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Cannabinoids in the treatment of rheumatic diseases: Pros and cons

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ABSTRACT

Medical cannabis is being increasingly used in the treatment of rheumatic diseases because, despite the paucity of evidence regarding its safety and efficacy, a growing number of countries are legalising its use for medical purposes in response to social pressure. Cannabinoids may be useful in the management of rheumatic disorders for two broad reasons: their anti-inflammatory and immunomodulatory activity, and their effects on pain and associated symptoms. It is interesting to note that, although a wide range of medications are available for the treatment of inflammation, including an ever-lengthening list of biological medications, the same is not true of the treatment of chronic pain, a cardinal symptom of many rheumatological disorders. The publication of systematic reviews (SR) concerning the use of cannabis-based medicines for chronic pain (with and without meta-analyses) is outpacing that of randomised controlled trials. Furthermore, narrative reviews of public institution are largely based on these SRs, which often reach different conclusions regarding the efficacy and safety of cannabis-based medicines because of the lack of high-quality evidence of efficacy and the presence of indications that they may be harmful for patients. Societal safety concerns about medical cannabis (e.g. driving risks, workplace safety and pediatric intoxication) must always be borne in mind, and will probably not be addressed by clinical studies. Medical cannabis and cannabis-based medicines have often been legalised as therapeutic products by legislative bodies without going through the usual process of regulatory approval founded on the results of traditional evidence-based studies. This review discusses the advantages and limitations of using cannabis to treat rheumatic conditions.

1. Introduction

The history of cannabis is as old as it is colourful and controversial [1,2]. Cultivated in Central Asia for over 5000 years, it has been used for a variety of recreational, medical, ceremonial and even religious purposes, and so it is not surprising that one of the first documents attesting its medicinal use for indications such as rheumatic pain, constipation, female genital disorders and malaria dates back to 2737 BCE. Different parts of the plant have been used over time and in different populations: for example, the Chinese mainly used the seeds, which consist of essential fatty acids and proteins, but are deficient in D9-tetrahydrocannabinol (D9-THC). In India, cannabis is considered one of the five sacred plants and it has always been widely used for both medical and recreational purposes [3–5]: the different parts of the plant are used to obtain preparations with different concentrations of active cannabinoids (bhang, ganja, charas…), and consequently different psychotropic effects.

It quickly spread to the West, and its use in Europe was documented as long ago as in pre-Christian times [3]. The use of cannabis has always been strongly influenced by socio-economic factors. In the West, its prescription peaked in the XIX-XX centuries with the marketing of cannabis extracts by a number of pharmaceutical companies, but then the American Controlled Substances Act prohibited the possession of any quantity regardless of purpose.

However, the XXI century has witnessed a significant socio-political change, and cannabis has become increasingly socially accepted, and public demand for its legalisation has led to its possession being allowed in different amounts in different countries, and it has been

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approved by the regulatory authorities in the treatment of various disorders. It is not surprising that this radical change has led to a need for more information concerning the plant's potential benefits and safety. However, there is currently a paucity of high-quality evidence supporting the use of cannabinoids for medical purposes, which makes it legitimate for the scientific community to question the way in which cannabis is approved largely as a result of social and political pressure rather than in the usual regulatory manner, even if there is a pressing need for new drugs to treat a number of disabling diseases.

The aim of this article is to provide an objective analysis of the various points of view concerning the use of medical cannabis in rheumatic diseases, and discuss whether "putting the cart before the horse" was appropriate or inappropriate.

2. The use of cannabinoids in rheumatic diseases: pros

There is no disputing the fact that the cannabinoids have been a part of human culture for millennia and have always been used for various medicinal purposes, but this clearly is not sufficient to prove that they are useful or safe in the treatment of any specific indication. Humans have consistently found some of their effects pleasant or otherwise attractive, and this has gradually led many healthcare professionals to suspect that they are simply agents of vice and addiction, and regard with scepticism any evidence (or any attempt to acquire evidence) that may substantiate their usefulness. The following paragraphs will objectively describe the various lines of evidence suggesting that cannabinoids may play an even uniquely important role in the management of rheumatic disorders. This is by no means intended to encourage their indiscriminate use or suggest that they can replace evidence-based treatments that are crucially important in avoiding irreversible damage to patients; it is simply a plea for a modicum of mental flexibility and openness to change on the part of rheumatologists who, like all other physicians, can be expected to value such qualities.

