

Cannabis against chronic musculoskeletal pain: A scoping review on users and their perceptions

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Abstract

Background Chronic musculoskeletal pain (CMP) may lead to reduced physical function and is the most common cause of chronic non cancer pain. Currently, the pharmacotherapeutic options against CMP are limited and frequently consist of pain management with non-steroidal anti-inflammatories, gabapentinoids or opioids, which carry major adverse effects. Although the effectiveness of medical cannabis (MC) for CMP still lacks solid evidence, several patients suffering from it are exploring this therapeutic option with their physicians.

Objectives Little is known about MC users suffering from CMP. We aimed to increase this knowledge, useful for health care professionals and patients considering this treatment, as well as for researchers planning rigorous randomized clinical trials on the effectiveness of MC.

Methods We conducted a scoping literature review, according to the methods developed by Arksey and O'Malley, to describe the views and perceptions of adult patients who had consumed MC to relieve chronic CMP. The review includes patients' perceptions on MC against other non-cancer pain since most of the literature reports on both, as well as their demographic characteristics, patterns of MC use, and perceived positive and negative effects.

Results Participants of the 49 included studies reported that MC use helped them to reduce CMP and other chronic non-cancer pain, with only minor adverse effects, and some reported improved psychological well-being.

Where MC was legally available, persistent users were frequently young or middle-aged men, and the preferred form of use was smoking. The information from these studies has several methodological limitations and results are exploratory.

Conclusion MC users suffering from CMP or other chronic non-cancer pain, perceived more benefits than harms. However, these user reported experiences must be examined by well-designed and methodologically sound clinical or observational studies, particularly regarding CMP, since reports on CMP are very scarce.

Background

Musculoskeletal pain

Musculoskeletal pain is a condition affecting bones, muscles, ligaments and joints, that results from underlying diseases or health problems such as osteoarthritis, inflammatory rheumatic diseases and fibromyalgia, although in many cases the exact cause cannot be identified [1]. Musculoskeletal pain is the most common type of severe long-term pain and it impacts on all aspects of life by typically affecting dexterity and mobility, and by limiting work and activities of daily living [2]. It has been recently reported that one in two American adults lives with a musculoskeletal disease [3] and in Canada approximately 17% of the adult population are affected, nearly half of whom (44%) are aged 65 years or older [1]. Some cases of musculoskeletal pain are of short duration and have no long-term consequences. Chronic musculoskeletal pain (CMP), which persists for more than three months [4], however, is associated with a range of problems such as sleep disorders, depression, anxiety, fatigue, reduced quality of life and inability to work or socialize [5]. In the USA, the impact of CMP on the economy in terms of health-care costs and lost productivity is estimated at US \$213 billion [3].

Effective therapeutic options for the relief of CMP are limited and the treatment remains suboptimal for many patients [6]. Examples for this are the use of gabapentinoids (e.g., pregabalin and gabapentin) or the antidepressants duloxetine and milnacipran, which have shown clinical efficacy in the treatment of fibromyalgia and may have benefit in osteoarthritis and low back pain. However, it is estimated that only about one third of patients will have at least 50% pain relief with one of these agents used as monotherapy; due to significant adverse effects, patients often fail to achieve recommended doses, further diminishing the medications' effectiveness [7]. Opioids are also used to manage CMP, although the effectiveness of this approach remains uncertain [8, 9] and the clinical management of CMP with opioids is challenging due to adverse effects such as dependence, overdose and death [10–13]. It is therefore urgent to explore new treatment options to relieve pain in persons affected by CMP and thus improve their quality of life and social participation [14–16]. Many persons for whom CMP is not satisfactorily relieved

are turning to alternative therapies on their own. Among these, the products derived from cannabis are perceived as an interesting analgesic option [17, 18], although its use is controversial [19, 20].

Cannabis and cannabinoids

The *Cannabis sativa* plant contains some 545 constituents, including over 100 cannabinoids [21]. The most abundant cannabinoid, delta-9-tetrahydrocannabinol (THC), is responsible for the main psychoactive effect of cannabis, but preclinical studies suggest that THC also has some analgesic and anti-inflammatory effects [22]. The second most abundant cannabinoid, cannabidiol (CBD), is non-psychoactive and has antipsychotic effects [23, 24]. Preclinical studies also support anti-inflammatory and analgesic effects of this compound [25–27]. The quantities and proportions of the different cannabinoids vary between different sources and preparations of cannabis [28, 29]. Furthermore, there are differences between herbal preparations and consumption methods of cannabis regarding levels of individual cannabinoids, and between patients regarding the pharmacokinetics of these molecules [30]. These differences affect treatment experiences (i.e., anxiety compared to relaxation), making it hard to come up with evidence-based information to guide physicians and patients on the most appropriate prescribing and dosing of cannabis for a given case [31, 32]. Worldwide, several cannabinoid-based medicines are available in several countries. The first product, nabiximols (tradename Sativex®), contains the cannabinoids THC and CBD. The most common indication for its use is multiple sclerosis associated spasticity. The second product, nabilone (tradename Cesamet®) contains a synthetic cannabinoid similar to THC and is used to alleviate nausea and vomiting associated with chemotherapy treatments. The third product, dronabinol (tradename Marinol®), is a synthetic cannabinoid chemically identical to THC and its main indications are anorexia associated with weight loss in patients with AIDS, as well as severe nausea and vomiting caused by cancer chemotherapy [33]. Quite recently, a product containing cannabidiol, Epidiolex®, has been approved by the United States' Food and Drug Administration for the treatment of Dravet syndrome and Lennox-Gastaut syndrome, which are severe epileptic encephalopathies.

Medical cannabis and musculoskeletal pain: gaps in knowledge

Given the confusion between the terms cannabis, cannabinoids and cannabis for medical purposes, we will refer to the term “medical cannabis” (MC) in this review, in order to describe cannabis products (plant-based products or pharmaceutical products) used for CMP or other non-cancer chronic pain. Chronic pain in general, including CM, is the most common reason given for the therapeutic use of MC among adults [6, 34–37]. The effectiveness of MC in the management of such pain, however, remains controversial. In a systematic review and meta-analysis on cannabinoids for medical use by Whiting et al., only 4 of the 79 trials included were judged at low risk of bias [38]. Individual studies suggested improvement in pain intensity, but most of the differences did not reach clinical significance and there was no clear evidence for an effect of the type of cannabinoid or the mode of administration. It is also important to note that different products were used in the individual studies, plant based or pharmaceutical, making comparisons between the studies even more difficult. Moreover, none of the studies assessed the long-term effects of cannabinoids.

In 2015, Lynch et al. published a systematic review of randomized controlled trials published since 2010 and examining cannabinoids for the treatment of chronic non-cancer pain, including CMP. They reported that seven out of the 11 included studies demonstrated a significant analgesic effect. Several trials also demonstrated improvement in secondary outcomes (e.g., sleep, muscle stiffness and spasticity) [16]. Adverse effects most frequently reported, such as fatigue and dizziness, were mild to moderate in severity and generally well tolerated.

In 2017, the National Academies for Science, Engineering and Medicine of the US published an exhaustive review on the health effects of cannabis and cannabinoids and concluded that “there is conclusive or substantial evidence that cannabis or cannabinoids are effective for the treatment of chronic pain in adults”, based on a review of reviews, following the conclusions of Whiting et al. [38], as well as two primary studies [39]. It should be pointed out, however, that the conclusions reported in the paper of Whiting et al. should be regarded with caution, as most of the studies assessed in this systematic review showed a high risk of bias.

In 2018, Stockings et al. performed another systematic review and meta-analysis of 47 randomized controlled studies and 57 observational studies on cannabinoids for the treatment of chronic non-cancer pain, and concluded that the evidence for the

effectiveness of MC on chronic non-cancer pain is limited [pooled events rates for 50% reduction in pain were not significant: 18.2% (cannabinoids) vs 14.4% (placebo); moreover, the number needed to treat was high (NNT = 24; 95% CI: 15–61) and the number needed to harm was low (NNH = 6; 95% CI: 5–8)]. From the results of the reviewed studies, the authors considered it as unlikely that cannabinoids would become an important treatment option in chronic non-cancer pain [40]. Similarly, Nugent et al. reported in his 2017 review that the utilization of MC to alleviate chronic pain might be associated to several harms, including increased risk for motor vehicle accidents, psychotic symptoms, and short-term cognitive impairment, in addition to negative impacts on the respiratory tract [41].

Thus, available evidence on the effectiveness of MC against CMP and other chronic non-cancer pain remains limited and the results of systematic reviews are somewhat inconclusive. It is even more difficult to conclude about the use of cannabis specifically in the management of CMP because, according to two systematic reviews of clinical trials on cannabis [6, 40], only two clinical trials have focused exclusively on musculoskeletal conditions. The authors of these clinical trials reported that cannabinoids (nabilone or Sativex®) led to a significant decrease in some aspects of pain in patients with fibromyalgia [42] or rheumatoid arthritis [43]. However, only a small number of patients were studied for a short period of time in these trials and further methodological limitations may have affected their quality [6, 40]. In conclusion, more high quality randomized controlled trials comparing herbal cannabis or pharmaceutical cannabinoids with established therapies or placebo are necessary to define their role in the management of CMP or other chronic pain [6].

Although the use of MC remains controversial, it is gaining popularity and is increasingly legalized under certain conditions in a growing number of countries, i.e. Australia, France, Israel, the Netherlands, the United Kingdom, New Zealand, Spain, Germany, 29 US states and since 1999 in Canada [44], where “serious arthritis” was mentioned as one of the main diagnosis justifying a license to obtain cannabis for medical use in 2013 [37]. Several countries are therefore already confronted with increasing use of MC against CMP, even though its efficacy and safety are still unknown.

Two recently published reviews reported the reasons of MC use in patients suffering from different diseases, including chronic pain, anxiety, depression, HIV/AIDS, and multiple sclerosis [45, 46]. None of these publications, however, extensively reported the perceived effects of MC use in persons suffering from CMP or other chronic non cancer pain. Therefore, we conducted a scoping review to summarize the current knowledge about persons using MC specifically against chronic non-cancer pain, including CMP. This review represents a first step toward developing high quality research on this topic.

