RHEUMATOLOGY

Rheumatology 2021;60:549–556
doi:10.1093/rheumatology/keaa534
Advance Access publication 7 November 2020

Systematic review and meta-analysis

Cannabis use assessment and its impact on pain in rheumatologic diseases: a systematic review and meta-analysis

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Abstract

Objectives. Despite classic analgesic or effective treatments in rheumatic diseases, such as synthetic DMARDs in RA, patients remain in pain and often turn to non-prescribed pharmacological alternatives, such as cannabis self-therapeutic use. However, this medical use of cannabis has not been thoroughly studied.
Methods. We performed a systematic literature review up to June 2020. The incidence of cannabis consumption was calculated by metaproportion. Differences between cannabis users and non-users were expressed as standardized mean differences using the inverse-variance method. We also assessed the effects of cannabis on pain.
Results. A total of 2900 patients reported cannabis consumption in a sample of 10 873 patients [incidence 40.4% (95% confidence interval (CI): 0.28, 0.54)], and 15.3% (95% CI: 0.07, 0.27) specified that they were currently taking cannabis. Cannabis use was higher in the four fibromyalgia studies [68.2% (95% CI: 0.41, 0.90), $n = 611$] compared with seven articles concerning RA or lupus [26.0% (95% CI: 0.14, 0.41), $n = 8168$]. Cannabis consumption was associated with a decrease in pain intensity [VAS pain at baseline 8.2 (2.9) *vs* 5.6 (3.5) mm over time; pooled effect size −1.75 (95% CI: −2.75, −0.76)]. Cannabis users were younger [58.4 (11.4) *vs* 63.6 (12.1) years; $P < 0.001$], more often smokers [OR 2.91 (95% CI: 1.84, 4.60)] or unemployed [OR 2.40 (95% CI: 1.31, 4.40)], and had higher pain intensity [5.0 (2.4) *vs* 4.1(2.6) mm; $P < 0.001$] than non-users.
Conclusion. Nearly 20% of patients suffering from rheumatologic diseases actively consume cannabis, with an improvement in pain. The issue of cannabis use in the management of these patients should be addressed during medical consultation, essentially with cannabis-based standardized pharmaceutical products.

Key words: cannabis, rheumatology, meta-analysis

Rheumatology key messages

- Nearly 20% of patients suffering from rheumatologic diseases actively consume cannabis.
- Cannabis consumption was associated with an improvement of pain.
- Cannabis users were younger, more often smokers, unemployed and painful than non-users.

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Submitted 5 May 2020; accepted 24 July 2020

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Introduction

Rheumatic diseases, such as RA and ankylosing spondylitis, are characterized by synovitis, causing pain and disability. The number of disease-modifying anti-rheumatic drugs is increasing, with TNF-alpha inhibitors, methotrexate, and IL6 inhibitors allowing better control of disease activity and more frequent clinical remission.

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This clinical remission is mostly associated with reduced pain. In addition, JAK inhibitors were recently reported to rapidly decrease patient-reported pain [1, 2]. However, despite effective treatments for rheumatic disease and clinical remission, some patients still report pain of high intensity that affects their quality of life.

In the same way, other rheumatologic diseases, such as fibromyalgia, degenerative back pain, and OA, suffer from a lack of effective treatments and cause pain that is hardly relieved by conventional analgesic treatments. Therefore, it is not uncommon that patients suffering from these rheumatic diseases admit during consultation to taking pharmacological alternative treatments, such as a self-therapeutic cannabis use, to relieve their pain.

Several studies have shown an interesting effect of cannabis as an adjuvant treatment in chronic diseases, such as Parkinson's and multiple sclerosis, to improve symptoms [3–6]. Recently, application of transdermal cannabidiol was shown to decrease pain in temporomandibular disorders [7]. In a meta-analysis of chronic non-cancer pain (neuropathic pain, central pain in multiple sclerosis, and one study on RA), Lynch *et al.* concluded that cannabis demonstrates a significant analgesic effect compared with placebo, with significant improvement in sleep [8]. In rheumatology, the number of studies assessing the effects of cannabis in patients with RA or OA is low. In animal studies, cannabis has been associated with a decrease in OA pain in rats and an increase in comfort and activity in dogs with OA [9, 10]. In a previous meta-analysis in 2016, Fitzcharles *et al.* only found four randomized controlled trials assessing the efficacy and safety of cannabis in RA, OA or fibromyalgia, and no article was useful for quantitative analysis [11]. However, the medical community is well aware that cannabis could have an interesting effect. An editorial and another article by Fitzcharles *et al.* recently recalled the potential effects of cannabis in rheumatology, but also warns of the need for medical supervision in cannabis use, and that more studies are needed [12, 13].

