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Editorial

Cannabis for musculoskeletal pain and arthritis: Evidence is needed

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1. Introduction

Cannabis-based medicines have been approved for pain management in a number of countries. However, there are uncertainties and controversies about their role and the appropriate use of these medicines for the management of chronic pain, particularly in musculoskeletal conditions. These ancient drugs are now being rediscovered and considered as modern analgesic approaches in the context of cannabis legalization in more and more countries. The fight for cannabis legalization is frequently confused with the search for new analgesics in a medical context. Furthermore, there is a confusion between herbal cannabis, medical cannabis and cannabinoids. Therefore, it is important to differentiate products and situations and look beyond prejudice and misconceptions, to discover whether there are pharmacological and clinical data to support the use of medical cannabis and cannabinoids in musculoskeletal conditions and arthritis. Aside from media and social discussions, the current hot question for a clinician is "Is it possible to recommend medical cannabis as a new analgesic option in musculoskeletal conditions?"

2. Cannabis and cannabis-based medicines: convergence of advocacy groups

Recently, the emerging interest by patients for cannabis products for medical purposes has been stimulated by advocacy for the legalization of marijuana for recreational and medical use by laymen organizations and political parties, especially in Europe and North America. Some European governments have legalized herbal cannabis for medicinal use with a wide range of potential indications, mainly for chronic pain management [1]. A recent survey conducted by the European Pain Federation (EFIC) found important differences among European countries in the availability of plant-derived and synthetic cannabinoids and of medical cannabis for pain management, for symptom control in palliative care, and in coverage by health insurance companies or state social security systems [2]. In fact, these differences in availability and reimbursement are mainly related to political decisions rather than to scientific reasons.

3. From cannabis to cannabis-derived medicines: for a precise terminology

The golden age of cannabis pharmacology began in the 1960s as Raphael Mechoulam and his colleagues in Israel isolated and synthesized cannabidiol, tetrahydrocannabinol, and other phytocannabinoids [3]. Actually, the term "cannabis" is widely found to cover very different uses, confusing illicit street drugs with the therapeutic use of prescribed medicinal cannabinoids. Cannabis is a recreational drug. But there are also chemically defined, plant-derived cannabinoids (i.e. phytocannabinoids), synthetic pure cannabinoids and pharmacological modulators of the endogenous cannabinoid system (endocannabinoids) that may be proposed as treatments for different conditions. The fact that cannabidiol (CBD)-containing oils such as low CBD extracts are proposed as nutritional supplements (so-called cannabis-oils) adds to the confusion.

In this context, it is recommended that the term 'herbal cannabis' should only be used for plants and plant material (e.g. flowers, marijuana, hashish, buds, leaves, or full plant extracts). The term "medical cannabis" (or medical marijuana) should refer to the whole, unprocessed marijuana plant or its extracts for medical reasons. Medical cannabis must be clearly distinguished from cannabinoid agents (cannabinoids) that are either synthetic, semi-synthetic or plant-derived natural, but always chemically defined, single compounds, e.g. Δ^9-tetrahydrocannabinol (THC) or cannabidiol (CBD). Nabilone is completely synthetic THC and Dronabinol is a plant-derived semi-synthetic cannabinoid (THC). Registered medicinal cannabis extracts with defined and standardized THC and THC/CBD content, such as nabiximols, should be classified as 'cannabis-derived' or 'cannabis-based" medicines (Table 1).

In addition to phytocannabinoids, cannabis-derived or cannabis-based medicines and cannabis extracts, other pharmacological approaches under development for manipulation of the endocannabinoid system include selective synthetic cannabinoid receptor agonists or antagonists, and inhibitors of the catabolism (e.g. fatty acid amide hydrolase [FAAH] inhibitors) or re-uptake of endogenous cannabinoid ligands (endocannabinoids).

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Table 1
Terminology and classes of products.