Methods

Search strategy

This scoping review followed guidance by Arksey and O'Malley, Levac et al. and Colquhoun et al. [47–49] and examined the published knowledge regarding MC users suffering from CMP or chronic non-cancer pain. Early search results revealed the scarcity of publications studying MC users for CMP specifically, and since CMP represents the most common etiology for chronic non-cancer pain, we expanded our search to all studies including patients using MC for chronic non-cancer pain [50]. Moreover, given the scarcity of studies on the perceptions of users of MC, we decided to include both plant-based products and pharmaceutical products such as nabilone or nabiximols in the present review, similarly to some of the included studies [51]. As such, in the remainder of the manuscript, the abbreviation MC refers to both plant-based products and cannabis-derived medicine.

Three large databases (MEDLINE, EMBASE, and Web of Science) were searched using keywords from the controlled vocabulary and free text, and combined to identify publications on users of cannabis for therapeutic purposes (see search strategies in Appendix 1). The searches were conducted during the second half of 2016, updated in June 2019, and were restricted to publications in English, French, or German with no time limit.

Selection of articles

Initial eligibility was assessed by screening the titles and abstracts of retrieved references by three persons Daniela Furrer, Martine Marcotte and Norma Perez). Then, full texts of eligible references were reviewed by three persons (Daniela Furrer, Martine Marcotte and Rosa Martins). Included studies had to comprise adults, aged 18 years or more, having used cannabis or

cannabinoids for therapeutic purposes, including CMP or other chronic pain. Moreover, study samples had to have included at least several participants with chronic musculoskeletal or non-cancer pain. Qualitative, quantitative and mixed methods studies were considered.

Studies that were specific to only one disease, other than musculoskeletal conditions or chronic non-cancer pain, such as HIV/AIDS, cancer, multiple sclerosis, epilepsy, inflammatory bowel disease, glaucoma, Tourette's syndrome, neuropathic pain, spinal cord injury, migraine, post-traumatic stress disorder, dementia, or mental illness, as well as palliative care, were excluded. Furthermore, all studies that did not report any patient perceptions or results - including clinical trials on the therapeutic or adverse effects of cannabis - were excluded. Books, meeting abstracts, editorials, letters, policy evaluations or newspaper articles were also excluded. Included publications that reported about one study in two or more articles were combined into a single study, with one exception (see below). Thereafter, reference lists of relevant reviews and of included studies were hand searched for additional references following the same procedure.

Data collection and quality appraisal

For this narrative synthesis, the following data were extracted by three persons (Daniela Furrer, Martine Marcotte and Rosa Martins) from the included studies: study design and setting, period of data collection, sample size, participants' age and sex, indications for MC consumption, patterns of MC use, perceived benefits and adverse effects of use, and financial support for the study. When available, MC consumption as a substitute for other drugs, as well as barriers to MC use, were also documented.

Results

A total of 3,639 references were first identified, and the full-text was screened for 201 articles, of which 55 publications reporting on 49 studies met the inclusion criteria (Figure 1). In one publication [52], a sub-sample from a previous study [53] was used but, since study objectives and measures were different, they were treated as two different studies.

Characteristics of the included studies

The main characteristics of the included studies are summarized in Table 1. These studies were published between 1999 and June 2019, with 27 (55%) of them published in the last four years. Twenty-one studies were conducted in the US [18, 36, 52-72], nine in Canada [73-82], ten in Europe [83-92], three in Australia [34, 93, 94], three in Israel, and three included data from several countries (up to 43) in Europe and North America [51, 98, 99].

Data were obtained using different approaches. Nine studies were qualitative and data were collected by interview [56, 58, 63, 74, 77, 84, 91, 93, 96]. Three studies used closed-ended questions with free space for comments or open-ended questions [60, 65, 98]. Thirty-four studies used quantitative methods. Among these studies, 29 primarily used questionnaires [18, 34, 52-55, 57, 59, 60, 62, 66, 67, 70, 72, 73, 75, 76, 78, 80-83, 85, 87, 88, 92, 94, 95, 97, 99], five collected data through retrospective chart review [36, 79, 86, 89, 90], and two combined questionnaires with retrospective chart review [64, 69]. Only one study used mixed methods [61]. Sample size varied between 15 [56] and 5,540 participants [89]. Participants had been recruited at different locations, with MC or cannabis dispensaries, MC associations or MC advocacy groups as the most frequent recruitment sites (reported in 20 out of the 49 included studies) [18, 54-58, 60-62, 65, 66, 70, 73, 75, 78, 81, 87, 88, 92, 97-99]. Other reported recruitment sites were MC clinics [52, 53, 59, 71], pain or health-care clinics [36, 63, 64, 68, 69, 72, 76, 79, 80, 82, 86, 95, 96], pharmacies specialized in MC distribution [83, 89], other pharmacies [85, 93], newspapers, university websites, mass media, restaurants or bookstores [34, 77, 84, 99], social media or social networks [84, 91, 98, 99], online forum or websites of MC association [51, 74, 94], a Public Health Agency [89, 90] and industry-based consumers directed organizations or consumers/patients' organizations [67, 91].

Among all included studies, only one examined the prevalence of cannabis use exclusively among patients suffering from CMP [80]. Most of the studies focused on mixed samples that included patients with CMP (between 2% and 91% of participants) (31 studies) [34, 36, 51, 53-55, 58, 62-65, 68, 70, 73-79, 81, 82, 84, 85, 87, 90-93, 95, 99] or experiencing unspecified chronic non cancer pain (between 24% and 97% of participants) (17 studies) [18, 52, 56, 57, 59-61, 66, 67, 69, 71, 72, 83, 86, 88, 89, 98].

Funding

Funding information was reported in 28 of the 49 (57%) included studies (Table 1). Twenty-three studies were funded by research grants or governmental scholarship funding [36, 52, 54, 55, 58, 59, 61-63, 73, 75, 78-81, 83, 85, 91, 93, 95, 96, 98, 99]. Two studies were supported by non-governmental organizations [51, 87]. Five studies received mixed funding from research grants, non-governmental organizations, dispensaries or private foundations [57, 64, 65, 68, 82, 94]. All the five studies that were supported by mixed funding also had received funding from commercial enterprises with a specific focus towards cannabis, or from cannabis interest or patients groups [51, 57, 64, 68, 87, 94].

Participants' characteristics

Participants' characteristics are described in Table 1. Mean age of participants ranged from 28 to 61 years; the youngest participants were 14 years old [89] and the oldest 93 years old [51, 89]. Most studies were not balanced regarding women and men, and proportions of included women varied between 12% and 82%. Only thirteen studies out of 49 (28%) included more female than male participants [63, 65, 69, 74, 79, 80, 83, 85-87, 89, 90, 97]. Participants used MC to relieve several painful conditions, including CMP (i.e., arthritis, rheumatoid arthritis or osteoarthritis, fibromyalgia, neck, back or low back pain) [34, 36, 51, 53, 55, 58, 62-65, 68, 70, 73-82, 84, 85, 87, 90-97, 99], myofascial pain syndrome [36], chronic non-cancer pain [61, 93, 95] and other unspecified chronic pain [18, 34, 36, 52, 54-57, 59, 60, 64-66, 68-73, 75-77, 81, 83, 85, 86, 88-90, 96, 98, 99].

Out of 49 studies, 21 included exclusively qualified MC users [18, 54, 56-58, 60, 61, 63, 72, 75, 76, 78, 83, 85-87, 89, 90, 92, 95, 97], i.e. those patients who were using MC to treat qualifying health conditions – i.e. medical conditions, including cancer, glaucoma and severe pain, for which the use of MC has been legally authorized – under medical supervision or recommendation [55]. In the remaining studies, nine included exclusively “self-identified MC users”, i.e. those patients who are using MC without the advice of a physician or without an MD confirmed diagnosis [34, 73, 74, 77, 81, 84, 91, 94, 98, 99], four included both self-identified and qualified MC users [51, 65, 79, 93], seven included patients who were seeking MC certification or recertification [52, 53, 59, 64, 67, 68, 71, 96], and eight did not provide sufficient details to discriminate between the two categories [36, 62, 66, 69, 70, 80, 88, 100].

Patterns of MC use

The reported patterns of MC use are presented in Table 2. The mode of cannabis administration was described in 36 studies. The most common form of MC consumption was inhalation (reported in 35 studies), either via smoking (joint or blunt, joint with tobacco, pipe, water pipe) or vaping (vaporizer) [34, 36, 51, 58-63, 65, 68-70, 72, 74-86, 88, 92, 94-97, 99, 101]. Reported smoking prevalence ranged from 20% [85] to 91% [59] and vaping prevalence from 7% [60] to 53% [78]. Ingested (cannabis tea, baked goods, oils, tinctures, tablets and capsules) [51, 58-61, 63, 65, 67-70, 72, 75, 76, 80-83, 85, 86, 88, 95, 97, 99] and topical administration [58, 59, 63, 75, 80, 99] were less common forms of MC use (reported in 25 and 6 studies, respectively). The reported prevalence of ingested MC varied from 0.5% [99] to 70% [85] and the prevalence of topical administration varied from 0.6% [99] to 11% [59]. A combined mode of cannabis consumption (e.g., smoked MC and edible MC products) was also reported [78, 79, 88, 95]. Frequency and quantity of MC consumption was described in 23 [34, 36, 51, 57, 59-62, 68-70, 72, 75-78, 81-85, 94, 99] and 22 studies [36, 51, 57, 59, 62, 64, 68, 70, 72, 75-81, 83, 86, 88, 95-97, 99], respectively. Between 38% [82] and 90% [83] of participants reported daily MC consumption. Consumed quantity of MC varied from 0.05 [86] to 28 grams per day [62]. It was not possible to further classify study participants according to daily cannabis consumption from the information provided in the articles.

Perceived positive and negative effects

MC smoking was described by the participants as enjoyable, easy to titrate, and procuring immediate pain relief [34, 65, 74, 77, 78, 84]; however, respiratory side effects and bad smell and taste were perceived as negative effects of cannabis smoking [65, 74, 78, 96] (Table 2). Edible MC products were considered healthier, tasty when cooked in a recipe, and with long-lasting pain relief effects [34, 63]. Study participants also found smoking to be less expensive compared to edible or vaping cannabis [34, 74, 77,

78]. Following MC use, a significant proportion of study participants (24% to 95%) reported considerable alleviation of pain, headache, and anxiety [34, 36, 52, 54, 55, 57, 60-65, 68, 70-73, 75-77, 80-84, 86-88, 91-97, 99] (Table 1). In addition, they perceived positive effects on mood, and an improvement of their general quality of life [18, 60, 65, 74, 82, 91, 96]. Participants also reported longer effects of MC with milder adverse effects, as compared to opioids and other prescription medication [34, 58, 67, 72]. The most frequently reported adverse effects were increasing appetite, drowsiness, cognitive effects, and, in case of cannabis smoking, respiratory effects [60, 62, 65, 71, 77, 94, 96, 97]. Although in general participants considered adverse effects not severe, they had led some participants (up to 15%) to stop their MC treatment [34, 51, 86, 95].