We performed a meta-analysis of published studies or abstracts to better estimate the incidence of cannabis consumption, assess the effects of cannabis on pain in patients suffering from rheumatologic diseases, and compare the characteristics of cannabis users to those of non-users.

Methods

Literature search

We searched PubMed, the Cochrane library and the EMBASE databases to find reports of interest published up to 30 June 2020 . All observational or case/control studies monitoring cannabis use in a retrospective survey or trial were included. We also searched all studies that assessed the effects of cannabis on pain over time or compared with controls. The following search terms were used in Pubmed: '(cannabis OR cannabinol OR cannabinoids) and (rheumatoid OR OA OR ankylosing OR arthritis OR arthralgia OR pain OR spondylitis)'. In the Cochrane Library and in EMBASE, the search equation used the same terms with more combination (supplementary material, section Key-words equations for literature search, available at *Rheumatology* online). Our search involved articles published in English or French only. A manual search of references was also carried out. We collected data from the electronic abstract databases of the annual scientific meetings of the European League Against Rheumatism and American College of Rheumatology from 2009 to 2019 using the term 'cannabis'.

Trial selection

Two investigators (M.G. and S.M.) selected potentially relevant articles after reading the title, keywords, abstract and then the full text. Disagreements in article selection were resolved by consensus after discussion between the two previous investigators and a third one (M.S.). The inclusion criteria for the full text were: study population comprising patients with rheumatologic diseases (RA, lupus, arthritis, fibromyalgia) using cannabis, observational or case/control study, published in English or French before 30 June 2020, and provides data on the number of patients using cannabis or mean standard deviation of pain. Studies on neuropathic pain or other types of pain were included if patients were suffering from rheumatologic diseases. On the contrary, studies assessing the effects of cannabis on neuropathic pain in patients with systemic sclerosis, diabetes, VIH or treated by chemotherapy were excluded. The other exclusion criteria were: commentary or discussion papers, case reports and studies including fewer than five patients, no data on cannabis incidence, full-text article not available, data not suitable for statistical analysis (no standard deviation or interquartile range), study on chronic cancer pain, or study on chronic non-cancer pain without patients with rheumatologic diseases.

Data extraction

One investigator (S.M.) extracted all data using a standardized data abstraction form. For all extracted data, a central value (mean or median) and variability (standard deviation or interquartile range) were obtained.

Extraction of cannabis information

For observational studies, we extracted the number of patients who had ever used cannabis and were currently taking cannabis. These patients were defined as cannabis users. We also found the number of patients who never used cannabis (cannabis non-users). For these populations, we extracted the mean and standard deviation age, pain and the percentage of females, smokers and unemployed.

Extraction of pain parameters

For longitudinal studies, we recorded the mean and standard deviation pain at baseline *vs* controls and over time.

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Statistical analysis

Baseline characteristics were summarized for each study sample and reported as the mean with standard deviation or number and percentage for continuous and categorical variables, respectively. The incidence of cannabis consumption was then calculated by a meta-analysis of proportions estimated using the inverse-variance method. The Mantel–Haenszel procedure was used to determine the odds ratio (OR) for tobacco use and unemployment. This method provides a common OR estimate and 95% confidence interval (CI). For continuous variables (i.e. age and pain intensity), means and standard deviations were compiled when available, or estimated using Hozo *et al.* when median and interquartile range were reported [14]. The differences between cannabis users and non-users were expressed as the standardized mean difference (SMD) using the inverse-variance method. The SMD was interpreted according to Cohen [15]: <0.2 as trivial, 0.2–0.3 as small, 0.5–0.8 as moderate and >0.8 as large. For paired comparisons, the standard deviation of the difference between time points was estimated using the following formula:

$$\sqrt{\left((SD_{T0}^2 + SD_{T1}^2) - (2 \times 0.5 \times SD_{T0} \times SD_{T1})\right)}.$$

