, and can be augmented by opioids. Oral administration results in a more delayed effect, lower peak plasma levels, more protracted pharmacologic effects and less abuse related psychoactive effects (11). However, gastrointestinal absorption is more erratic and much of the ingested cannabinoid is eliminated by first-pass metabolism in the liver (11).

The mean concentration of THC in illicit marijuana has almost doubled worldwide in the past decade (12). With THC content of the plant material varying between 1 to 30%, and the bioavailability varying between 2-56%, there is no reasonable method to estimate dosing of the herbal compound (13). As acquisition of herbal cannabis for medical reasons is mostly via the illegal route, even where medical use is legalized, these higher concentrations of THC might lead to increased physical and psychomotor effects. Therefore the lack of the most elementary requirements for responsible drug administration must call into question any use of herbal cannabis for rheumatic pain treatment at this time.

3. Pain Management of Patients with Rheumatic Pain

As arthritis pain contributes to poor patient global well-being, pain relief is an important outcome goal, but unfortunately pain treatments remain suboptimal in most patients (14). The overriding principle for any pain treatment is to maintain function, without sacrificing cognitive or psychomotor function, a concept clearly different from pain management for medical conditions predominantly requiring palliation.

Chronic rheumatic pain remains a challenge as pain mechanisms are complex dynamic interactions of molecules and nerve pathways subject to nervous system plasticity. Available drugs generally offer a modest effect only, and pain co-associates with sleep disturbance and mood disorders. As treatment success is considered a 30% reduction in pain, and because most pain relieving medications are associated with considerable side effects, the compliance with prescribed treatments is often poor. It is therefore understandable that patients will continue to seek other remedies to reduce symptoms. Rheumatic disease patients commonly use complementary and alternative medicine, and with increasing advocacy for legalization of herbal cannabis as a recreational drug, cannabis may be perceived as a safe treatment option.

4. The Evidence for Herbal Cannabis in Rheumatic Conditions

To date, there is no formal study examining the efficacy or adverse effects of herbal cannabis in rheumatic diseases (15). Since our previous review, there has been only a single additional study reporting poorer function and psychological health in fibromyalgia patients using cannabinoids (16). While there is good evidence for efficacy of cannabinoids for treating some chronic pain conditions, such as cancer and neuropathic pain, these pain types have different underlying mechanism from the mostly peripheral/nociceptive pain in rheumatic diseases (17). Thus one cannot extrapolate efficacy to patients with rheumatic conditions.

Information about the effects of cannabinoids in rheumatic diseases is currently derived from anecdotal reports, two small epidemiological studies, a single study of the oromucosal spray of nabiximols, a combination of Δ^9-THC and cannabidiol, in patients with rheumatoid arthritis, and two studies of nabilone, a synthetic analogue of THC, in fibromyalgia (1, 2, 18-20). The two population studies from the United Kingdom and Australia, with prevalent use for musculoskeletal complaints, raise a number of concerns: diagnosis and outcome was by patient self-report, patients self-medicated without knowledge of dosing or concomitant treatments, and a third of the users reported recreational use (1, 2). Conclusions based on these studies are therefore questionable. In contrast, when the nabiximol (Sativex®) was examined in a randomized clinical trial of 58 patients with rheumatoid arthritis over a 5 week period, there was improvement in pain and quality of sleep (20). The nabilone studies in fibromyalgia patients showed improved pain in one, and non-inferiority to amitriptyline for effect on sleep for the other (18, 19). However, the reported effects of these agents, which indeed belong to the class of cannabinoids, cannot necessarily be applied to herbal cannabis which is a different substance, as described above.

It therefore follows that critical evaluation of safety issues which pertain to both short term and long term effects of herbal cannabis has also never been formally reported in persons with classic rheumatic diseases. There is also no sound information regarding the recommended dosing of herbal cannabis, other than patient report. Therefore, the available evidence for efficacy of medical herbal cannabis represents the least convincing form of scientific evidence.

5. The Evidence for Risks

Contrary to public belief, inhaled herbal cannabis is not innocuous. Risks can be categorized as the immediate effects on cognition, psychomotor function, cardiovascular effects and mood, and the chronic consequences on mental ability, pulmonary function, potential cancer risk and drug dependence. Information on risks of herbal cannabis is also mostly derived from reports of recreational users, who are usually younger and in better health than those with a chronic disease. Additionally, the interaction of herbal cannabis with other medications that are being used therapeutically is mostly unknown.