Medical cannabis used as a substitute for prescription medications

Of the 20 studies that examined the impact of MC use on the utilization of other prescribed medications [18, 34, 58, 60, 61, 64-72, 75, 76, 95-99], 19 reported that MC consumption was accompanied by a decrease in the number and amount of prescribed drugs used, including opioids, antidepressants, anxiolytics and benzodiazepines, and non-opioid-based pain medication [18, 34, 58, 60, 61, 64-68, 70-72, 75, 76, 95-99] (Table 2). In twelve studies, it had been observed that participants discontinued their use of opioids or other prescription drugs following the start of MC consumption [34, 58, 64, 66, 68, 71, 72, 75, 95-99], in a proportion varying from 6% [71] to 63% of participants [75]. Participants also reported preferring the use of MC to prescription medication [61], mainly because of the adverse effects of their prescription drugs [76].

Past and current use of cannabis and other licit and illicit substances

In 18 studies, 20% [80] to 90% [62] of participants reported that they had previously consumed cannabis recreationally or that they consumed it simultaneously to their therapeutic cannabis use [34, 51, 61-64, 68, 69, 73, 75, 77, 80-82, 85, 88, 92-94, 97] (Supplemental Table S1). One study reported that 29% of participants discovered the therapeutic effects of cannabis while using it recreationally [34]. Six studies suggested that there might be a link between current MC use and past consumption of licit and illicit substances, as a proportion of MC users (3% to 89%) reported a past history of substance abuse, including alcohol, cocaine, amphetamines, hallucinogens, or other prescription drugs [52, 53, 57, 61, 62, 72]. Moreover, some MC users considered cannabis as a substitute for alcohol (up to 26% of participants) [75] or illicit drugs (up to 16% of participants) [72]. No study explicitly investigated perceived addiction to cannabis as a treatment consequence.

Reported barriers to the medical use of cannabis

Obstacles to the medical use of cannabis have been reported at several levels (Supplemental Table S2), including stigmatization from others [65, 77], fear of discrimination [73], and physicians' unwillingness to prescribe MC [36, 73, 75, 91]. Some MC users expressed health concerns such as pulmonary health or fear of addiction [34, 61, 63, 65]. Difficulties in finding a consistent and affordable MC supply and fear of legal problems associated with MC consumption, especially in places where MC is illegal, represent further obstacles to MC utilization [34, 36, 54-56, 63, 65, 73, 75, 77, 84, 88, 94].

Discussion

Main findings

In the included studies, participants who used cannabis for therapeutic purposes to relieve painful conditions were mainly young or middle-aged men. The most frequent mode of cannabis administration was smoking. The majority of MC users consumed cannabis daily, in a quantity ranging between 0.05 and 28 grams/day.

MC users from reviewed studies reported positive effects on symptoms alleviation in addition to "secondary outcomes" such as psychological well-being. Reported adverse effects associated with MC utilization were few and of minor intensity and were mainly associated with cannabis smoking, such as negative impacts on pulmonary health. MC users from included studies reported that MC use had led to a reduction in the use of prescription drugs for the management of chronic pain.

Strengths and limitations of the review

To the best of our knowledge, this is the first comprehensive literature review that explores the perceptions of persons suffering from CMP and including other chronic non-cancer pain, who used cannabis for therapeutic reasons. The information gathered in this review represents an opportunity to better understand the perspective of MC users on the multiple dimensions of MC consumption, in particular its advantages and drawbacks.

However, this review has several limitations, related principally to weaknesses of the included studies. For an important proportion of the included studies (41%), participants have been recruited at MC dispensaries, MC associations or MC advocacy groups. This might have introduced selection and information biases, as it has been reported that people who are already familiar with cannabis through recreational use, may use cannabis for medical reasons [102, 103]. Indeed, among the about 30% of studies reporting on prior cannabis use, many MC users reported recreational cannabis use prior or simultaneously to MC use. Some MC users reported that it was during the recreational use of cannabis that they discovered its therapeutic effects. Moreover, people who are attending these centers may not use cannabis exclusively for medical reasons. In addition, former MC users who stopped MC consumption participated only marginally in some of these studies. Prevalence of adverse effects might therefore be underestimated. Furthermore, for a subgroup of the studies for which the source of funding was reported, studies were financially supported by enterprises commercializing cannabis or by cannabis interest or patient group. This may have introduced a positive bias toward the use of cannabis against chronic pain.

Therefore, we can argue that study participants were not necessarily representative of the general population with CMP or other chronic non-cancer pain, since a relevant subgroup of persons suffering from CMP or chronic non-cancer pain, but not considering MC as therapeutic option, may not be represented in the included studies. For instance, the mean age of MC users in the included studies (28-61 years) was lower than that of patients suffering from CMP, the incidence of which increases with age [3]. In addition, overall, the proportion of male participants in the included studies was higher than that of female participants, although CMP affects more often women than men [3]. One might thus argue for the existence of a “gender effect”. With cannabis consumption being more popular among men than women [104] and considering that individuals who already have consumed cannabis seem to be more disposed to use it as a therapeutic agent, it is possible that men are more prone to using cannabis for therapeutic purpose than women [34].

In addition, in many studies it was difficult to distinguish between qualified and self-identified MC users, as it was not specified whether MC use was endorsed by a physician-confirmed diagnosis. It was impossible to estimate the prevalence of each type of users in all selected studies and it was thus not possible to estimate the overall prevalence of self-medication in the included studies. Prevalence of self-medication is an important aspect, as self-identified MC users may have different characteristics than qualified MC users.

Moreover, data obtained during interviews or from questionnaires were self-reported and may therefore suffer from recall or social desirability bias, while chart reviews may not allow to capture patient perceptions as well as prospective studies.

The included studies also varied greatly in terms of objectives, methodology, and participants' populations, with 13 studies out of 49 (27%) having less than 100 participants. The different legal frameworks regarding MC use across the different countries and periods of time might have influenced the availability and quality of MC, sample size of the studies and the availability of information on MC users. The conditions permitting to be registered as a MC user as well as access to MC vary between states, countries and over time. For example, MC can be obtained from pharmacies in the Netherlands [83, 85, 89], from special dispensaries in some cities of the US [36, 54, 57, 61, 65, 70, 72], and since 2013 from registered producers in Canada [75, 78, 80]. The included studies, therefore, recruited participants from different sources: dispensaries, registration clinics, or through online advertisement.

Although our scoping review aimed to report on MC users dealing with CMP, we identified only one study that specifically assessed this type of chronic pain [80]. The remaining studies comprised various proportions of participants suffering from CMP or non specified chronic non-cancer pain. This heterogeneity among MC users may have influenced the reported information on MC consumption and its effects, since no distinction has been made relative to participants' disease. Considering that the

pathophysiology of pain varies depending on the syndrome [105], clinical characteristics of participants should be as homogeneous as possible in order to conclude on the effects of MC on participants' pain perception. It is thus somewhat reassuring that the sole article reporting specifically on patients suffering from CMP observed similar results as the other studies reporting on more heterogeneous populations. Indeed, among 1,000 consecutive rheumatology patients, Ste-Marie et al. observed that 28 patients consumed MC. In agreement with the other studies, the authors observed that MC users were younger than the other patients of this clinic (52.8 vs. 62.8 years) and were more likely to be male ($P=0.051$). In addition, MC users had previously consumed cannabis recreationally and 39.3% of the MC users reported to consume cannabis recreationally, in addition to MC [80].

GAPS IN THE LITERATURE

This scoping review identified some gaps in the literature that need to be addressed to better understand patients' utilization of MC against MCP and unspecified chronic non-cancer pain. First, future studies should include participants who have stopped MC consumption, in order to understand the reasons that led to discontinuation of MC, such as stigmatization of cannabis users or onset of adverse effects associated with MC use. As an example, Zolotov et al. reported that among participants who consumed cannabis for medical reasons, including chronic non-cancer pain (47.5%), those who abandoned MC (20%) experienced more frequently adverse effects (dizziness, dehydrated mouth, fatigue, mild anxiety, and feeling "weird") than those who continued MC use ($p<0.05$) [106].

Moreover, it would be interesting to investigate the point of view of the prescribers. It might be interesting to explore whether there are physicians who are open to propose the use of MC without the patient asking for it. This would bring new knowledge on whether prescribers need support during the informed decision-making regarding the use of MC to treat CMP. The debate among physicians whether or not to prescribe MC is ongoing and has recently been presented in the literature [107].

In the context of an aging population, it is possible that MC prescriptions among older patients will increase, as they are more likely to be suffering from CMP and may have had experience with cannabis in their youth. Moreover, a changing legal framework for recreational cannabis may influence the perception of physicians regarding treatment with MC.

Use of MC as a substitute for other drugs, including opioids and other prescription medications, is an important question to consider during the process of decision making regarding the prescribing of MC. From this perspective, several studies suggest to investigate whether MC might represent a new avenue for substitution of opioids, which present serious, well documented adverse effects. Currently, clinical guidelines in some countries, e.g. Canada, support the use of MC for specific medical conditions, including neuropathic pain, palliative cancer pain, chemotherapy-induced nausea and vomiting, and spasticity related to multiple sclerosis or and spinal cord injury, especially for those patients who do not respond to conventional therapies [108].

Further randomized clinical trials that evaluate the efficacy and safety of MC in the management of CMP, other chronic pain or as substitute for opioids are urgently needed, but methodological challenges remain, including difficulties in participants' recruitment and follow-up, and the surveillance of adverse effects. Scarcity of information about current MC users suffering from CMP represents an additional limit to the development of rigorous clinical studies, also required to eventually determine appropriate formulation and dosing of MC for the management of CMP.

Conclusion

In conclusion, although the included studies are frequently exploratory and might be biased by several factors, they describe the perspective of MC users and allow a better understanding of their attitudes and experiences regarding MC use against CMP and other chronic non-cancer pain. These users perceive MC to have more benefits than drawbacks regarding quality of life and adverse effects, and some report on the possibility that MC might decrease the use of some prescription drugs, particularly opioids. However, these user reported experiences must be examined by well-designed and methodologically sound clinical or observational studies.