Statistical heterogeneity was assessed by examining forest plots, CIs and calculating the I^2 index, which is the most common metric for measuring the magnitude of between-study heterogeneity and is easily interpretable. I^2 values range between 0% and 100% and are typically considered low when <25%, modest when 25–50%, and high when >50%. Random-effects models assuming between and within study variability (DerSimonian and Laird approach) were used if heterogeneity was present; otherwise, a fixed effect model was used.

Type-I error was fixed at 5% and two-sided. All statistical analyses were performed using Review Manager software (version 5.0) produced by the Cochrane Collaboration, and Stata software (version 15, StataCorp, College Station). All of the items required in the PRISMA checklist were fulfilled in this study.

Results

Eligible studies

Fig. 1 is a flow chart of the literature search and study inclusion. A total of 3332 citations were obtained from the initial search. After reading the title, abstract and full text, we obtained 16 eligible studies, plus seven found searching abstract databases, for a total of 14 342 patients with rheumatologic diseases (Fig. 1). The weighted mean age was 57.3 (12.8) years ($n = 6912$); 75.3 76.4% of assessed patients were women ($n = 7167$), and the weighted mean pain intensity at baseline was 6.6 (2.9) mm ($n = 2079$).

Study characteristics

Of the 23 publications, seven were abstracts, seven were cross-sectional, including six surveys sent to patients, and nine were longitudinal studies. Fifteen studies assessed the occurrence of cannabis consumption. Eight studies provided the characteristics (age, pain intensity, sex, unemployment) of cannabis users and non-users and allowed comparisons. Five studies assessed the effects of cannabis on pain over time, but only one of these studies also concerned controls without rheumatologic diseases (Supplementary Table S1, available at *Rheumatology* online).

Cannabis consumption

In the 15 studies on rheumatologic diseases, comprising a sample of 10 873 patients, 2900 patients attested to having already used cannabis, resulting in an incidence of 40.4% (95% CI: 0.28, 0.54). The purpose of cannabis use was rarely specified. Only three studies described it as an analgesic use and two said 'medical cannabis'. In five studies ($n = 4122$ patients), 485 patients specified that they currently were taking cannabis, for an incidence of 15.3% (95% CI: 0.07, 0.27). Considering only the four studies assessing the incidence of cannabis use in fibromyalgia ($n = 611$patients), we found a higher incidence than in the entire sample of articles [68.2% (95% CI: 0.41, 0.90)]. In contrast, in the seven articles on inflammatory rheumatic diseases only (e.g. RA and lupus; $n = 8168$), the incidence of cannabis consumption was lower [26.0% (95% CI: 0.14, 0.41)].

Comparison of cannabis users and non-users

Eight case/control studies distinguished patients as cannabis users ($n = 1775$) or non-users ($n = 8372$). Cannabis users were younger (Fig. 2), and more often smokers and unemployed (Table 1). Only two studies assessed the link between cannabis and alcohol use. A significant relationship was found, with a three-fold risk of cannabis use among alcohol drinkers [148/304 (48.7%) *vs* 382/1581 (24.2%); OR 3.12 (95% CI: 2.41, 4.04)]. The proportion of cannabis users was lower in female patients [OR 0.59 (95% CI: 0.34, 1.03); $P = 0.06$]. In the five studies assessing pain intensity, weighted mean pain was higher in cannabis users than non-users [5.0 (2.4) *vs* 4.1 (2.6) mm; $P < 0.001$, Fig. 3].

