Editorial

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Medical cannabis: what advice should we be giving our rheumatology patients?

Driven by public advocacy rather than by standards of evidence-based medicine, cannabis is rapidly entering mainstream medicine in many countries. While reports of cannabis use by humans exist since the beginnings of recorded history, the past few decades have seen an increasing scientific appreciation of the importance of the endocannabinoid system in the human body. Preclinical studies have demonstrated that the endocannabinoid signaling system functions to maintain homeostasis, thereby moving the organism back to equilibrium [1]. This explains the attraction of cannabinoids as having therapeutic effects on various physiological functions ranging from stress reduction, promotion of appetite and sleep, to modulation of pain and inflammation.

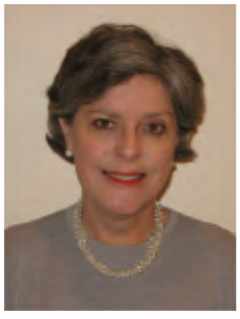
These findings have driven the pharmaceutical industry to create preparations of cannabinoids, resulting in the commercialization of three products: dronabinol, a stereoisomer of tetrahydrocannabinol (THC); nabilone, a synthetic analogue of THC; and the oromucosal nabiximols spray, a combination of Δ^9-THC and cannabidiol, with postulated less psychoactive effects and augmented anti-inflammatory effects attributed to cannabidiol. In contrast, cannabis, derived from the leaves and flowers of the plant *Cannabis sativa*, contains a vast array of molecules, including at least 66 different cannabinoid molecules, in varying concentrations depending on the strain [2,3]. Classed as an illegal/controlled substance in most jurisdictions, cannabis is used worldwide as a recreational substance due to its psychoactive effects.

With many patients, especially those with musculoskeletal complaints, currently self-medicating with cannabis, the healthcare community must be informed of current evidence for use as a therapeutic agent, with particular attention to purported benefits and risks [4]. The reason why patients may be seeking additional symptom relief is centered on the suboptimal effects of almost all current analgesic therapies, with adverse effects often limiting use. Familiarity with cannabis due to prior recreational experience, as well as the prevalent perception that an herbal product is more natural and associated with less risk, may contribute to these self-medication practices. Therefore, as rheumatologists will necessarily engage in dialogue with patients, we will endeavor to provide some guidance for the counseling of patients.

Clinical encounter regarding therapeutic use of cannabis

In advising patients, physicians must provide a balanced view, free of personal bias, and with the objective of sufficiently educating the patient to allow for informed and shared decision-making [5]. Physicians should aim to provide care using the best available evidence, while ensuring that the individual and society are protected from harm. Patients may have their own specific ideas and agendas, at times possibly poorly informed, requiring physicians to adhere to the ethical standards of providing informed care that is empathetic.

In the first instance, the healthcare professional should acknowledge current understanding of the endocannabinoid system in health and disease, but with the qualification that much remains unknown. Furthermore, the wide range of available nonpharmacologic and pharmacologic strategies to treat rheumatic pain should be explained. Patients



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should be informed that cannabinoid molecules are diverse and therefore not interchangeable. The pharmacological cannabinoid products, available in some countries, have the advantage of known dosing and pharmacokinetics, as well as known efficacy and side effects for a variety of conditions, as is required for standard drug approval by regulatory authorities. However, there is only limited evidence for their use in rheumatology patients, which constitutes mostly off-label use, and therefore should not be considered as a first line treatment option [6–8].

In the absence of any guidelines for screening or monitoring patients using cannabis, a comprehensive clinical assessment, akin to that for opioids, is required, with full clinical documentation. This should include a record of the disease as well as the specific symptoms that require treatment, an assessment of previous treatment trials, a history of current or past recreational cannabis use, other substance abuse, risk for addiction, and a personal or family history of mental or psychiatric disease. Knowledge of any previous encounter with the law regarding cannabis in particular, or for other reasons, may point to particular risks in an individual. Expectation of outcome should include not only symptom relief, but also functional status, which should include work status. The physician should also explore the true motive for use, even in a patient with a valid medical condition, which may represent an indistinct line between recreational and therapeutic use. With this preliminary information, a physician may choose to counsel against use of cannabis for some patients when reasons stated above raise concerns.