Abbreviations

CMP: Chronic musculoskeletal pain

MC: medical cannabis

THC: delta-9-tetrahydrocannabinol

CBD: cannabidiol

NNT: number needed to treat

HIV/AIDS: Human immunodeficiency virus and acquired immune deficiency syndrome

Declarations

Ethics approval

Not applicable.

Consent for publication

Not applicable.

Competing interests

Edeltraut Kröger, Daniela Furrer, Martine Marcotte, Nathalie Jauvin, Richard Bélanger, Guillaume Foldes-Busque, Michèle Aubin, Pierre Pluye and Clermont E. Dionne declare that they have no conflict of interest relevant to the content of this study. Mark Ware took a leave of absence from McGill University in 2018, well after most of this review was performed, and is now the Chief Medical Officer at Canopy Growth, Canada. We want to stress that at no time Dr Ware's new affiliation influenced any step of this scoping review. Having been critically involved in research and in raising interest in the knowledge gap and growing request of patients to use cannabis for the treatment of chronic pain, he continues to be a collaborator in this research. Daniela Furrer has started to work at the Quebec Ministry of Health in July 2019.

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Authors' contributions

DF performed part of the study selection and most of the synthesis of results and wrote subsequent drafts of the article; EK was the responsible supervisor for DF, wrote the protocol for the review and was involved in all steps from the review to the writing of the article. MM and NJ both performed several steps of the review and commented on the article; RB, MW, GF-B, MA and PP contributed to the research question at the origin of the review and to the writing at the article, while CED was involved in all steps of the review and the writing of the article and had the original research idea.

Availability of data and materials

Not applicable.

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Tables

Table 1: Brief summary of included studies

Article	Study Objectives / Design: data source; Recruitment	Study Location /Period, legality ¹	Participants Number / Age / Sex	Reasons for using cannabis medically	Reported effects and perceptions of MC	Funding
Aggarwal et al. 2009[36]	To characterize chronic pain patients seeking MC treatment. Quantitative: Retrospective chart review; recruitment via a regional pain clinic.	Washington State, US. 2007-2008, study, access points for MC dispensing in urban centers were informally tolerated.	139 patients seeking treatment with MC. Median 47 (18-84) y. 63% men.	Chronic pain: 82% myofascial pain syndrome 64% neuropathic pain 27% osteoarthritis.	The majority of patient records documented significant symptom alleviation.	Scholarship funding *National Institute of General Medical Sciences of the NIH- * National Science Foundation
Aggarwal et al. 2013a & 2013b[54, 55]	To present data from a dispensary-based survey of MC users. Quantitative: Dispensary-based survey; recruitment through an MC dispensary.	Washington State, US. 2007-2008, access points for MC dispensing in urban centers were informally tolerated.	37 chronically ill, qualified MC users. 41 (21-61) y. 65% men.	25% qualified with intractable pain. 51% used MC to reduce musculoskeletal pain.	59% of the participants reported that 3.4 grams of MC provided 97% pain relief for 65 hours.	Scholarship funding National Science Foundation Graduate Research Fellowship

Article	Study Objectives / Design: data source; Recruitment	Study Location /Period, legality ¹	Participants Number / Age / Sex	Reasons for using cannabis medically	Reported effects and perceptions of MC	Funding
Alexandre 2011[56]	To identify patient's expectations and experience of the enrollment to the Rhode Island MC program. Qualitative: Semi-structured face-to-face interviews of patients enrolled in the MC program; recruitment via an information sheet distributed by the Rhode Island Patient Advocacy Coalition (RIPAC), supporting patients in the use of MC.	Rhode Island, US. 2009-2010, legal MC use.	15 MC qualified users enrolled in the MC program. 23-60 y. 67% men.	Not reported for the study sample (67% of registered users diagnosed with chronic or debilitating disease or treatment, including chronic pain not related to cancer).	Reports of significant relief from pain.	No funding
Boehnke et al. 2016[18]	To examine whether using MC for chronic pain changed individual patterns of opioid use. Quantitative: Retrospective cross-sectional survey (online questionnaire carried out in collaboration with an MC dispensary)	Michigan, US. 2013-2015 Legal MC use.	185 qualified MC users who completed the 2011 Fibromyalgia Survey Criteria. 18-75 y. 64% men.	Chronic pain.	MC use was associated with a 64% decrease in opioid use, decreased number and side effects of medications, and an improved quality of life (45%).	N/A

Article	Study Objectives / Design: data source; Recruitment	Location /Period, legality ¹	Participants Number / Age / Sex	Reasons for using cannabis medically	Reported effects and perceptions of MC	Funding
Bonn-Miller et al. 2014[57]	To describe population; To examine association psychological & pain symptoms vs. MC use motives. Quantitative: Cross-sectional questionnaires; recruitment via an MC dispensary.	California, US. Legal MC use.	217 qualified MC users receiving MC at dispensary. 41.2 ± 14.9 y. 73% men.	62% reported anxiety, 58% chronic pain, 49% stress, 48% insomnia, 45% depression, 30% appetite, 26% headaches, 22% nausea, 20% muscle spasms, 19% PTSD; less than 10% of the sample reported to use MC against cancer.	Regardless of condition, MC reported as moderately to mostly helpful.	(Mixed) Research grant VA Clinical Science Research and Development (CSR&D) Career Development Award-2 Local resource funding San Francisco Patient and Resource Center
Bottorff et al. 2011[74]	To describe perceived MC health effects. Qualitative: Semi-structured, individual face-to-face or telephone interviews; recruitment through an online forum and through compassion centers.	British Columbia, Canada. 2007-2008, MMAR* but adults recruited from tolerated but illegal dispensaries.	23 self-reporting MC users. 45 (25-66) y. 43% men.	26% HIV/AIDS 22% fibromyalgia 17% arthritis 13% mood/anxiety disorders.	Reports of immediate effects and, for the first time in many years, participants “could manage life again.”	N/A

Article	Study Objectives / Design: data source; Recruitment	Study Location /Period, legality ¹	Participants Number / Age / Sex	Reasons for using cannabis medically	Reported effects and perceptions of MC	Funding
Bruce et al. 2018[58]	To learn more on how MC is used by persons living with chronic conditions in tandem with or instead of prescription medications. Qualitative: Semi-structured telephone interviews with open-ended questions; recruitment through flyers at MC dispensaries.	Illinois, US. Legal MC use.	30 qualified MC users. 44.6 ± 15.9 y. 63% men.	23% rheumatoid arthritis 20% Crohn's disease 20% spinal cord injury/disease 13% cancer 10% severe fibromyalgia.	MC perceived as acting more quickly, having longer effects, reducing potential harm versus opioids/narcotics. Multiple benefits replacing a range of medications.	Fellowship grant <i>Provost's Collaborative Research Fellowship, DePaul University</i>
Brunt et al. 2014[83]	To assess therapeutic satisfaction with pharmaceutical-grade cannabis. To compare the subjective effects among the available strains. Quantitative: questionnaires; recruitment through pharmacies specialized in MC distribution.	The Netherlands. 2011-2012, pharmaceutical-grade cannabis distributed for medicinal purposes since 2003.	113 qualified MC users. 52.8 ± 12.3 y. 49% men.	53% chronic pain 23% multiple sclerosis; only 11% indicated to use MC against cancer.	86% (almost) always experienced therapeutic satisfaction, mainly pain alleviation.	Governmental funding <i>Ministry of Health, Welfare and Sport</i>

Article	Study Objectives / Design: data source; Recruitment	Location /Period, legality ¹	Participants Number / Age / Sex	Reasons for using cannabis medically	Reported effects and perceptions of MC	Funding
Coomber et al. 2003[84]	To report the experiences of MC users. Qualitative: Semi structured interviews; recruitment via advertisements in newspapers, disabled people's organizations or friends.	UK. Illegal.	33 self-identified MC users. 44 (26-65) y. 58% men.	To relieve symptoms of chronic illness or disability: 42% multiple sclerosis 27% arthritic/rheumatoid complaints.	MC perceived to be highly effective in treating symptoms, to complement existing medication, and to produce fewer unwanted effects.	N/A
Corroon et al. 2017[98]	To survey cannabis users to determine whether they had intentionally substituted cannabis for prescription drugs. Online survey; recruitment through social media, cannabis dispensaries and word of mouth.	83% US (all 50 states represented) and over 42 countries represented. 2013-2016 Legality differed between US states and countries.	Convenience sample of 2 774 cannabis users. 63% were under 36 y, 56% men. 60% identified themselves as MC users.	1040/2774 (37%) of respondents reported pain and/or intractable pain.	46% have substituted cannabis for prescription drugs.	Research grant <i>NIH NCCAM K01ATTA</i>
Cranford et al. 2016[59]	To examine the prevalence and correlates of vaporization as a route of cannabis administration in MC users. Quantitative: data from the screening assessment; recruitment at MC clinics.	Michigan, US. 2014-2015 Legal MC use.	1 485 adults seeking MC certification either for the first time or as a renewal (66%). 45.1 ± 13 y. 57% men.	91% severe chronic pain 26% severe and persistent muscle spasms.	NR	Research grant <i>National Institute on Drug Abuse (NIDA), National Institutes of Health</i>

Article	Study Objectives / Design: data source; Recruitment	Study Location /Period, legality ¹	Participants Number / Age / Sex	Reasons for using cannabis medically	Reported effects and perceptions of MC	Funding
Crowell 2017[60]	To ascertain the impact of MC on patients in New Jersey. Quantitative: survey with open-ended questions; recruitment via a non-profit organization dispensing MC	New Jersey, US. Legal MC use.	955 qualified MC users. 49.3 ± 13.6 (9-84) y. 51% men.	17 conditions were listed, including: 28% intractable skeletal spasticity 24% chronic/severe pain 16% multiple sclerosis 11% inflammatory bowel disease.	Improvement to general condition and quality of life. Decrease in pain, inflammation, nausea, intraocular pressure, spasms, seizure. Increase in appetite, mobility, mood and energy.	N/A
Degenhardt et al. 2015[93]	To investigate patterns and correlates of cannabis use in people who had been prescribed opioids for chronic non-cancer pain. Qualitative: interview; recruitment via a database of pharmacies and chemists across Australia.	Australia. Legal MC use.	242 patients prescribed opioids for chronic non-cancer pain which had used cannabis for pain. 48.7 ± 10.1 y. 62.5% men.	Chronic non-cancer pain, including: 84% back/neck problems 57% arthritis/rheumatism.	Among those using cannabis for pain, the average pain relief was 70% while the average pain relief from prescribed opioids was 50%.	Research grant <i>Australian National Health and Medical Research Council</i>
Erkens et al. 2005[85]	To characterize: MC users, symptoms and conditions; daily use of MC. Quantitative: structured questionnaire; recruitment via pharmacies.	Netherlands. 2003-2004, since 2003, pharmaceutical-grade cannabis is distributed for medicinal purposes.	200 patients who filled a prescription for MC. ≥ 30 y. 33% men.	Cannabis mainly used for chronic pain (including rheumatic disease) and muscle cramp/stiffness.	NR	Governmental funding <i>Ministry of Health, Welfare and Sports, The Netherlands</i>