Effects of cannabis on pain over time

Six studies assessed the effects of cannabis on pain ($n = 1079$ patients). Compared with baseline, cannabis consumption was associated with a significant decrease in pain [visual analogic scale (VAS) pain at baseline: 8.2 (2.9) *vs* 5.6 (3.5) mm over time; pooled effect size: −1.75 (95% CI: −2.75, −0.76); Fig. 4]. We found no time effect in the meta-regression [$P = 0.47$; Supplementary Fig. S1, available at *Rheumatology* online, and no effect of publication bias (Egger test $P = 0.10$)]. In these six studies, cannabis products were

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Fig. 1 Flowchart of study selection

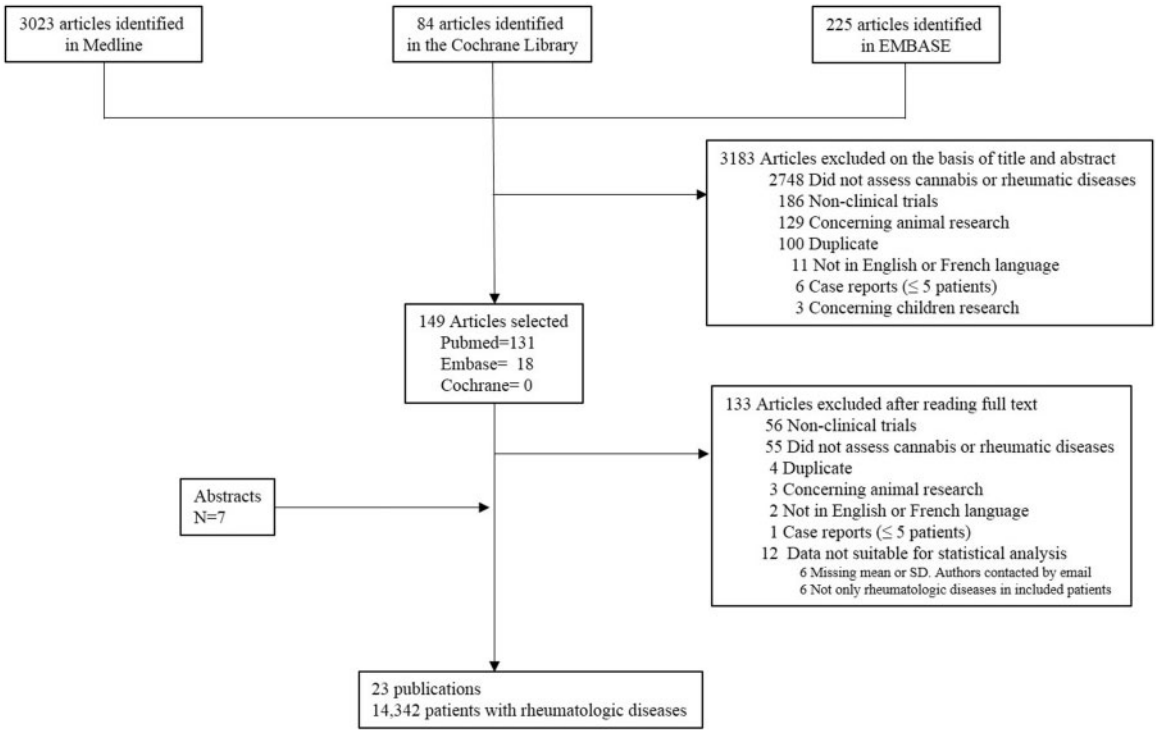
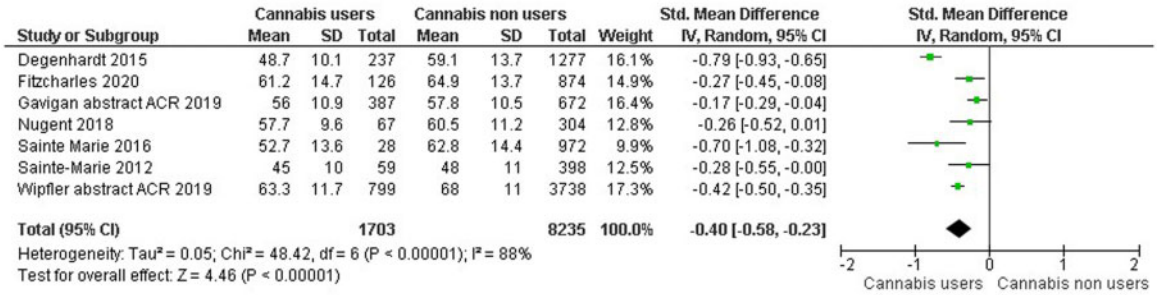