2.1. Why might cannabinoids be good for rheumatic disorders?

Broadly speaking, there seem to be two major aspects of cannabinoids that may be useful in the management of rheumatic disorders; their anti-inflammatory and immunomodulatory activity, and their effects on pain and associated symptoms. It is interesting to note that, although a wide range of medications are available for the treatment of inflammation, including an ever-lengthening list of biological drugs, the same is not true of the treatment of chronic pain, a cardinal symptom of many rheumatological disorders. When considering whether cannabinoids should or should not be used, it is always necessary to bear in mind whether are any alternatives and how they compare with cannabis in terms of safety and efficacy. In the case of chronic pain, for which the chronic use of opioids is a highly hazardous and even lethal alternative, there may be a place for cannabinoids even though there are still many open questions.

2.2. The endocannabinoid system

The endocannabinoid system has finally become a subject of intense research and our understanding of it is rapidly increasing [6]. It is beyond the scope of this article to describe the system in detail, but it is necessary to mention some of its aspects in order to allow further discussion of how its manipulation can aid the management of rheumatological disorders.

Trans-Δ9-tetrahydrocannabinol (THC), the main psychoactive component of cannabis, was identified > 50 years ago and has since been extensively studied but, interestingly, cannabidiol (CBD), another important component of the phyto-cannabinoid system, seems to have attracted less scientific interest, possibly because it is not psychoactive [7]. Subsequent research has led to the discovery of cannabinoid receptors 1 and 2 (CBr1 and CBr2), their endogenous ligands anandamide (N-arachidonoyl-ethanolamine or AEA) and 2 arachidonoylglycerol (2-AG), and other molecules. The enzymes involved in the synthesis and degradation of endocannabinoids have also been identified, including fatty acid amide hydrolase 1 (FAAH) and monoacylglycerol lipase (MAGL, also known as MGL).

2.3. Cannabinoids in rheumatoid arthritis (RA)

There is a paucity of high-quality evidence supporting the use of cannabinoids in the treatment of RA, the prototypical inflammatory joint disease. Furthermore, the ever-increasing array of effective biological anti-inflammatory agents makes it even more challenging to consider cannabinoids.

Nabiximols is a cannabis-based medicine that has been clinically tested in RA patients in a preliminary randomised, placebo-controlled study in which 58 patients were treated for five weeks [8]. The treatment had a significant analgesic effect and suppressed disease activity to a greater extent than placebo.

Despite the dearth of evidence regarding their clinical usefulness, there are some interesting findings at the level of basic research that suggest cannabinoids have unique anti-inflammatory effects that may be relevant to the treatment of RA. For example, there is evidence of the presence of cannabinoid receptors in the synovial tissue of patients with RA or osteoarthritis [9], and it has been found that a cannabinoid compound is capable of decreasing the in vitro production of inflammatory mediators in the synovial fibroblasts of RA patients [10]. In one study based on the classical murine collagen-induced arthritis (CIA) model, the oral administration of cannabidiol had an efficacious anti-inflammatory effect [11], and another CIA study has found that the activation of CBr2 reduces joint destruction [12]. Other synthetic and plant-derived cannabinoids that have been effective in the CIA model, include JWH-133 [13], HU-320 [14] and THC [15]. Finally, as recently extensively reviewed by Gui et al. [16], cannabinoids have important in vitro anti-inflammatory effects on many other components of the immune system related to the pathogenesis of RA, and could therefore target multiple processes simultaneously.

2.4. Cannabinoids in systemic sclerosis

Systemic sclerosis (SSc) is a chronic, progressive, multi-system autoimmune disorder that is associated with significant morbidity and mortality [17]. Although considerable progress has been made in understanding its pathogenesis, the lack of suitable disease-modifying treatments highlights the importance of investigating new mechanisms.