Term	Definition	Products
Herbal cannabis	The whole plant or parts or material from the plant (e.g. buds, resin, leaves) Contains more than 100 distinct cannabinoid compounds	*Cannabis sativa*, hashish, marijuana, . . .
Medical Cannabis	Medical cannabis refers to using the whole, unprocessed marijuana plant or its extracts for medical reasons	Medical marijuana
Cannabinoids	Chemically defined, single compounds having affinity for and activity at cannabinoid receptors: synthetic, semi-synthetic or plant-derived natural,	Tetrahydrocannabinol: THC Cannabidiol: CBD Cannabis-oils CP55,940, WIN55,212-2, HU210
Cannabis-based or cannabis-derived medicines	A compound found in the cannabis plant or purified/extracted from plant material registered for medical purpose	Dronabinol: plant or synthetic derived THC (Marinol) Nabilone: synthetic THC (Cesamet), Nabiximols (Sativex): THC/CBD Epidiolex: synthetic CBD
Endocannabinoid	An endogenous ligand which has activity at cannabinoid receptors	Anandamide, 2-AG
Cannabinoid receptor agonists or antagonists	Selective synthetic cannabinoid receptor agonists or antagonists	Rimonabant: CB1 receptor antagonist
FAAH inhibitors	Drugs that inhibit the catabolic enzyme fatty acid amide hydrolase (FAAH) and elevate the levels of endogenous cannabinoids, including anandamide	PF-3845, URB597, BIA 10-2474

4. Cannabis-based medicines: the new "holy grail" for numerous conditions in the 21st century?

Cannabis has been proposed to alleviate pain and spasticity, but also sleep disorders, nausea, vomiting and to improve quality of life in chronic conditions. Currently, all medical disciplines are discussing the use of cannabis-based medicines, mostly in neurology, gastroenterology, nephrology, oncology, and pain medicine [4]. Cannabis and cannabis-based medicine may exhibit anti-cancer properties [5], reduce chemotherapy-induced nausea and vomiting [6], improve epilepsy [7], hypertension [8] and play an important role in psychiatry, movement and neurodegenerative disorders [9]. There are several ongoing studies in multiple sclerosis, anorexia, epilepsy, glaucoma, schizophrenia, cardiovascular disorders, cancer, obesity, metabolic syndrome related diseases, Parkinson's disease, Huntington's disease, Alzheimer's disease and Tourette's syndrome, using drugs that modulate the endocannabinoid system. Presently, cannabinoid receptor agonists like nabilone and dronabinol are used for reducing chemotherapy-induced vomiting. Sativex (cannabidiol and THC combination) is approved in the UK, Spain and New Zealand to treat spasticity due to multiple sclerosis. In the US, it is under investigation for cancer pain. Epidiolex (cannabidiol) is also under investigation in the US for childhood seizures. Rimonabant, a CB1 receptor antagonist, appeared to be a promising anti-obesity drug during clinical trials but also exhibited psychiatric side effects and was suspended in Europe.

5. Medical cannabis and cannabinoids: the new analgesics in all painful conditions?

More specifically, in pain conditions, there are clinical trials and meta-analyses on the analgesic effects of these substances. In palliative care, cannabis and cannabinoids can be considered as add-on therapy for cancer pain in persons without sufficient relief from opioids or other established analgesics [10]. Cannabis-based medicines can be considered as third line therapy for chronic neuropathic pain since some studies demonstrate weak evidence of their efficacy in neuropathic pain [11], especially in diabetic neuropathy, central pain and HIV neuropathy. More precisely, there is limited evidence to use medical cannabis and nabiximols, but not dronabinol or nabilone, for chronic neuropathic pain [12]. However, globally, there is insufficient evidence to promote one specific cannabis-based drug, since no head-to-head comparisons of different cannabis-based medicines or phytocannabinoids for pain management have been developed.

6. Cannabis-based medicine in musculoskeletal and arthritis conditions: acting on pain and inflammation

Musculoskeletal pain and arthritis represent a group of chronic pain conditions where classical analgesics show poor efficacy, and high unmet needs. This is where cannabis-based medicine may represent a new and interesting therapeutic option. The rationale for its use in musculoskeletal conditions and arthritis is based not only on its analgesic effects, but also on its putative anti-inflammatory effects, since cannabinoid receptors are also involved in inflammation [13].