Fig. 2 Forest plot for the difference in age between cannabis users and non-users



composed of two major active components: tetrahydrocannabinol 5%, 12.5% or 19% and cannabidiol CBD from 1% to 20%. Method of cannabis consumption was smoking from 27% to 77%, vaporizing from 35% to 100%, oil under tongue or oral capsules. Tolerance was good with mild or moderate side effects. Patients reported red eyes (7–90%), dry mouth (7% to 27%), hunger feeling (1–15%), sore throat (10%), nausea (1% to 5%), somnolence (2–3%), hyperactivity (1% to 5%) or mood deflection (7%). Two studies reported a significant improvement of quality of life and depression related symptoms (Geraldi *et al.* [16] and Sagy *et al.* [17]). Sleep disorders were also improved after cannabis use but in a significant way only in one of these two studies.

Discussion

In this meta-analysis, we found an increased incidence of cannabis consumption, both ever and current, among patients with rheumatologic diseases. Assessment of cannabis consumption is difficult because it is often underestimated when linked to the declarative collection of patients, who hesitate to disclose their use considering its illegal nature. These results are similar to those of a survey conducted in France in 2016 with a representative sample of the population aged 15–75 years [18]. Cannabis experimentation occurred among 42% of adults and current use was reported by 11% of 18 to 64-year-olds. Unfortunately, mean age of the sample of

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Table 1 Comparison of characteristics between cannabis users and non-users

Characteristic	*n* studies	Cannabis users	Non-users	Fixed or random effects	*P*-value	I^2
Age, years, weighted mean (S.D.)	7	58.4 (11.4)	63.6 (12.1)	SMD −0.40 [−0.58, −0.23]	<0.001	88%
Tobacco use, %	6	702/1329 (52.8%)	2652/7302 (36.3%)	OR 2.91 [1.84, 4.60]	<0.001	88%
Female, %	8	1349/1775 (76.0%)	6418/8372 (76.7%)	OR 0.59 [0.34, 1.03]	0.06	93%
Unemployment, %	5	486/837 (58.1%)	1296/4193 (30.9%)	OR 2.40 [1.31, 4.40]	0.005	88%
Pain intensity, mm, weighted mean (S.D.)	5	5.0 (2.4)	4.1 (2.6)	SMD 0.38 [0.32, 0.44]	<0.001	52%

OR: odds ratio; SMD: standardized mean difference.

Fig. 3 Forest plot for the difference in pain intensity between cannabis users and non-users