The ability of the cannabinoid system to modulate fibrosis has been investigated in murine models of SSc. BALB/c mice with hypochlorite injection-induced SSc were treated with WIN-55,212 (a CBr1 and CBr2 agonist), JWH-133 (a selective CBr2 agonist) or phosphate-buffered saline (PBS), and underwent histological and biochemical assessments of skin and lung fibrosis, an assessment of fibroblast proliferation by means of thymidine incorporation, and an assessment of auto-antibody production [18]. It was found that treatment with WIN-55,212 and JWH-133 prevented the development of skin and lung fibrosis, and also reduced fibroblast proliferation and auto-antibody production, thus suggesting the potential of cannabinoid manipulation in the future management of SSc. Interestingly, it has been shown that inactivating CBr1 prevents experimental fibrosis in another murine model, thus indicating that CBr1 may have a deleterious effect [19], whereas activating CBr2 has anti-fibrotic effects in an experimental model of dermal fibrosis model [20]. Although establishing the clinical usefulness of manipulating cannabinoid pathways will obviously require a more precise understanding of its effects on fibrosis, given the impression that CBr2 activation may be beneficial, the selective CBr2 agonist lenabasum (JBT-101) has been tested in patients with diffuse cutaneous SSc in a phase II trial and open-label extension. It proved to have a favourable safety and tolerability profile, and led to a clinical

improvement [21,22]. A phase III trial of lenabasum is currently ongoing (ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2017 Dec 18 -. Identifier NCT03398837 Trial to Evaluate Efficacy and Safety of Lenabasum in Diffuse Cutaneous Systemic Sclerosis (RESOLVE-1) [23].

2.5. Cannabinoids in dermatomyositis

Another systemic autoimmune disorder in which cannabinoids are currently being investigated is dermatomyositis (DM). Corticosteroids are highly effective in achieving remission in DM patients but their well-known side effects make it imperative to identify other safe and effective disease-modifying agents.

One in vitro study has investigated the effect of ajulemic acid (anabasum, a chemically modified THC with a higher affinity for CBr2) on peripheral blood mononuclear cells taken from DM patients [24], and found that the use of moderate and high concentrations significantly reduced the production of TNF-α, IFN-α and IFN-β, all of which are key cytokines in the pathogenesis of DM.

A phase II, double-blind, randomised, placebo-controlled study has investigated the safety, tolerability and efficacy of lenabasum in the treatment of refractory skin-predominant DM using the primary endpoints of the change in the Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI) from baseline to 84 days, and the number of participants experiencing treatment-emergent adverse events (AEs) [25]. All of the patients involved in this study had a CDASI of > 14, minimal active muscle involvement, and had failed on or were intolerant of hydroxychloroquine and stable DM medications including immunosuppressants. They were followed up for 12 weeks on treatment (vs placebo) and another four weeks off treatment. There were no lenabasum-related serious, severe or unexpected AEs, but the study found consistent evidence of clinically beneficial effects on multiple efficacy outcomes, and an acceptable safety and tolerability profile. The patients participating in the double-blind study were subsequently eligible to receive lenabasum 20 mg twice daily in an open-label extension during which they continued the treatment for 28 weeks. The patients showed improvements in the CDASI and physician Likert-scale assessments of global disease activity, skin disease activity, and extra-muscle disease activity from the beginning of the open-label extension and from the start of the study. Moreover, there were improvements in multiple patient-reported outcomes, including patient 10 cm visual analogue scale (VAS) scores of global disease activity, skin disease activity, itching and pain, the Skin-dex-29 symptoms domain, and the PROMIS-29 physical function, fatigue, pain interference and anxiety domains [26]. Lenabasum is currently being evaluated in an ongoing phase III, multicentre, double-blind, randomised, placebo-controlled study assessing its efficacy and safety in the treatment of dermatomyositis [27].