Article	Study Objectives / Design: data source; Recruitment	Location /Period, legality ¹	Participants Number / Age / Sex	Reasons for using cannabis medically	Reported effects and perceptions of MC	Funding
Fanelli et al. 2017[86]	To present the first snapshot of the Italian experience with cannabis use for chronic pain over the initial year of its use. Quantitative: retrospective case series (physician-filled case report form); recruitment via second-level pain clinics.	Pisa, Italy. 2015-2016, initial year of authorized MC use for chronic pain. Legal MC use.	614 qualified MC users. 61.3 ± 15.3 y. 29% men.	91% chronic pain.	49% reported an improvement associated with the therapy. 15% stopped the treatment due to side effects (none of which were severe).	N/A
Gorter et al. 2005[87]	To investigate indications for cannabis prescription. To assess cannabis efficacy and side effects. Quantitative: standardized questionnaire; recruitment via questionnaires accompanying shipment of medical-grade cannabis directed to both patient and prescribing physician.	Netherlands. 1997-1999, before legalization but consumption of small amounts under certain conditions was then condoned.	107 patients receiving medical-grade cannabis on prescription. Median 58 y. 45% men.	39% neurologic disorders 21% musculoskeletal/connective tissue disorders 14% malignant tumors and symptoms thereof.	64% reported good to excellent effect on their symptoms. Generally mild side effects.	Non-governmental organization funding <u>Maripham</u>
Grella et al. 2014[61]	To collect descriptive data on individuals using MC dispensaries. Mixed: focus groups and survey; recruitment via MC dispensaries. S	California, US May-October 2012, legal MC use.	Users of MC dispensaries: Focus groups: n=30, 38 ± 12 (20-64) y, 70% men. Survey: n=182, 28.4 ± 5.3 y, 74% men.	Conditions most often cited (not mutually exclusive): 60% anxiety 56% insomnia/sleep problems 33% depression 42% chronic (non-cancer) pain.	Nearly all believed MC beneficial in treating their health problems.	Governmental funding <i>Los Angeles County Department of Public Health, Substance Abuse Prevention and Control Programs</i>

Article	Study Objectives / Design: data source; Recruitment	Location /Period, legality ¹	Participants Number / Age / Sex	Reasons for using cannabis medically	Reported effects and perceptions of MC	Funding
Groten-hermen & Schnelle 2003[88]	To investigate indications for cannabis prescription. To assess cannabis efficacy and side effects. Quantitative: questionnaires; recruitment via an MC association.	German speech area of Europe. 2001: illegal use of natural cannabis products but THC could be prescribed.	143 participants with cannabis or THC experience. Median 40.3 (16-87) y. 61% men.	28% neurological symptoms 25% painful conditions.	75% reported their conditions much improved by cannabis or THC. 73% reported no side effects.	N\A
Haroutounian et al. 2016[95]	To determine the long-term effect of MC on pain and functional outcomes in participants with treatment resistant chronic pain. Quantitative: prospective, open-label, single-arm longitudinal study (questionnaires); recruitment via an ambulatory pain clinic.	Jerusalem, Israel. 2010-2013, legal MC use.	206 qualified MC users. 51.2 ± 15.4 years 62% men.	93% chronic non-cancer pain, including: 37% musculoskeletal pain 34% peripheral neuropathic pain 19% radicular low back pain.	Pain symptom score improved (P<0.001) in association with improvement in physical function (P<0.001). 9 (4%) discontinued treatment due to mild to moderate AEs; 2 (1%) discontinued to serious side effects (1 elevated liver transaminases, 1 elderly admitted to ED in a confusional state).	Research grant Support from the Hadassah-Hebrew University Pain Relief Unit

Article	Study Objectives / Design: data source; Recruitment	Location /Period, legality ¹	Participants Number / Age / Sex	Reasons for using cannabis medically	Reported effects and perceptions of MC	Funding
Harris et al. 2000[62]	To better understand relationships between past experience with drugs and reasons for cannabis use; perceived effectiveness of cannabis as a therapeutic agent. Quantitative: questionnaires; recruitment via advertisements posted at the Cannabis Cultivator's Club.	California, US (after 1996) Legal MC use.	100 Cannabis Cultivator's Club members. 40 ± 8 y. 78% men.	33% AIDS (appetite) 21% musculoskeletal/ arthritis 15% gastrointestinal (most often nausea) 15% psychiatric (primarily depression) 13% neurologic and non-musculoskeletal pain syndromes.	66% rated effectiveness as 80% compared with 52% for other medications. 56% reported no side effects. less severe side effects than other treatments. Anxiety effects frequently reported on the checklist but not listed as side effects.	Research grant <i>US Public Health Service grants, National Institute on Drug Abuse</i>
Hazekamp & Heerdink, 2013[89]	To analyse the incidence and prevalence of MC use and characteristics of users. Quantitative: Retrospective database study; recruitment through the Dutch Foundation for Pharmaceutical Statistics and the only Dutch pharmacy specialized in MC dispensing.	Netherlands, 2003-2010, pharmaceutical-grade cannabis distributed for medicinal purposes since 2003.	5 540 patients with ≥1 MC prescription. 56 (14-93) years. 43% men.	Reason for MC use not reported but 43% had analgesics prescribed in the 6-month period preceding start of MC use. Only 2.7% received oncologicals, thus cancer is unlikely to be present in all pain patients in the study.	NR	N/A

Article	Study Objectives / Design: data source; Recruitment	Location /Period, legality ¹	Participants Number / Age / Sex	Reasons for using cannabis medically	Reported effects and perceptions of MC	Funding
Hazekamp et al. 2013[51]	To compare different administration forms of cannabinoids and identify their relative advantages and disadvantages as described by actual users. International, web-based, cross-sectional survey; recruitment via the official website of the International Association for Cannabinoid Medicines.	31 countries including US (40 states represented), Germany, France, Canada, Netherlands & Spain. 2009-2010, legality differed by country.	953 adults self-reporting experience with ≥ 2 different cannabinoid-based medicines or administration forms, 87% current MC users. 40.7 (14-76) y. 64% men.	Top 5 conditions: 12% back pain 7% sleeping disorder 7% depression 6% pain resulting from injury or accident 4% multiple sclerosis. Pain medication was consumed by 53.6% of MC users	Herbal MC received higher appreciation than pharmaceutical cannabinoids. Side effects: irritation of the lungs (inhalation), drowsiness, uncontrollable appetite, "getting high".	Non-governmental organization funding <i>Dutch Association for Legal Cannabis and its Constituents as Medicine (NCSM foundation)</i>
Hoffman et al. 2017[63]	To begin the development of a cannabis use registry in Oregon. Qualitative: semi-structured interviews; recruitment via an outpatient health-care clinic.	Oregon, US. July-August 2015: legal MC use, nonmedical used became legal on July first.	22 qualified MC users. Median 38 (20-64) y. 45% men.	59% musculoskeletal pain 27% PTSD.	Some reported physiologic relief from pain, others said it helped take their mind off of it. Respondents felt that the benefits outweighed the risks.	Research grant <i>National Institute of Drug Abuse supported this study</i>

Article	Study Objectives / Design: data source; Recruitment	Study Location /Period, legality ¹	Participants Number / Age / Sex	Reasons for using cannabis medically	Reported effects and perceptions of MC	Funding
Ilgen et al. 2013[53]	To describe adults seeking MC; To compare them with those renewing their MC card on substance use; pain; functioning. Quantitative: questionnaires; recruitment at the waiting room of an MC clinic.	Michigan, US. Legal MC use.	348 adults seeking MC certification either for the first time (56%) or as a renewal (44%). 41.5 ± 12.6 y. 66% men.	87% used MC for pain relief, including 7% for musculoskeletal problems.	NR	N/A
Kilcher et al. 2017[90]	To study medical uses of cannabinoids as part of the Swiss Federal Office of Public Health (FOPH) programme of exceptional licenses. Quantitative: data from the formal requests for medical use of cannabinoids; recruitment via formal requests of MC use.	Switzerland. 2013-2014, exceptional licenses for medical use of cannabinoids.	1 193 qualified MC users. 57 ± 15 y. 43% men.	Most common symptoms: 49% chronic pain 40% Spasticity Diagnosis: 25% musculoskeletal conditions 22% multiple sclerosis.	Licences were initially granted for 6 months, physicians requested extensions when the treatment had been satisfactory. The number of extensions increased from 26% in 2013 to 39% in 2014.	N/A

Article	Study	Participants	Reasons for using	Reported effects	Funding	
	Objectives / Design: data source; Recruitment	Location /Period, legality ¹	Number / Age / Sex	cannabis medically	and perceptions of MC	
Lavie-Ajayi and Shvartzman 2018 [96]	To evaluate the subjective experience of pain relief by MC. Qualitative: In-depth semistructured interviews; recruitment through a pain clinic.	Israel. 2016-2017, legal MC use.	19 patients seeking treatment with MC. 52 (28-79) y. 53% men	Chronic pain: 37% arthritis 32% spinal cord injuries 32% CRPS 5% cancer.	Immediate sensation of chronic pain relief, improved sleep quality, improved life quality. Side effects: increased appetite (74%), drowsiness (67.1%), ocular irritation (40.7%), lack of energy (37.5%), memory impairment (31.6%), palpitations (15.4%), and paranoia (15.2%) or confusion (12.4%).	Research grant <i>Ben Gurion University of the Negev, Faculty of Humanities and Social Sciences.</i>