Turning now to the evidence for efficacy or risks, it is mandatory to inform the rheumatology patient of the current absence of sound information in this regard [9]. Extrapolation from the few studies of other molecules, that is, synthetocannabinoids or nabiximols, cannot attest to efficacy or adverse effect of cannabis. Similarly, the evidence for risks is mostly by extrapolation from studies of recreational users, a population different from patients who may be using other medications and have comorbid conditions.

Prior to any consideration of cannabis use, there should be a comprehensive discussion of conventional treatment options and evaluation that other treatments have indeed had a reasonable therapeutic trial [10]. Therefore, in the absence of sound evidence for use of cannabis, the physician should recommend against use for the majority of rheumatology patients, and reserve use for only the exceptional patient.

The ideal method of administration of cannabis remains speculative. As cannabis requires heating to transform the acid precursor of Δ^9-THC to the active compound THC, most users smoke the product [11]. Smoking is however not recommended because of inhalation of noxious compounds such as polycyclic aromatic hydrocarbons, tar and carbon monoxide. Administration via a vaporizer that does not excessively heat the plant substance is possibly safer, with less production of toxic hydrocarbons. Oral administration results in a more delayed effect, lower peak plasma levels and more protracted pharmacologic effects [12]. However, gastrointestinal absorption is more erratic and much of the ingested cannabinoid is eliminated by liver first-pass metabolism [12].

What to say to a patient already using cannabis for medical purposes

When a patient has already chosen to use cannabis for therapeutic means and communicates this information to the treating physician, certain obligations exist. In the first instance, the physician may be discomforted by the knowledge of use, particularly if illegal, and may also have personal biases. Apart from the illegalities in some jurisdictions, physicians may lack confidence in their personal knowledge of cannabinoids as well as being insecure with the current available broader scientific knowledge. The second consideration is to pay attention to the particular characteristics of the patient by examining the diagnosis, reasons for current use, and report of effect for specific symptoms. Additionally, consideration must be given to reduction of harm for the patient, with attention to method of administration, the amount and frequency of use, current other prescribed or nonprescribed substances that may have psychoactive effects, functional and employment status, and perceived benefit. Although often cited as used for pain relief, some patients report that stress reduction and sleep promotion are desirable effects. These latter symptoms may be more effectively addressed by other modalities rather than by cannabis use.

For the patient already using cannabis, it is incumbent on the physician to ensure that the patient is knowledgeable of the risks associated with use. Therefore, the current knowledge of both acute and chronic adverse effects of cannabis use must be clearly elaborated [13]. Acute adverse effects of cannabis may be classified as cognitive and psychomotor impairment, mood effects, cardiovascular changes and respiratory symptoms related to smoking. When cannabis is smoked, as occurs for most users, the immediate serum peak level is achieved within a few minutes, whereas the effects on pain, cognition and other effects are more prolonged, emphasizing the disconnect between psychoactive effects and blood level [12]. With therapeutic effects desirable over a more prolonged time period, there also exists a risk for delayed psychoactive effect that could predispose an individual to harm [11].

Apart from the immediate psychoactive responses, other short term adverse effects include those related to smoke inhalation, risk of adverse cardiovascular events due to vasodilatation and resulting cardiovascular compromise, and increased appetite which although an advantage in some conditions, may be a disadvantage for rheumatic disease patients needing to maintain a healthy weight [14,15]. Although many report a calming and anxiolytic effect, this is not universal, with some persons developing acute severe anxiety [16]. Although there is a common perception that cognition and psychomotor function is unaffected by acute use, there is clear evidence of psychomotor dysfunction with slower reaction time, difficulty multitasking and poor immediate short-term memory retention [17]. These effects are compounded when other agents having psychoactive effects such as opioids, tranquilizers, anticonvulsants and alcohol are used.