2.6. Cannabinoids in osteoarthritis (OA)

OA is the most common joint disease worldwide and a major cause of disability [28], but there is still no effective disease-modifying agent. It has recently been recognised as a true chronic pain condition, with elements of pain sensitisation similar to those associated with other chronic pain conditions [29,30]. CBr1 and CBr2 (considered to play a role in OA-related central pain sensitisation) are expressed on OA synovia and chondrocytes, and the endocannabinoid anandamide has been found in the synovial fluid of OA patients but not in that of healthy controls. In a murine model of surgically induced OA, treatment with a CBr2 agonist was associated with milder disease [31], and it has been found that CBr2 is associated with the regulation of the central sensitisation and pain of knee OA [32]. Although there is a lack of clinical trials, it therefore seems that cannabinoids are well placed to enter the field of OA treatment with their possible effects on both pain and inflammation.

2.7. Cannabinoids in fibromyalgia syndrome

Fibromyalgia syndrome (FMS) is a chronic widespread pain condition classically considered to be a prototype of centralised pain (also recently called nociplastic pain) [33,34]. Its etiology is still unclear but a leading pathogenetic hypothesis suggests that FMS-related pain is due to an increase in the processing/decrease in the inhibition of pain within the central nervous system. It has also been hypothesised that FMS represents a state of “endocannabinoid deficiency” [35], although there is no specific evidence to support this hypothesis.

As in the case of many other chronic pain conditions, the usefulness and tolerability of pharmacological treatment is limited and, although patients receive some benefit from non- pharmacological interventions, there is still a real need to identify a means of relieving the salient symptoms of pain and disturbed sleep. Patients are therefore understandably interested in the use of cannabinoids, particularly phytocannabinoids, but there are only very limited data concerning their clinical usefulness, although nabilone, a synthetic cannabinoid, has shown some promise [36,37]. A report published by the US Academies of Science, Engineering and Medicine has stated that there is conclusive evidence supporting the treatment of chronic pain with cannabis, and moderate evidence supporting the treatment of sleep disorders in patients suffering from chronic pain [38]. However, despite this broad assertion, it is clear that further evidence is required concerning the rational use of cannabinoids, and it will be necessary to answer questions such as which cannabinoid should be used for which indication, what is the long-term safety profile, and what is the optimal route of administration, which explains why a significant amount of industry-driven research seems to be directed towards evaluating various cannabinoid-based solutions.

2.8. Can cannabinoids solve the opioid epidemic?

Despite the use of effective anti-inflammatory treatment, chronic pain is a serious problem to rheumatological patients, and Basu et al, have recently elegantly demonstrated that RA patients are affected by some of the neurobiological features of FMS [39]. At the same time, alarming data from the USA indicate that as many as 41% of RA patients are regularly using opioids, and an additional 19% are intermittent users [40]. Given the catastrophic epidemic of opioid overdosing and the associated mortality [41], even in the absence of sufficient evidence, it is imperative to consider cannabinoids as an alternative for rheumatic patients suffering from chronic pain if only because of their superior safety profile (mainly due to the lack of respiratory suppression).

In brief, given the protean aspects of managing rheumatic diseases, cannabinoids offer a fascinating and rapidly expanding field of bench-to-bedside research. Their effects on chronic pain, inflammation, autoimmunity and fibrosis are all under investigation and they may eventually cover specific therapeutic niches in the field of rheumatology. Although caution and clinical judgement are always necessary, and other questions remain, cannabinoids should now be directly compared with the available alternative measures, and rheumatologists need to acquire greater knowledge and confidence in considering cannabinoids because they are not going away any time soon.

3. The use of cannabinoids in rheumatic diseases: Cons

Rheumatic diseases are lifelong and, even in the case well-controlled inflammation, more than half of all patients experience ongoing chronic pain. Furthermore, pain is the predominant symptom of the degenerative joint diseases that afflict almost everybody in the later years of life. As it has been pre-clinically shown that cannabinoids have effects on both pain and inflammation, it is not difficult to understand why they are beginning to be considered an attractive option in the treatment of rheumatic diseases. It is not only because the currently

available drugs are sub-optimal in managing pain, but also because the most prevalent category of analgesic drugs (the opioids) have led to catastrophic health-related adverse effects, including addiction and overdose-related deaths.