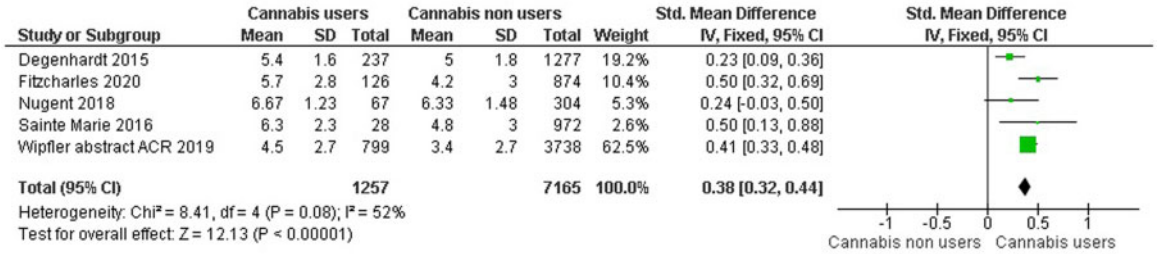
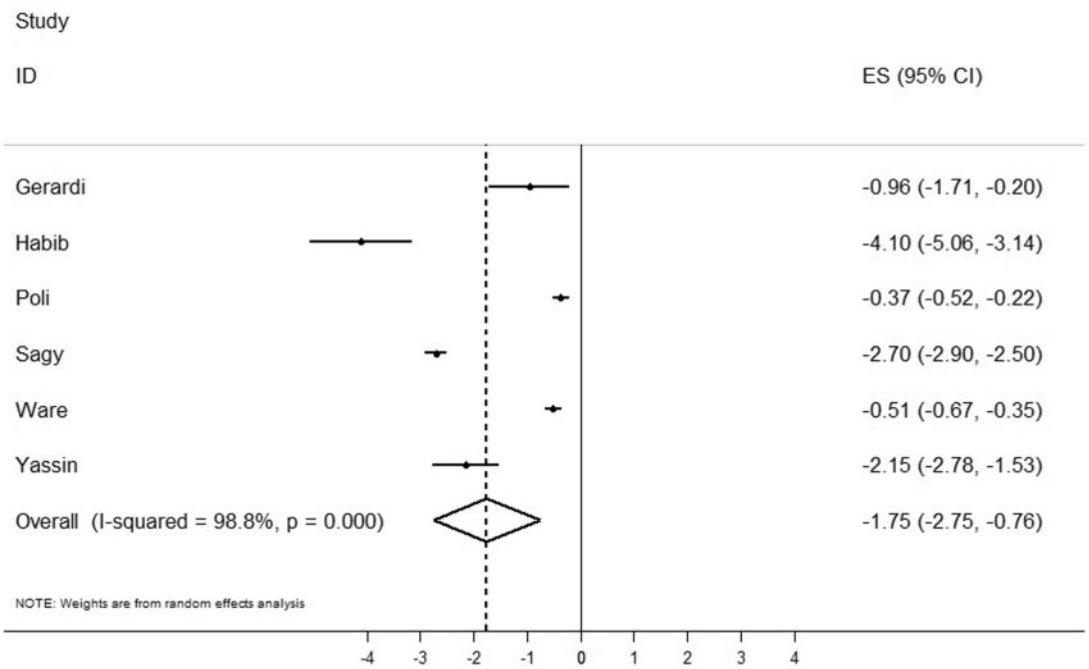


Fig. 4 Forest plot for the effect of cannabis on pain over time



ES: effect size

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general population was not reported. Prevalence of cannabis use decreases with age. In our meta-analysis, weighted mean age was 57 years that might be older than the mean age of the general population. In this case, prevalence of cannabis use might be higher in patients with rheumatologic disease matched for age compared with the general population. Current consumption was mainly reported by the youngest adults and men. Importantly, consumption has often been reported in young adults and may be more therapeutic than recreational, in contrast to what could be supposed [19, 20]. Therefore, it is difficult to know the exact reasons for cannabis use in patients with rheumatologic diseases: to improve pain, decrease anxiety, improve sleep or for recreational purposes. Cannabis users had a higher intensity of pain. We can suppose that cannabis was used in the most painful patients for pain relief. We found a higher incidence of cannabis use in patients with fibromyalgia (68%) than patients with inflammatory rheumatic diseases (26%). This difference may be due to a higher level of anxiety and alexithymia in fibromyalgia [21,22]. In the same way, sleep disorders may require more attention because they may play a role in cannabis use in patients with rheumatologic diseases [23, 24]. The prevalence of insomnia and sleep disturbances was 63% and 20%, respectively, in Mustafa *et al.*'s study of sleep quality in 101 RA patients [25].

In our meta-analysis, we noticed that smoking was associated with a higher risk of cannabis use. The available information was insufficient to assess the link between alcohol and cannabis in our sample, as only two studies also concluded the presence of a 3-fold risk of cannabis use in alcohol drinkers. The relationship between cannabis consumption and other addictive products (alcohol, tobacco) is well-known, and particularly favoured either by a festive atmosphere or personal difficulties (depression, alexithymia, poor family environment) [26–31]. Cannabis use and purpose of use should be researched in rheumatologic patients who are smokers or alcohol users. Substance abuse should concern tobacco, alcohol and cannabis for global patient management. Smoking is associated with a decrease in the efficacy of RA treatments [32]. The impact of alcohol is debated more because of less radiographic progression or better quality of life have been reported in alcohol drinkers with RA, but lower self-reported disease activity [33, 34]. The question with alcohol consumption is whether minimal consumption is better than no consumption. The answering opinions remain divergent [35–37]. Changes in, or at least discussions on, life habits should be an integral part of patient care in rheumatologic diseases [38].