Chronic effects may similarly be classified as risk for chronic respiratory disease and lung cancer, effect on memory and learning ability in younger persons, and the spectrum of psychological and mental disorders that range from depression with suicide risk, cannabis use disorder and addiction, and development of schizophrenia [16,18,19].

Societal risks posed by persons using cannabis are only beginning to be appreciated. Acute cannabis use is associated with twice the risk of serious injury or death due to motor vehicle accidents, with some authorities recommending against driving for 24 h following use [20]. Exposure of family members, particularly children, may be an opportunity for persons to experiment and be an introduction to recreational use, as has occurred with prescription opioids over the last two decades. Children and adolescents may also not easily distinguish between true medicinal use by their family members and recreational use. Whether secondhand smoke will pose similar risks to that recognized for tobacco smoke is also currently unknown.

To prescribe or not to prescribe?

Similar to any other medical scenario, the physician is responsible for the global health of a patient and is therefore required to assess all aspects of health and advise accordingly. When assessing a patient who genuinely appears in need, it may be challenging for the physician to simply say 'no' [21]. Taking into consideration all available clinical information, it is the prerogative of the physician to reasonably conclude that a prescription of cannabis may not be in the best interests of a particular patient. There are a few points that may aid the physician in coming to this final decision.

Similar to a prescription for all psychoactive substances, the physician should have a *bona fide* relationship with the patient, with existing mutual trust. This might extend to the need for a formally signed informed consent document. There should also be professional contact with other healthcare providers contributing to the care of the patient.

Cannabis should not be prescribed for vague nonspecific complaints, or for symptoms of anxiety or insomnia, for young people or those with psychiatric disease or cardiovascular risks. Current recreational use should preclude a physician from prescribing cannabis for medicinal use as there may be poor distinction between true therapeutic effect and recreational psychoactive effects. Coadministration of some another psychoactive medication or substance such as benzodiazepine or an opioid may be a contraindication for use. Prior to medicinal use of cannabis, there should have been an adequate trial of a pharmacologic cannabinoid preparation. Finally, an outcome measure of retained or improved function must be documented to justify continued use.

Laws allowing for use of cannabis, either for recreational or medical purposes, greatly differ throughout the world, with some jurisdictions within the same country at polar opposites. It is therefore important to be cognizant of the laws and regulations applicable to one's medical practice and to act accordingly. In jurisdictions where cannabis remains an illegal substance but where medical use is legally allowed, it must be explained that this use represents an exemption. Another potential legal issue surrounding cannabis prescriptions arises as this agent has never undergone the usual due process and scrutiny by drug regulatory authorities. Healthcare professionals prescribing cannabis can expect to be held accountable as a result of adverse reactions.

Similarly, patients must adhere to the laws of their particular jurisdictions regarding the legality of possession of cannabis, as well as any regulations governing their employment, health and safety in the workplace. Patients should also be cautioned regarding travel to other areas that may have different regulations in place.

Conclusion

While for some conditions, cannabis has been shown to be effective and its use is no longer questioned, such evidence is currently lacking to recommend widespread use in rheumatic conditions. While we cannot currently recommend the use of cannabis in rheumatology, physicians acting within the legal boundaries of their jurisdictions may choose to tolerate such use by a select number of patients who report pain reduction, improvement of function and mitigation of risks associated with use of cannabis. It is to be expected that physicians practicing evidence-based medicine

will demonstrate lack of confidence and discomfort in the medical use of an agent that has not undergone the usual formalities required of typical pharmacologic therapies. For these reasons, we advocate for further research of cannabis, particularly in the setting of rheumatic pain. 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.

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