However, competent XXI century patient care must be founded on evidence-based medicine and not on anecdotal cases, advocacy or political interests, and there is still a lack of evidence supporting the use of cannabinoids in the management of rheumatology patients. On the basis of evidence concerning their effects on all chronic pain conditions, evidence relating to rheumatic diseases, and questions that are particularly pertinent to rheumatology patients, we still support D'Souza's editorial comment of five years ago that medical cannabis is a case of "the cart is before the horse" [42].

3.1. Lack of high-quality evidence supporting the efficacy of medical cannabis and cannabis-based medicines

3.1.1. Chronic pain in general

The publication of systematic reviews (SR), with and without meta-analyses, of the use cannabis-based medicines in the treatment of chronic pain is outpacing that of randomised controlled trials (RCTs) and, although often reaching conflicting conclusions concerning the efficacy and safety of cannabis-based medicines, these SRs are subsequently widely used as the basis of for narrative reviews of public institutions. Furthermore, their conclusions are all the more sobering when rigorous study inclusion criteria are applied (e.g. studies with a duration of at least four weeks), when the search strategy is more complete (e.g. the inclusion or otherwise of unpublished studies, which often describe negative results), and when high standards are used to judge the quality of the evidence (e.g. the Grading of Recommendations Assessment, Development and Evaluation [GRADE] [43] vs undefined criteria of evaluation) [44].

For example, a quantitative analysis by Aviram et al. considered 24 RCTs involving a total of 1334 patients with any chronic pain syndrome, and included studies of any duration that tested any cannabis-based or cannabis-like drugs (e.g. experimental drugs not available for clinical use). The authors concluded that there was "limited evidence showing more pain reduction in chronic pain" (standardised mean difference [SMD] -0.61, 95% CI from −0.78 to −0.43; moderate effect size) [45]. This analysis did not include the studies with mainly negative results that are only available in databases [46], whereas Stockings et al. included "grey literature" in their meta-analysis of 30 RCTs of cannabis-based treatments in patients with chronic non-cancer pain, and found a non-substantial SMD (0.14, 95% CI from −0.20 to −0.08). Furthermore, the duration of the individual studies influenced the reported effects: the one-day and very short-term (4-week) studies remained significant, whereas the effect sizes of those lasting 4–12 weeks, 13–26 weeks or > 26 weeks progressively decreased [47].

Some frequently cited SRs with meta-analyses have methodological flaws: for example, the conclusion of Whiting et al. [48] that "there was moderate-quality evidence to support the use of cannabinoids for chronic pain" is questionable for various reasons. It is based on the results of only seven RCTs even though additional studies would have been available; the studies included one of medical cannabis, six of nabiximols for neuropathic pain, and one of nabiximols for cancer pain that found ≥30% pain relief; and the odds ratio (OR) was 1.41 (95% CI 0.99–2.00) which, as the CI included 1, gives a significance level of > 0.05.

The widely cited and influential report of the US National Academies of Science, Engineering and Medicines [38] relied on the SRs by Whiting et al. [48] and Andreae et al. [49], and concluded that "there is substantial evidence that cannabis is an effective treatment for chronic pain in adults." However, how was the quality of the evidence graded and what was the basis for these conclusions? The weight of the evidence was "determined during private deliberations of subgroups of the committee", but this hierarchy of evidence does not reflect the magnitude of the observed effect or the importance of the health effect from an individual or population standpoint [38].

3.1.2. Chronic pain in rheumatic diseases

Medical cannabis has not been assessed in rheumatic diseases in any published RCT. Only five RCTs of medical cannabis for the treatment of chronic pain have been published, and these included a total of 178 participants with different neuropathic pain syndromes. One systematic review reported clinically relevant ≥30% pain relief, with six (95% CI 3–13) as the number of patients needed to treat for an additional benefit (NNTB) [49]. However, only one of these studies lasted four weeks, and two lasted only one day (so-called experimental studies). Two studies recruited only patients with HIV-associated polyneuropathy, most of whom were previous users of recreational cannabis, and were conducted before the era of highly active anti-retroviral therapy. [49]. In brief, the applicability of the results of these studies to all patients with chronic pain conditions is limited.