6.1. Cannabis-based medicine in musculoskeletal pain

In low back pain, nabilone was not able to significantly reduce pain intensity and no valid trial with cannabis-based medicines is available [14]. In fibromyalgia, also, several studies on nabilone did not reach significance compared to placebo [14]. In a 5-week study of 58 patients with rheumatoid arthritis, THC/CBD was statistically significantly superior to placebo in reducing morning pain, but not for reducing total intensity of pain [15]; there is no other available study.

6.2. Herbal cannabis in musculoskeletal conditions: population surveys

There are currently no available trials examining the effect of herbal cannabis in rheumatic diseases. This is probably due to the contentious status of cannabis as a highly controlled substance, with strong restrictions on access for research purposes. However, some data about herbal cannabis for the management of rheumatic symptoms may be found in population surveys of persons with chronic pain conducted in the UK, Canada, and Australia [16–19]. In these cohort studies, musculoskeletal or arthritis symptoms are reported in 15% to almost 40% of subjects and the majority of patients perceived herbal cannabis to be therapeutically effective. Interestingly, recreational use of cannabis either before medicinal use or concurrently was common in all cohort studies. Based on that, no conclusions for efficacy or safety of herbal cannabis in rheumatic conditions can be made, although the safety profile of cannabis appears relatively good.

6.3. New modulators of endocannabinoid system for pain and inflammation?

FAAH inhibitors/inactivators have been developed because of their ability to increase the concentration of endocannabinoids. Their targets are the cannabinoid receptors CB_1 and CB_2, but other receptors can be involved in their action, such as GPR_{55}, peroxisome proliferator-activated receptors (PPARs) and vanilloid receptors ($TRPV_1$). This class represents a new interesting approach, but lethal issues have halted some research programs [20].

7. Cannabis-based medicines: organic, thus safe?

Adverse events related to pharmaceutically prepared cannabinoid treatments are common but, although not serious, may be sufficiently troubling to impact well-being. In their meta-analysis, Fitzcharles et al. [14] reported that between one-quarter and one-half of subjects demonstrated side effects, mostly dizziness and drowsiness, and some form of cognitive effect. Gastrointestinal effects of dry mouth, nausea, and constipation are also reported in the studies. It is, however, reassuring to note that there were no serious adverse events reported in any of the studies with cannabis-based medicine.

This is different from what has been recently observed in the new class under development for manipulation of the endocannabinoid system [20]. This class includes selective synthetic cannabinoid receptor agonists or antagonists, and inhibitors of the catabolism (e.g. fatty acid amide hydrolase [FAAH] inhibitors) or reuptake of endogenous cannabinoid ligands (endocannabinoids) that have demonstrated lethal risks.

8. Conclusion

In view of the considerable limitations of the available studies and according to the conclusions of several meta-analyses [12,14,21], it is not currently possible to recommend cannabis and cannabis-based medicine as therapy for patients with musculoskeletal pain and arthritis. There is a need for larger, well-controlled clinical trials to better understand potential benefits and risks of these substances in rheumatic conditions. It is obvious that there are very few effective analgesics available in musculoskeletal conditions, all classical analgesics associated with important side effects. New pharmacological analgesic approaches, including cannabis and cannabis-based drugs, can be helpful and should not be abandoned solely due to prejudice and misconceptions. It is important to separate recreational and medical use in research and also in all discussions with patients and health authorities. The debate is open, research is starting, patient demands are important and relevant, but lessons from the opioid epidemic should be taken into account to avoid a cannabis crisis.

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The authors declare that they have no competing interest.