Acute Risks

The acute dose-related effects on cognition and psychomotor function are the most well-known immediate consequences of herbal cannabis use with implications for patient safety. Following administration of inhaled cannabis in varying THC concentrations, regular cannabis users showed impairment in reaction time, selective attention, short term memory, and motor control for up to 5 hours following consumption, with increasing effects for increasing doses (21). Similarly, the memory impairing effects of acute cannabis use, possibly specifically attributable to THC, should be kept in mind. These acute effects have implications for medicinal use for two reasons: THC content in street cannabis is increasing, and chronic pain management requires continued treatment.

Adverse acute effects on psychomotor function are particularly relevant when subjects drive motorized vehicles. Arthritis per se is seldom a contraindication to drive, and driving in the developed world is an important contribution to independence and quality of life. Acute cannabis use is increasingly appreciated as an accident risk for drivers. In a systematic review and meta-

analysis of 9 studies, with inclusion of 49,000 participants, acute cannabis use was associated with at least twice the risk of serious and fatal motor vehicle collisions (22). Indeed, cannabis was also the most prevailing illicit drug identified in 0.5 to 7.6% of seriously injured drivers from six European countries (23). Although alcohol remains the most common substance identified in injured drivers, cannabis was ranked second, with risk increased when combined with alcohol. Health Canada warns that the ability to drive or perform activities requiring alertness or coordination may be impaired for up to 24 hours following a single consumption (24). Therefore, driving with the concomitant use of herbal cannabis is both a personal and a societal safety risk, which may be further compounded in the presence of other medications. At the very least, medical practitioners must now advise patients that herbal cannabis may impair motor coordination, particularly when driving. However, advising patients not to drive is a recommendation counter intuitive to maintaining normal function.

A less appreciated effect of acute cannabis is noted for the cardiovascular system. Tachycardia and hypotension could compromise cardiovascular status in those with underlying heart disease and be a risk for cardiovascular events (25). Cannabis increases the risk of myocardial infarction five-fold and reduces the exercise capacity of those with angina pectoris by half (26, 27). Lastly, immediate psychiatric effects are increasingly associated with acute cannabis use, including anxiety, agitation, suicidal ideation and acute psychosis (28).

Chronic Risks

The long term risks of herbal cannabis use in rheumatic disease patients are unknown. Risks generic to all persons using herbal cannabis include effect on psychological health and association with mental illness, development of dependence and addiction, effects on memory and cognition and respiratory health (28). Aggravation of depression and smoking associated risks may be particularly important for rheumatology patients. These issues seem to be particularly problematic in younger individuals, where we appreciate that many neuroactive drugs may have additional or more pronounced side effects (29). For example, just as suicidality with selective serotonin reuptake inhibitors seems more pronounced in individuals under age 25, there is a similar age predisposition for the increase risk of psychosis in young cannabis users.

Although the long term effect on mood and especially depression still remains unclear, depression is more prevalent in current cannabis users (30). In a US study of over 8,000 adults, those with a past year use of cannabis had 1.4 times higher odds of current depression than non-users (30). Aggravation or unmasking of serious psychiatric disease also occurs with herbal cannabis use. Although previously disputed, cannabis is now generally accepted as an agent with addictive potential, especially in a context of an adverse psychosocial setting. Over a 3 year period the cumulative incidence of cannabis dependence was 37.2% (95% CI 30.7-43.8%) for young recreational users (31).

While cigarette smoking associated risks for arthritis patients cannot immediately be attributed to the smoking of herbal cannabis, the potential for these adverse effects exists. Apart from the consequences of inhalation of an irritant on respiratory mucosa with development of chronic respiratory disease, there is increasing evidence that herbal cannabis may independently increase risk of lung cancer (32-34). When Swedish military conscripts aged 18-20 years were tracked over a 40-year period, those who had smoked cannabis on at least 50 occasions had a twofold

risk (hazard ratio 2.12, 95% CI 1.08 – 4.14) of developing lung cancer, even after adjustments for other risks for lung cancer (34). Although it is recommended that herbal cannabis not be smoked, this remains the most common route of administration for most persons.

Finally, the true motive for use of herbal cannabis, even in persons with an identifiable medical condition requires careful scrutiny. Often, persons using marijuana for medical reasons have previously been recreational users, raising the possibility of misusing a medical diagnosis to justify use primarily for non-medical reasons (1, 2, 35).