Cannabis-based medicines (but not medical cannabis) have been studied in a total of 162 patients. Nabilone has been assessed in two very low-quality studies (according to Cochrane standards) of fibromyalgia patients lasting four weeks, neither of which included an intention-to-treat analysis. Skrabek et al. carried out a a cross-over study of 40 patients treated with nabilone or placebo [50] and found that "there were significant decreases in the VAS (pain) (-2.04, $p < 0.02$) and the FIQ (-12.07, $p < 0.02$) in the nabilone-treated group at 4 weeks. There were no significant improvements in the placebo group. The treatment group experienced more side effects per person at 2 and 4 weeks (1.58, $p < 0.02$ and 1.54, $p < 0.05$ respectively). Nabilone appears to be a beneficial, well-tolerated treatment option for fibromyalgia patients" [50]. However, the conclusions of this study are questionable as the study did not follow the standard method of reporting the results of pain trials. The pre- and post-treatment comparisons of the study outcomes were presented separately, but without a comparison of nabilone and placebo at the end of treatment. Failing to obtain clarification from the authors, the Cochrane authors compared the pain score and the total Fibromyalgia Impact Questionnaire (FIQ) score at the end of treatment on the basis of the data given in the figures of the paper, and found no statistically significant difference between nabilone and placebo in terms of either outcome [51]. Another cross-over study of 34 patients compared nabilone with amitriptyline, and found that nabilone was statistically significantly superior in terms of one of two sleep scales, but there were no significant differences in pain relief or the health-related quality of life [52].

One five-week RCT conducted before the era of biological treatment tested oro-mucosal nabiximols in 58 patients whose RA was inadequately controlled by standard medication, but the primary efficacy variable of "morning pain on movement" is not a standard measure in rheumatology trials. There were seven other outcome measures, and nabiximols was statistically significantly superior to placebo in only three out of six pain outcomes and the reduction in the DAS 28 score [53].

A 14-week cross-over study of 30 patients with chronic musculoskeletal pain treated with nabilone in addition to conventional analgesics (4-week treatment periods with a 2-week washout period) found that nabilone was statistically superior to placebo in terms of pain reduction in only one out of four pain measures, but the study did not have a defined primary outcome [54].

Regulatory bodies such as the European Medicines Agency require adequately powered, double-blind RCTs lasting at least 12 weeks and, in order to obtain approval, an experimental drug must demonstrate superiority in relieving pain in comparison with placebo or an established drug treatment [55]. Neither medical cannabis nor any cannabis-based medicine would meet these requirements for any rheumatic disease.

3.1.3. Uncertainties about the concentration and ratio of tetrahydrocannnibol (THC) and cannabidiol (CBD) in medical cannabis flowers

Many patients are currently using or experimenting with medical cannabis, and some seek advice from friends, the social media, or "experts" who claim a detailed knowledge of the ideal strain to treat a specific condition. However, any advice they may receive is more likely to be based on personal opinions than sound clinical evidence.

The cannabis strains currently available for medical use have TBC concentrations ranging from 1% to 22% and CBD concentrations of < 1–9% [56] There are limited data on the optimal dosing of THC for some chronic pain syndromes, but none for rheumatic diseases. One RCT tested smoked cannabis with TBC concentrations of 0%, 2.5%, 6% and 9.4% over four 14-day periods in a crossover trial involving 23 patients with different peripheral neuropathic pain syndromes, and found that only the concentration of 9.4% led to a statistically significant reduction in pain. However, the total number of adverse events and the number of participants reporting at least one adverse event increased with the concentration of THC. No data were given concerning CBD content [57].