Article	Study Objectives / Design: data source; Recruitment	Location /Period, legality ¹	Participants Number / Age / Sex	Reasons for using cannabis medically	Reported effects and perceptions of MC	Funding
Lintzeris et al., 2018 [94]	To explore patterns of MC use. Quantitative: online survey; recruitment through online media, consumer group webpages, and MC consumer forums.	Australia. 2016, illegal MC use.	1748 MC users. 37.9 y. 68% men.	51% anxiety, 50% back pain, 49% depression, 44% sleep problems, 26% neck pain, 23% PTSD. 69.4% of respondents used MC to manage pain.	Most participants reported that MC reduced significantly chronic pain. Side effects: increased appetite (74%), drowsiness (67%), ocular irritation (41%), lack of energy (38%), memory impairment (32%), palpitations (16%), paranoia (15%) or confusion (12%).	Mixed Research grant <i>Australian Research Council and the National Health and Medical Research Council (NHMRC)</i> Local research grant <i>Lambert Initiative for Cannabinoid Therapeutics</i>
Lucas & Walsh 2017[75]	To describe MC access, use and substitution for patients enrolled in the Canadian Marihuana for Medical Purposes regulations. Quantitative: online cross-sectional survey; recruitment through a licensed producer of cannabis.	Canada. July 2015, legal MC use (MMPR*). (MMPR*).	271 qualified MC users (MMPR). 40 (20-77) y. 73% men.	53% pain-related conditions: 36% chronic pain, 12% arthritis, 5% headache. Most highly endorsed symptoms: 73% chronic pain, 60%, stress, 57% insomnia, 46% depression, 32% headache.	95% reported that cannabis often or always helped alleviate their symptoms.	Research grant <i>Institute for Healthy Living and Chronic Disease</i>

Article	Study Objectives / Design: data source; Recruitment	Location /Period, legality ¹	Participants Number / Age / Sex	Reasons for using cannabis medically	Reported effects and perceptions of MC	Funding
Lynch et al. 2006[76]	To describe MC users. Quantitative: structured follow-up questionnaire; recruitment of patients followed at a tertiary care pain management center.	Nova Scotia, Canada. 2001-2005, legal MC use (MMAR*).	30 qualified MC users (MMAR). 45 (31-61) y. 60% men.	Chronic severe pain that had not responded to traditional approaches: 47% neuropathic pain 13% low back pain 10% arthritis.	93% reported moderate or greater pain relief. 95% reported subjective improvement in function. No serious adverse events reported.	N/A
Nunberg et al. 2011 and Reinerman et al. 2011[64, 68]	To describe MC users: demographics; symptoms; physician evaluations; conventional treatments tried; use practices. Quantitative: Physician records and patients' questionnaire; recruitment through nine MC clinics.	California, US. June-August 2006, legal MC use.	1 746 MC applicants. 33% ≥ 45 y. 75% men.	82.6% report using MC to relieve pain. 58.2% diagnosed with chronic pain disorders, including: 26% low back pain 18% arthritis 2% fibromyalgia.	Patients typically report at least one therapeutic benefit: 83% relief of pain 41% muscle spasms 41% headache 38% anxiety 28% nausea and vomiting 26% depression.	Mixed funding Research grant <i>RAND Corporation</i> ; Non-governmental organization funding Cannabis 'industry' <i>MediCann</i> ; Private Foundation <i>Rosenbaum Foundation</i>

Article	Study Objectives / Design: data source; Recruitment	Location /Period, legality ¹	Participants Number / Age / Sex	Reasons for using cannabis medically	Reported effects and perceptions of MC	Funding
Ogborne et al. 2000[77]	To explore reasons for MC use; MC effects; methods and patterns of use; experiences with physicians; encounters with the law. Qualitative: interview; recruitment through advertisements in newspapers and on bulletin boards at an Addiction Research Foundation and at different town locations (bookstores, grocery stores, restaurants, laundromats, etc).	Toronto, Canada. Before the 2001 <i>Marihuana Medical Access Program.</i>	50 self-identified MC users. 38 (26-57) y. 66% men.	22% HIV/AIDS-related symptoms 14% chronic/recurrent pain due to injury of unknown origin 12% depression 2% arthritis.	MC described as superior to other treatments. Reported lethargy, apathy, cough or throat irritation from smoking, thirst, loss of concentration, short-term memory loss, paranoia, and depression.	N/A
Pedersen & Sandberg 2013[91]	To investigate the medical motives of Norwegian cannabis users. Qualitative: Semi-structured interviews; recruitment through internet advertisements, authors' own social networks, among students at the University of Oslo, and from organisations such as the National Organisation for the Reform of Marijuana Laws.	Norway. 2006-2010, illegal.	100 long-term cannabis users (25 stated explicitly they used cannabis medically). 20-62 y. 88% men.	Cannabis was used therapeutically for conditions such as multiple sclerosis, attention deficit hyperactivity disorder and rheumatism, as well as for quality of life conditions such as quality of sleep, relaxation and wellbeing.	Cannabis typically described as useful for treating stress, insomnia and pain, as well as for relaxation.	Research grant <i>Research Council of Norway</i>

Article	Study	Participants	Reasons for using	Reported effects	Funding	
	Objectives / Design: data source; Recruitment	Location /Period, legality ¹	Number / Age / Sex	cannabis medically	and perceptions of MC	
Perron et al. 2015[52]	To better elucidate, among MC users with and without concurrent use of prescription pain medication (PPM): patterns of alcohol and other drug use; functioning; perceived efficacy of pain treatments. Quantitative: questionnaires; recruitment via a survey conducted among persons seeking MC certification or recertification at an MC certification clinic.	Michigan, US. Legal MC use.	273 adults reporting past-month cannabis use for pain-related purposes (subsample of Ilgen et al.. 2013 study). 40.3 ± 12.5 y. 69% men.	Subset of subjects who endorsed using cannabis in the past month specifically for pain reduction.	Prescription pain medication (PPM) users perceived cannabis as more efficacious than PPMs.	Research grant <i>National Institute on Drug Abuse grant</i>

Article	Study Objectives / Design: data source; Recruitment	Study Location /Period, legality ¹	Participants Number / Age / Sex	Reasons for using cannabis medically	Reported effects and perceptions of MC	Funding
Piper et al. 2017[65]	To provide an in-depth qualitative exploration of patient perspectives on the strengths and limitations of MC. Online survey with open-ended questions; recruitment via MC dispensaries.	Maine, Vermont and Rhode Island, US. 2015-2016 (chronic pain was not a condition to become part of the Vermont registry).	984 members of MC dispensaries. 49.1 ± 0.5 y. 47% men.	64% reported a diagnosis of chronic pain: 91% back/neck pain 30% neuropathic pain 23% postsurgical pain 22% abdominal pain 20% chronic pain after trauma/injury.	75% relief of symptoms. Reported benefits: pain relief, better sleep, safe/natural (limited addictive potential), quality of life, functionality. Negative themes: respiratory effects, increased appetite, cognitive (decrease ability to concentrate, non-alert feeling...).	(Mixed) Nonprofit organization funding <i>Center for Wellness Leadership</i> Local resource funding <i>Wellness Connection of Maine;</i> Research grant <i>National Institute of Drug Abuse</i>

Article	Study Objectives / Design: data source; Recruitment	Location /Period, legality ¹	Participants Number / Age / Sex	Reasons for using cannabis medically	Reported effects and perceptions of MC	Funding
Reiman 2009[66]	To examine drug and alcohol use, and the occurrence of substitution among MC users. Quantitative: Survey data collected at a MC dispensing collective; recruitment through an MC dispensing collective.	California, US. Legal MC use.	350 MC users 39 (18-81) y. 68% men.	52% use cannabis for a pain related condition, including 45% who used it against pain resulting from an alcohol related accident. 75% use cannabis for a mental health issue.	65% use MC as a substitute for alcohol, illicit or licit drugs with less adverse side effects.	N/A
Reiman et al. 2017[67]	To gather the impressions of patients who have used cannabis on how it compares with pain medications. Quantitative: Cross-sectional survey; recruitment through e-mails addressed to MC patients of an MC patient database (67,422 patients).	California, US.	2 897 MC respondents seeking MC certification. ≥ 20 y. 55% men.	63% pain-related conditions including back pain and arthritis.	Respondents overwhelmingly reported that cannabis provided relief on par with their other medications, but without the unwanted side effects.	N/A

Article	Study Objectives / Design: data source; Recruitment	Location /Period, legality ¹	Participants Number / Age / Sex	Reasons for using cannabis medically	Reported effects and perceptions of MC	Funding
Sagy et al. 2019 [97]	To investigate the characteristics, safety and effectiveness of MC in fibromyalgia over a period of 6 months. Quantitative: Questionnaire; recruitment via MC provider.	Israel. 2015-2017, legal MC use.	367 fibromyalgia patients, qualified MC users. 52.9 (± 15.1) y. 18% men.	100% fibromyalgia.	Overall pain intensity assessed by NRS reduced from a median of 9.0 at baseline to 5.0 after six months of MC treatment (p<0.001). Side effects: dizziness (7.9%), dry mouth (6.7%), nausea/vomiting (5.4%), hyperactivity (5.5%), increased appetite (3.8%).	N/A
Schnelle et al. 1999[92]	Quantitative: questionnaire; recruitment via an MC association.	Germany, Austria and Switzerland. 1998-1999.	128 qualified MC users. 37.5 ± 9.6 y 68% men	12% depression 11% multiple sclerosis 9% HIV infection 5% back pain.	Symptoms improvement from much (72.2%), to none (4.8%). 1.6% experienced worsening of symptoms. 70.8% experiences no adverse effects.	N/A

Article	Study Objectives / Design: data source; Recruitment	Location /Period, legality ¹	Participants Number / Age / Sex	Reasons for using cannabis medically	Reported effects and perceptions of MC	Funding
Sexton et al. 2016[99]	To collect epidemiologic data to inform medical practice, research, and policy to provoke discussion about the discrepancies between medico-legal recommendations and patient-reported outcomes. Quantitative: Cross-sectional online survey); recruitment through links posted on University (Bastyr University California (US)) websites, social media and cannabis dispensaries.	Respondents came from 18 countries, with the US (78%), UK (6%), and Canada (3%) being the most represented. 2013-2016. Legality varies across countries.	Convenience sample of 1 429 self-identified MC users. 36.3 ± 14 (15-80) y. 55% men.	61% pain 58% anxiety 50% depression 35.5% headache/migraine 27% nausea 18% muscle spasticity 17% arthritis 15% irritable bowel 11.5% intractable pain.	On average, participants reported an 86% reduction in symptoms.	Research grant <i>NIH NCCAM</i> <i>KO1ATTA</i>
Shah et al. 2017[69]	To examine clinical and treatment characteristics for patients who are admitted to a 3-week outpatient inter-disciplinary chronic pain rehabilitation program. Quantitative: Self-report questionnaire and chart review; recruitment of patients admitted to a 3-week outpatient inter-disciplinary chronic pain rehabilitation program.	US. March-December 2015. NR	24 patients with THC positive urine test participating to a pain rehabilitation program. 45.4 ± 15.3 y. 42% men.	Chronic pain.	NR	N/A