References

[1] Abuhasira R, Shbiro L, Landschaft Y. Medical use of cannabis and cannabinoids containing products – regulations in Europe and North America. Eur J Intern Med 2018;49:2–6.
[2] Krcevski-Skvarc N, Wells C, Häuser W. Availability and approval of cannabis-based medicines for chronic pain management and palliative/supportive care in Europe: a survey of the status in the chapters of the European Pain Federation. Eur J Pain 2018;22:440–54.
[3] Russo EB, Marcu J. Cannabis pharmacology: the usual suspects and a few promising leads. Adv Pharmacol 2017;80:67–134.
[4] Maccarrone M, Maldonado R, Casas M, et al. Cannabinoids therapeutic use: what is our current understanding following the introduction of THC, THC: CBD oromucosal spray and others? Expert Rev Clin Pharmacol 2017;10:443–55.
[5] Ramer R, Hinz B. Cannabinoids as anticancer drugs. Adv Pharmacol 2017;80:397–436.
[6] Badowski ME. A review of oral cannabinoids and medical marijuana for the treatment of chemotherapy-induced nausea and vomiting: a focus on pharmacokinetic variability and pharmacodynamics. Cancer Chemother Pharmacol 2017;80:441–9.
[7] Perucca E. Cannabinoids in the treatment of epilepsy: hard evidence at last? J Epilepsy Res 2017;7:61–76.
[8] Malinowska B, Toczek M, Pędzińska-Betiuk A, et al. Cannabinoids in arterial, pulmonary and portal hypertension – mechanisms of action and potential therapeutic significance. Br J Pharmacol 2018, http://dx.doi.org/10.1111/bph.14168.
[9] Lim K, See YM, Lee J. A systematic review of the effectiveness of medical cannabis for psychiatric, movement and neurodegenerative disorders. Clin Psychopharmacol Neurosci 2017;15:301–12.
[10] Mücke M, Weier M, Carter C, et al. Systematic review and meta-analysis of cannabinoids in palliative medicine. J Cachexia Sarcopenia Muscle 2018;9:220–34.
[11] Lee G, Grovey B, Furnish T, et al. Medical cannabis for neuropathic pain. Curr Pain Headache Rep 2018;22:8.
[12] Häuser W, Petzke F, Fitzcharles MA. Efficacy, tolerability and safety of cannabis-based medicines for chronic pain management – an overview of systematic reviews. Eur J Pain 2018;22:455–70.
[13] Kaur R, Ambwani SR, Singh S. Endocannabinoid system: a multi-facet therapeutic target. Curr Clin Pharmacol 2016;11:110–7.
[14] Fitzcharles MA, Baerwald C, Ablin J, et al. Efficacy, tolerability and safety of cannabinoids in chronic pain associated with rheumatic diseases (fibromyalgia syndrome, back pain, osteoarthritis, rheumatoid arthritis): a systematic review of randomized controlled trials. Schmerz 2016;30:47–61.
[15] Blake DR, Robson P, Ho M, et al. Preliminary assessment of the efficacy, tolerability and safety of a cannabis-based medicine (Sativex) in the treatment of pain caused by rheumatoid arthritis. Rheumatology (Oxford) 2006;45:50–2.
[16] Aggarwal SK, Carter GT, Sullivan MD, et al. Characteristics of patients with chronic pain accessing treatment with medical cannabis in Washington State. J Opioid Manag 2009;5:257–86.
[17] Swift W, Gates P, Dillon P. Survey of Australians using cannabis for medical purposes. Harm Reduct J 2005;2:18.
[18] Ware MA, Adams H, Guy GW. The medicinal use of cannabis in the UK: results of a nationwide survey. Int J Clin Pract 2005;59:291–5.
[19] Walsh Z, Callaway R, Belle-Isle L, et al. Cannabis for therapeutic purposes: patient characteristics, access, and reasons for use. Int J Drug Policy 2013;24:511–6.
[20] Mallet C, Dubray C, Dualé C. FAAH inhibitors in the limelight, but regrettably. Int J Clin Pharmacol Ther 2016;54:498–501.
[21] Whiting PF, Wolff RF, Deshpande S, et al. Cannabinoids for medical use: a systematic review and meta-analysis. JAMA 2015;313:2456–73.

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