The uncertainties concerning the concentration and ratio of THC and CBD were highlighted in a recent experimental, randomised, placebo-controlled, 4-way crossover trial involving 20 patients with FMS. The study tested single vapour inhalations of various cannabis strains: Bedrocan (22% THC, < 1% CBD), Bediol (13.4% THC, 17.8% CBD), Bedrolite (18.4% CBD, < 1% THC), and a placebo variety containing terpenes but no THC or CBD. None of the treatments had a more than placebo effect on spontaneous or electrical pain responses, although a greater proportion of subjects receiving Bediol experienced a significant 30% decrease in pain scores in comparison with placebo. Spontaneous pain scores correlated with the magnitude of the drug-induced high, but what is more interesting is that CBD inhalation increased THC plasma concentrations but diminished THC-induced analgesic effects, thus indicating the synergistic pharmacokinetics but antagonistic pharmacodynamic interactions of THC and CBD [58]. These observations not only highlight the complexity of the molecular make-up of cannabis plants, but also the nuances of their physiological effects.

These uncertainties mean that it is not possible to make any high-quality recommendations concerning the choice of cannabis strain but, unfortunately, there is an abundance of advice on the social media from individuals and organisations who stand to benefit financially.

3.1.4. Uncertainties about method of administration (inhalation or oral use)

Smoking of any combustible product is contraindicated because of its irritative bronchial effects, and specifically contraindicated in the case of people with inflammatory rheumatic diseases because of its adverse impact on the disease process. Many people today use dried cannabis and a vaporiser that heats it to lower temperatures (about 180–220 °C), thus reducing the production of toxic hydrocarbons and other by-products of combustion. However, the absorption of the ingredients of inhaled medical cannabis varies from 2% to 56% depending on the depth of inhalation and how long the breath is held, which makes it difficult to recommend doses [59]. Furthermore, inhalation rapidly leads to much higher plasma molecule levels than those needed to relieve pain [60], and also increases the risk of other psychotropic effects.("feeling high") that may promote dependency. For these reasons, the inhalation of cannabis is not recommended.

An alternative to inhalation that is preferred by many patients is the use of cannabis oil extracts but, as their effects develops more gradually, there is a risk that repeated doses may need to be administered before there is any noticeable symptom relief, and that leads to the risk of over-dosing. Secondly, the current culture of administering "a few drops" has echoes of medical practices a century ago, whereas patients and physicians should know the exact molecular content of any medical product, ideally measured in terms of milligrams of the active ingredient. Finally, the use of medicine administered in the form of food such as a biscuit, spread or sweet is to be decried because this is not the standard of medical care as the dose cannot be calculated and there is a risk of it being inadvertently taken by others, especially children.

3.1.5. Safety concerns

Any recommendation has to balance benefits and harms [61], but some authors have failed to address the risks of cannabinoids adequately and only concentrated on their potential benefits. For example, the conclusion of Whiting et al. did not take into account the harms associated with cannabinoids [48], whereas Stocking et al. considered all factors, including the high NNTB and the low number needed to treat for an additional harm (NNTH), and stated: "It seems unlikely that cannabinoids are highly effective medicines for chronic non-cancer pain "[47]. Furthermore, the Cochrane review of medical cannabis and cannabis-based medicines reported an NNTH of 3 for central nervous system disorders and 10 for psychiatric disorders [62]. Medical cannabis and cannabis-based medicines are therefore no miracle drugs in terms of safety.

3.1.6. Harms that are not captured by RCTs

Short-term studies of cannabis-based medicines may fail to capture less frequent harms or those that may occur after prolonged use. Potential psychomotor effects may affect safety when driving and increase the risk of an accident: given the increasing rates of cannabis-associated motor vehicle fatalities, it is likely that people using medical cannabis are more susceptible to having an accident, especially when the treatment is combined with other psychoactive drugs or alcohol. Secondly, it is known that the recreational use of cannabis is associated with addiction, but nothing is known about this possibility in the case of medicinal cannabis. Addiction is related to the frequency of use, and it can be expected that 25–50% of the people using cannabis daily will become addicted – a sobering thought given that cannabis may be used for many years by patients with chronic (life-long) rheumatic diseases. The inhalation of cannabis, and the consequent rapid increase in plasma THC concentrations may also give rise to the risk of abuse.