6. Understanding the Dilemma for the Health Care Professional

Responsible medical practice requires a physician to provide empathetic and judicious patient care without harm. In the light of the current lack of concrete medical evidence for either the efficacy or risks of herbal cannabis for the management of rheumatic complaints, physicians are obligated to caution patients about the known risks of herbal cannabis that have been reported for recreational users. Simply acceding to patient demands for a treatment on the basis of popular advocacy, without comprehensive knowledge of an agent, does not adhere to the ethical standards of medical practice. It is understandable that this lack of current scientific evidence must translate into physician insecurity and even distress when attempting to provide rational advice to a patient. Furthermore, any recommended therapy requires proof of concept by sound scientific study that attests to both efficacy and safety. Therefore, before physicians can provide medical recommendation or support for use of herbal cannabis, the minimal standards for pharmacotherapy must be met. At present, these elementary criteria are not fulfilled. In the absence of knowledge of effective dosing or true benefits for herbal cannabis for rheumatic complaints, the risks extrapolated from study of persons with recreational use seem to tip the balance against use. We, therefore, believe that herbal cannabis should not at this time be allowed exceptional status as a therapy, different from other modes of therapy.

The question arises, then, whether physicians have any basis on which to provide responsible advice to patients beyond the known risk of serious adverse effects. In many jurisdictions legislation is forcing physicians to accept medical responsibility for their patients who may be using herbal cannabis. For example, in Canada, physicians will be required to provide a document equivalent to a prescription stipulating dosing, frequency and duration of use (24, 36). An additional challenge is presented by the ambiguous terminology used by the courts whereby legal access to herbal cannabis is deemed a Charter Right when a “medical need” has been demonstrated by the patient. If physicians are to “prescribe” medical cannabis for their patients, medical ethics and deontology require physician competence with the prescribed treatment. It is also increasingly recognized that sanctioning use of herbal cannabis for therapeutic reasons is currently provided by a small numbers of physicians for the majority of patients (35). In the state of Colorado almost half of recommendations had been made by only 15 physicians. Motives for this medical behavior should be questioned and raises ethical concerns.

It is therefore not surprising that recent surveys report that physicians lack confidence in their knowledge of cannabinoids and in their competence to effectively advise patients on use of medicinal cannabinoids (35). In a survey of family physicians in Colorado, only 19% thought that physicians should recommend medical marijuana, with 92% reporting need for more education (35). Similarly, two thirds of Canadian rheumatologists recently surveyed 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 (37). Even in the setting of some reasonable knowledge of cannabinoid molecules and the endocannabinoid system, the absence of evidence for clinical use of herbal cannabis in rheumatic conditions must be discomforting for any health care professional or rheumatologist intending to provide herbal cannabis treatment recommendation. Additional knowledge of these molecules is required, but knowledge alone will not fill the void due to absence of clinical study. This evident mismatch between dictates from regulatory bodies, patient advocacy and prudent clinical care is troubling; irresponsible requirements by regulatory authorities might compromise patient and society well-being. In light of other available treatment options for the management of arthritis pain, lack of sound evidence for effect and potential for harm, herbal cannabis cannot be recommended for arthritis pain management at this time.

7. Conclusion

There is an ever increasing hiatus between public advocacy for herbal cannabis as a therapeutic agent in rheumatic conditions and the medical evidence for efficacy and side effects. This serious shortfall covers many aspects of herbal cannabis as a therapeutic agent, including uncertainty of compound content, unknown dosing, recommendations not to use by inhalation and the indicators of harm, both in the acute as well as chronic setting. Taking all factors into consideration, health care professionals should currently dissuade rheumatology patients from using herbal cannabis as a therapy. The evident mismatch between patients' needs and good medical practice may in part be politically driven with regulatory bodies acceding to public pressure. Rheumatologists should advocate for further study of individual cannabinoid molecules whereby dosing can be accurately controlled and efficacy and safety can be assessed using standard scientific method.

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Key points for medicinal use of herbal cannabis for rheumatic pain

- Legitimate use should be reserved only for patients with pain refractory to standard pharmacological and non-pharmacological therapies
- Herbal cannabis should not be smoked.
- The risk: benefit profile of herbal cannabis is inferior to all other analgesic classes other than opioids
- Persons aged less than 25 years should be strongly discouraged from any use of herbal cannabis.