We found a relationship between cannabis consumption and unemployment. This has already been reported, especially in younger patients compared with our population. Most publications have concerned younger individuals aged 30–35 years [39, 40]. However, Airagnes *et al.* found an association between cannabis use and job loss regardless of age. Patients >50 years old who use cannabis had a nearly 3-fold higher risk of job loss [41]. Boden *et al.* concluded that this is a two-way relationship. Unemployment plays a causal role in substance misuse, which increases the risk of unemployment [42]. It is difficult to know what the reasons are for this relationship: reduced work commitment [43], increased social welfare assistance [44], insufficient perceived social support [45] or psychological slowdown [46].

We did not find any significant difference in the proportion of patients using cannabis by sex. This result contradicts the literature, which often reports higher consumption in men [47]. This can be explained by the small percentage of men in our sample (nearly 25%), which may have resulted in underestimating the difference in consumption.

A favourable effect of cannabis on pain in our meta-analysis reinforces the idea that cannabis could be used for analgesic purposes. However, most of the included studies had no control group; therefore, it is not possible to draw strong conclusions. Moreover, the most important question for medical cannabis is its risk-benefit balance. Several studies have reported that therapeutic use of cannabis is safe, especially in the elderly [48], but others still ask for large well-designed clinical trials to determine the efficacy and safety of cannabis for chronic non-cancer pain [49].

Our study has some limitations. First, we decided to pool different diseases, such as fibromyalgia or RA, which increased the heterogeneity in our results. These two diseases are completely different in physiopathology and the degree of systemic inflammation. However, articular pain or musculoskeletal pain occur in these two diseases, which can be also associated in the same patients. Fan *et al.* reported if a sample of 691 patients with RA, SpA or connective tissue a concomitant fibromyalgia in 10% of patients [50]. Therefore, we decided to include all rheumatologic diseases to increase the number of included studies, the number of assessed patients, and the statistical power of this meta-analysis while taking into account the heterogeneity of included studies in the statistical analysis with random effects analyses. Heterogeneity of the included studies is always a limitation in a meta-analysis that can impact the conclusions. In this meta-analysis, because of the low number of studies assessing cannabis use in rheumatologic diseases, we decided to include studies with a wide heterogeneity from clinic surveys to randomized clinical trials with different inclusion and exclusion criteria. Further studies with larger sample of patients with rheumatologic diseases will be welcome to confirm and complete our conclusions on the effects of cannabis.

Second, the reason for cannabis consumption was often lacking in the articles included in our meta-analysis. It was difficult to know the proportion of patients who used cannabis for analgesic or therapeutic purposes compared with those who used it for recreational purposes. Two studies specified that cannabis consumption was consumed by 15% of patients to

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improve pain, whereas 40% of patients in total were consumers [51, 52], and one study distinguished global consumption (84%) and consumption for medical reasons (44%) [52]. Another limitation is related to publication bias. We cannot exclude that some investigations were not published because of insufficient interesting results or insufficient number of included patients. However, we searched relevant abstracts in European and American congresses and trial registries, such as PROSPERO (international prospective register of systematic reviews), and found no other references.

In this meta-analysis, we found that one in six patients suffering from rheumatologic disease actively consume cannabis, reducing in pain reduction. The issue of cannabis use in the management of these patients should be addressed during medical consultation, essentially with the development of cannabis-based standardized pharmaceutical products.

Acknowledgements

All authors were involved in drafting this article or critically revising it for important intellectual content, and all authors approved the final version to be submitted for publication.

S.M. had full access to all of the study data and takes responsibility for the data integrity and accuracy of the data analysis. Study conception and design: S.M., M.S. Acquisition of data: M.G., S.M. Statistical analysis: B.P., S.M. Interpretation of data, manuscript writing and revision: M.G., S.M., B.P., N.A., M.S.

Funding: No specific funding was received from any funding bodies in the public, commercial or not-for-profit sectors to carry out the work described in this manuscript.

Disclosure statement: The authors have declared no conflicts of interest.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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