Patients reporting the use of cannabis for medical reasons may be transforming recreational use into a more socially acceptable form. In a study of 1000 people with a rheumatologist-confirmed diagnosis attending a Canadian University Rheumatology Clinic, 82% of those who reported the use of medical cannabis had previously been recreational users, and 39% said that they were also currently using cannabis for recreational reasons. The cannabis users were younger, unemployed, and had poorer global health than the non-users [63], and similar characteristics have been observed in the case of abusers of prescribed opioids [64]. Finally, the US 2015 National Survey on Drug Use and Health found that medical marijuana users were significantly more likely to report the non-medical use of pain relievers, stimulants and tranquillisers in the previous 12 months [65].

3.1.7. Associations between cannabis and somatic diseases

The albeit limited and conflicting evidence provided by epidemiological studies has not identified a robust and consistent association between the use of cannabis and various types of cancer, with the possible exception of testicular cancer (i.e. testicular germ cell tumours). The association between chronic heavy cannabis smoking (without tobacco) and chronic obstructive pulmonary disease is unclear and, if present, is likely to have a small effect. Increasing but still limited evidence from case studies suggests that the use of cannabis is associated with allergic/hypersensitive reactions, and both case studies and observational studies suggest that the acute and chronic smoking of cannabis is associated with harmful effects on vascular, cardiovascular and cerebrovascular health (e.g. myocardial infarction, stroke, arteritis), especially in middle-aged and older users [59].

3.1.8. Guideline recommendations

We are not aware of any guideline endorsed by national guideline clearing houses or national or international rheumatology associations that recommends medical cannabis and cannabis-based medicines for pain management in rheumatic diseases. The position paper of the European Pain Federation recommends their use in the case of chronic non-cancer and non-neuropathic pain only in exceptional cases and as an individual trial. Oral and oro-mucosal cannabis-based medicines should be preferred over inhaled medical cannabis [66].

Despite the lack of evidence supporting the use of medical cannabis in rheumatology patients, the Canadian Rheumatology Association acknowledges the need to give patients empathetic and pragmatic guidance concerning medical cannabis. A prescription should only be drawn up by a healthcare professional who knows the patient well and is responsible for his/her care. Cannabis should not be prescribed following an on-line consultation or by so-called “cannabis experts” who restrict themselves to prescribing cannabis and neglect global patient care. Medical consultations should include documentation of the medical condition, the reason(s) for considering medical cannabis, associated co-morbidities, current medications and previous treatments; any psychosocial history must include an assessment of mental health status that takes into account any previous or present psychosis or substance use disorder [67].

The Canadian Simplified Guideline for Prescribing Medical Cannabinoids in Primary Care recommends against using medical cannabinoids in the treatment of pain associated with rheumatological conditions (including osteoarthritis and low back pain) because of the lack of evidence and known harms (strong recommendation) [68]. In conclusion, “The available evidence is not yet sufficient to support the recommendation of cannabinoid treatment for rheumatic diseases” [69].

Our concerns are based on the lack of high-quality evidence of efficacy and the reports of possible harms for patients. Furthermore, societal questions (e.g. driving risks, workplace safety, the inadvertent poisoning of children), which must always be borne in mind, are probably not captured by clinical studies. Medical cannabis and cannabis-based medicines have by-passed the usual evidence-based pathway to drug approval, and have been legalised as therapeutic products by the legislative bodies of various countries [70,42]. It should be remembered that the opioid epidemic in North America started with anecdotal evidence and expert advice: there is no place for a medical cannabis epidemic in the future [71].

4. Conclusions

The evidence justifying the use of cannabis in various medical conditions requires active, double-blind, randomised, placebo or active drug-controlled clinical trials in order to test short- and long-term efficacy and safety. At present, cannabinoids should only be considered as complementary therapy in the management of rheumatic diseases. Rheumatologists need to be prepared to develop a greater understanding of the real therapeutic role of cannabinoids, retain a modicum of mental flexibility and openness to change, and abandon any automatic “cannabinoid scepticism”. Medical cannabis is not a life-saving drug, and so it may be useful to begin by adopting a cautious approach to prescription until high-quality evidence is available to guide a rational treatment strategy.

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