Article	Study Objectives / Design: data source; Recruitment	Study Location /Period, legality ¹	Participants Number / Age / Sex	Reasons for using cannabis medically	Reported effects and perceptions of MC	Funding
Shiplo et al. 2016[78]	To examine modes of MC delivery following regulatory changes in 2014. Quantitative: Online cross-sectional survey; recruitment via nine Health Canada licenced MC producers.	Canada. April-June 2015. Legal MC use.	Convenience sample of 364 qualified MC users. 40.8 ± 12.6 y. 58% men.	45% for pain relief (chronic pain and fibromyalgia) 15% mental health 10% central nervous system.	NR	Research grant <i>Canadian Institute of Health Research (CIHR) Training Grant Program in Population Intervention for Chronic Disease Prevention</i>
Ste-Marie et al. 2012[79]	To document the self-identified prevalence of cannabinoid use in fibromyalgia patients seen in a fibromyalgia clinic. Qualitative: Retrospective chart review; recruitment via a tertiary care pain center.	Montreal, Canada. 2005-2010. Legal MC use.	59 MC users with a diagnosis of fibromyalgia. 24% used prescription cannabinoids. 45 ± 10 y 33% men.	Fibromyalgia (61%) or regional pain syndrome and spinal pain, rheumatic disease, neurologic condition.	NR	Research grant <i>Louise and Alan Edwards Foundation</i>

Article	Study Objectives / Design: data source; Recruitment	Study Location /Period, legality ¹	Participants Number / Age / Sex	Reasons for using cannabis medically	Reported effects and perceptions of MC	Funding
Ste-Marie et al. 2016[80]	To examine the prevalence of cannabis use among rheumatology patients; To compare the clinical characteristics of MC users and nonusers. Quantitative: Cross-sectional survey (questionnaires); recruitment via an university-affiliated community rheumatology clinic.	Ontario, Canada. April-May 2014. Legal MC use.	28 current MC users. 52.7 ±13.6 y. 43% men. 15 previous MC users, 62.8 ± 14.4 y, 26% men.	Specific rheumatic disease : 54% osteoarthritis or spinal pain 32% inflammatory arthritis 18% fibromyalgia.	MC reported to relieve pain, anxiety, nausea, improve sleep and appetite.	Research grant <i>Louise and Alan Edwards Foundation</i>
Swift et al. 2005[34]	To learn more about: patterns of use; experiences and concerns; interest in participating in a MC trial. Quantitative: mailed questionnaires; recruitment through opportunistic media stories in newspapers, on radio and television.	Australia. 2003-2004. Illegal.	128 MC users Median 45 (24-88) y. 63% men.	Condition: 60% depression 53% chronic pain 38% arthritis.	86% reported great relief from cannabis. Typically perceived as superior to other medications in terms of undesirable effects, and the extent of relief provided. 15% had stopped, 16% disliked the side effects or route of use (each 3/19).	N/A

Article	Study Objectives / Design: data source; Recruitment	Location /Period, legality ¹	Participants Number / Age / Sex	Reasons for using cannabis medically	Reported effects and perceptions of MC	Funding
Troutt & DiDonato, 2015[70]	To examine MC users' characteristics; perceptions; behaviors. To learn about experiences with cannabis before legalization. Quantitative: anonymous online survey; recruitment: via four MC dispensaries.	Arizona, US. After the 2012 Arizona Department of Health Services Medical Marijuana Rules.	367 patients recruited from MC dispensaries. 45.78 ± 13.76 (18-83) y. 64% men.	87% chronic pain 24.5% arthritis 11% osteoarthritis 7% fibromyalgia.	70% experienced a lot of or almost complete relief.	N/A
Walsh et al. 2013 and Belle-Isle et al. 2014[73, 81]	To examine: cannabis use history; medical conditions and symptoms; patterns of use; modes of access; perceived effectiveness. Quantitative: survey (online or at a cannabis dispensary); recruitment through local MC dispensaries and national organizations that assist MC users.	British Columbia, Canada. 2011-2012. Legal MC use.	628 self-identified current MC users. 39.1 ± 13.1 y. 71% men.	Pain, including chronic, spinal and non-spinal pain, arthritis (82%), anxiety, and sleep problems.	Cannabis perceived to provide effective symptoms relief: 72% reported MC always helpful, 24% often helpful.	Research grant <i>UBC Institute for Healthy Living and Chronic Disease Prevention</i>

Article	Study Objectives / Design: data source; Recruitment	Location /Period, legality ¹	Participants Number / Age / Sex	Reasons for using cannabis medically	Reported effects and perceptions of MC	Funding
Ware et al. 2003[82]	To determine current prevalence of MC in chronic non-cancer pain; estimate the dose size and frequency of cannabis use; describe main symptoms for which relief was sought. Quantitative: Cross-sectional survey; recruitment of all patients entering the ambulatory pain management unit of the Queen Elizabeth II Health Sciences Center.	Nova Scotia, Canada. June to July 2001. Legal MC use.	09 chronic non-cancer pain patients.35% had ever used cannabis, 15% have used cannabis for pain relief, and 10% were current MC users for pain relief.	Of MC users: 50% trauma/surgery 6% arthritis 6% multiple sclerosis.	Improved pain, sleep and mood. 78% of MC users reported at least moderate relief of pain. 25% reported no side effects, 37% very mild, 28% moderate, 9% strong side effects, no severe side effects.	(Mixed) University funding *Faculty of Medicine *Department of Anesthesia; Non-governmental organization funding Research-based pharmaceutical companies
Webb & Webb 2014[71]	To discover the benefits and adverse effects perceived by MC users, especially with regards to chronic pain. Quantitative: survey (questionnaires); recruitment via questionnaires hand-delivered to MC certified patients re-applying for certification.	Hawaii, US. 2010-2011. Legal MC use.	94 patients re-applying for MC certification. 49.3 y.	97% used cannabis primarily for chronic pain.	64% relative decrease in average pain. 71% reported no adverse effects, 6% reported a cough or throat irritation.	N/A

Article	Study Objectives / Design: data source; Recruitment	Study Location /Period, legality ¹	Participants Number / Age / Sex	Reasons for using cannabis medically	Reported effects and perceptions of MC	Funding
Zaller et al. 2015[72]	To characterize socio-demographics and reasons for MC use among dispensary patients. Quantitative: cross-sectional survey (questionnaires); recruitment through Compassion Centers of the Department of Health.	Rhode Island, US. After the 2013 authorization for MC dispensaries.	200 qualified MC users. Median 41 (18-76) y. 73% men.	The most common reason for MC use was chronic pain management.	Most participants report that MC improves their pain symptomology. 91.5% report less unwanted side effects than with prescription medications.	N/A

In Canada, 1999: right to possess cannabis for medical purposes (MC); 2001: Marihuana Medical Access Regulations (MMAR) enabled individuals with the authorization of their health care practitioner to access dried MC by producing their own plants, designating someone to produce for them or purchasing Health Canada supply; 2013: Marihuana for Medical Purposes Regulations (MMPR) commercial production and distribution of MC; 2015: production and sale of cannabis oil, fresh buds and leaves; 2016: Access to Cannabis for Medical Purposes Regulations (ACMPR) set out provisions for individuals to produce a limited amount for their own medical purposes (<https://www.canada.ca/en/health-canada/services/publications/drugs-health-products/understanding-new-access-to-cannabis-for-medical-purposes-regulations.html>).

The use, sale, and possession of all forms of cannabis in the United States is illegal under federal law. As of July 2016, 25 states and the District of Columbia have legalized cannabis for medical purposes. As of 2018, [Alaska](#), [Arizona](#), [California](#), [Colorado](#), [Maine](#), [Massachusetts](#), [Nevada](#), [Oregon](#), [Vermont](#), [Washington](#) and the district of Columbia have [legalized](#) personal use.

Abbreviations: AE: Adverse Effects; ED: Emergency Department; MC: medical cannabis/cannabis for therapeutic purpose/medical marijuana; MMAR: Marihuana Medical Access Regulations; MMPR: Marihuana for Medical Purposes Regulations; NR: not reported; PTSD: Post -Traumatic Stress Disorder; THC: delta-9-tetrahydrocannabinol; NRS: numeric rating scale; CRPS: complex regional pain syndrome.

Table 2. Patterns of MC use and utilization of MC as a substitute for prescription medications

Article	Mode of cannabis administration	Mode advantages	Mode Disadvantages	Quantity ² / Frequency of cannabis use	Cannabis used as a substitute for prescription medications
Aggarwal et al. 2009[36]	When mentioned, mainly smoking.	NR	NR	From "as needed" to over 10 times daily. From 0 to 14 g/week.	NR
Boehnke et al. 2016[18]	NR	NR	NR	NR	45% of respondents reported a 64% reduction in opioid use with MC use. Decrease in the number of medications classes used with MC use (2.38 to 1.81, p < .001).
Bonn-Miller et al. 2014[57]	NR	NR	NR	Participants used 2 to 3 times/day. They used 6-12 g/week.	NR
Bottorff et al. 2011[74]	Primarily smoking.	Smoking: <ul style="list-style-type: none"> • convenient • affordable • more effective regulation of dosing. 	Smoking-related concerns: <ul style="list-style-type: none"> • coughing • breathing difficulties • fear of lung cancer. 	NR	NR
Bruce et al. 2018[58]	60% of participants preferred smoking; 20% vaporizing; 17% ingestion; 3% topical use.	NR	NR	NR	MC use reported as: <ul style="list-style-type: none"> • alternative to prescription (opioids, anticonvulsants, anti-inflammatories) or OTC medications; • complementary, with prescription medications; • a means for tapering off prescription medications.

Article	Mode of cannabis administration	Mode advantages	Mode Disadvantages	Quantity ² / Frequency of cannabis use	Cannabis used as a substitute for prescription medications
Brunt et al. 2014[83]	81% inhalation; 19% tea.	NR	NR	90% of participants used daily. Mean cumulative dose: 0.65 ± 0.63 g/day [4.5 g/week].	NR
Coomber et al. 2003[84]	73% smoking.	Smoking: less amount required than eating or drinking.	NR	48% used daily; 24% used 1-3 times/week. 24% used 1-3 joints/day.	NR
Corroon et al. 2017[98]	NR	NR	NR	NR	Odds of reporting substitution 4.59 (95% CI, 3.87-5.43) times greater among self-identified MC than among non-medical cannabis users. Most common classes of drugs substituted: narcotics/opioids (36%), anxiolytics/BZD (14%) and antidepressants (13%).
Cranford et al. 2016[59]	91% reported smoking; 44% eating, drinking, or ingesting; 39% vaping; 11% topical use. > 50% indicated > 1 mode for past month cannabis use.	NR	NR	74% of participants used almost daily. From none to > 1 ounce (14.5% of participants)/month [0 to 6.5 g/week].	NR

Article	Mode of cannabis administration	Mode advantages	Mode Disadvantages	Quantity ² / Frequency of cannabis use	Cannabis used as a substitute for prescription medications
Crowell 2017[60]	Most frequent mode: 80% smoking; 7% vaporizing; 12% edibles.	NR	NR	3-4 times/day (41.6%-37.9%); 1-2 times/day (38.7%-27.1%).	At first visit: 50% of participants had reduced use of pain medication; at visit 2: 62.4%; at visit 3: 60%.
Grella et al. 2014[61]	NR	NR	NR	NR	A common theme among participants was the preference for using MC instead of prescription medications. In the previous 30 days, 7% had non-medical use of painkillers, 4% of stimulants, and 8% of tranquilizers.
Erkens et al. 2005[85]	70% as tea; 20% smoked.	NR	NR	1 to 4 times/day.	NR
Fanelli et al. 2017[86]	Primarily cannabis tea (smoking cannabis not permitted in Italy). 92% used 22% THC/< 1% CBD Bedrocan.	NR	NR	From 56.7 ± 45.5 mg/day [0.4 g/week] at treatment initiation; to 67.0 ± 58.8 mg/day [0.5 g/week] at follow-up (98 ± 145 days).	NR

Article	Mode of cannabis administration	Mode advantages	Mode Disadvantages	Quantity ² / Frequency of cannabis use	Cannabis used as a substitute for prescription medications
Grella et al. 2014[61]	51% used a pipe/water pipe, 47% smoked joints or blunts; 23% used vaporizers; 16.5% edibles; 3.3% oral tincture.	NR	NR	2.5 ± 2.6 dispensary visits/month. 57% of focus group participants used several times daily.	A common theme among participants was the preference for using MC instead of prescription medications. In the previous 30 days, 7% had non-medical use of painkillers, 4% of stimulants, and 8% of tranquilizers.
Grotenhermen & Schnelle 2003[88]	56% inhalation; 17% oral use; 23% used both modes.	NR	NR	Average doses of natural cannabis products (109 participants): 1.3 ± 0.9 (0.02-3.5) g/day [9.1 g/week].	NR
Haroutounian et al. 2016[95]	77% received cannabis cigarettes; 5% received a combination of cigarettes and drops; 10% only drops; 5% only cookies; 3% combination of cookies and drops.	NR	NR	Monthly prescribed cannabis: 43.2 ± 17.9 g/month	44% of participants on opioid therapy at baseline had discontinued (p < 0.001).
Harris et al. 2000[62]	Mainly smoking.	NR	NR	65% daily use. 86% used ≥ 2 cigarettes/day. 28 g/ day.	NR

Article	Mode of cannabis administration	Mode advantages	Mode Disadvantages	Quantity ² / Frequency of cannabis use	Cannabis used as a substitute for prescription medications
Hazekamp et al. 2013[51]	63% preferred smoking; 24% vaporizing; 8% food/ tincture; 2.4% tea.	NR	NR	On average Times per day: Smoking 6.0, vaporizing 5.2, tea 1.9, food/ tincture 1.8. Grams per day: smoking 3, vaporizing 3, tea 2.4, food/ tincture 3.4 g.	NR
	Fewer participants had experience with dronabinol 11.3%, nabilone 2.1%, nabiximols 1.1%.				
Hoffman et al. 2017[63]	73% smoking; 32% ingestion; 23% vaporizing; 9% topical use.	<ul style="list-style-type: none"> • Most felt vaporizing healthier than smoking. • Of those who ingested, most felt it more effective for pain relief than smoking. 	NR	NR	NR
Lavie-Ajayi and Shvartzman 2018 [96]	Smoking and others (NR)	NR	Unpleasant taste or smell of cannabis.	20-60 g/month	Reduction in side effects of prescription medication. MC use reported as alternative to other medication used for sleeplessness, irritability, restlessness, inability to focus, and depression.
Lintzeris et al. 2018 [94]	[94] Inhalation (83.4%)	NR	NR	Participants used 3 times/day	NR

Article	Mode of cannabis administration	Mode advantages	Mode Disadvantages	Quantity ² / Frequency of cannabis use	Cannabis used as a substitute for prescription medications
Lucas and Walsh 2017[75]	90% had tried joints, 86% vaporizers, 76% oral/ edibles, 16% topical. Primary methods of use: 38% vaporizing, 25% smoking joints, 14% oral/edibles, 12% waterpipe/bongs, 11% pipes, 1% topicals. Preferred method: 44% vaporization, 23% edibles.	NR	NR	88% of participants used at least daily. Modal: 1-2 g/day [7-14 g/week], with 29% (n = 79) using a larger amount.	63% of participants reported substitution for prescription medication. The most common form of substitution was for opioids (32%), BZD (16%), and antidepressants (12%).
Lynch et al. 2006[76]	All participants reported smoking some of the time. 30% used both the smoking and oral routes; 7% used primarily the oral route.	NR	NR	1 to > 6 times/day. 2.5 g/day [17.5g/week].	70% decreased use of other medications that had been causing side effects (NSAIDs, opioids, and antidepressants).
Nunberg et al. 2011 & Reinerman et al. 2011[64, 68]	NR	NR	NR	NR	51% reported using cannabis as a substitute for prescription medications.

Article	Mode of cannabis administration	Mode advantages	Mode Disadvantages	Quantity ² / Frequency of cannabis use	Cannabis used as a substitute for prescription medications
Ogborne et al. 2000[77]	Mainly smoking.	Smoking: <ul style="list-style-type: none"> enjoyable immediate, effective less expensive Eating/drinking: <ul style="list-style-type: none"> “less of a head stone...” <ul style="list-style-type: none"> longer lasting no smell 	Smoking: <ul style="list-style-type: none"> Respiratory side effects (cough, throat irritation) Eating/drinking: <ul style="list-style-type: none"> too slow less effective more difficult to regulate in terms of dose. 	70% of participants smoked every day. They smoked 1 to 10 joints/day. They used 28 to 56 g/month [6.5-13 g/week].	NR
Piper et al. 2017[65]	46% of participants smoked MC; 23% vaporizing; 14% edibles; 12% tincture.	Vaping: MC administered with joints was significantly more expensive than via vaporizer.	Smoking: <ul style="list-style-type: none"> not always convenient gross bad taste. Vaporizing: <ul style="list-style-type: none"> cumbersome too expensive. Edibles: <ul style="list-style-type: none"> Lack of availability. Tincture: <ul style="list-style-type: none"> takes too long complex dosing. 	NR	Decrease in prescription medications.
Reiman 2009[66]	NR	NR	NR	NR	66% of participants reported having used cannabis as a substitute for prescription drugs.

Article	Mode of cannabis administration	Mode advantages	Mode Disadvantages	Quantity ² / Frequency of cannabis use	Cannabis used as a substitute for prescription medications
Reiman et al. 2017[67]	50% smoking; 30% vaporizing; 10% edibles.	NR	NR	NR	97% of participants decreased the amount of opioids they consume when they also use cannabis. 96% do not need to take as much of their nonopioid-based pain medication when they use cannabis.
Reinarman et al. 2011[68]	86% smoking; 24% orally; 22% vaporizing.	NR	NR	67% daily use; 53% use 1-2 times per day. ≤ 3 grams (40%) to ≥ 7 grams (23%) per week.	NR
Sagy et al. 2019 [97]	Smoking, oil	NR	NR	From 670 mg/day to 1000 mg/day	After six months of MC therapy, a substantial proportion of participants stopped or decreased the dosage of other medical therapies.
Schnelle et al. 1999[92]	49% inhalation; 14% eating, drinking; 36% used both the oral and inhalation routes 4% used dronabinol.	NR	NR	NR	NR

Article	Mode of cannabis administration	Mode advantages	Mode Disadvantages	Quantity ² / Frequency of cannabis use	Cannabis used as a substitute for prescription medications
Sexton et al. 2016[99]	84% inhalation: 32% pipes, 19% bongs, 16.5% joints/blunts, 16% vaporizer; 8% oral (edibles, tinctures, capsules); 6% concentrates (oil, keif, hash); 0.6% topical; 0.5% fresh juice.	NR	NR	61% reported using 1-5 hits per smoking session, 21.3% reported 6-10 hits, 18% reported >10 hits/session. 25% reported using less than 1 once/day; 1-4 times/day (47.6%); 5-10 times/day (14.9%), and 12.2% reported using all day, every day. Reported use (g/week): < 1 (12.3%); 1-2 (20.3%); 3-5 (31.8%); 7 (26.1%); 28 (6%), > 28 (3.4%).	60% reported substitute MC for prescription drugs, 25% for pain medications, including opiates.
Shah et al. 2017[69]	54% smoking; 29% tablets; 8% edibles.	NR	NR	62.5% of MC users endorsed daily use, 21% weekly use.	Cannabis use was not associated with a significantly lower morphine equivalence level for participants using prescription opioids.
Shiplo et al. 2016[78]	53% of participants preferred vapourizing; 47% smoking a joint; Among those reporting multiple modes: 25% eating in food, 23% drinking.	<ul style="list-style-type: none"> • Time to onset of effect. • Ability to find correct dose. • Smoking lower cost and more accessible. • Eating/drinking had more durable effect. 	<ul style="list-style-type: none"> • Harm from smoking. Eating in foods: producing the worst high • most stigma • hardest to find a correct dose. 	Almost every day: 77%, > once a day: 82%. 1.8 ± 1.6 g/day [12.6 g/week].	NR

Article	Mode of cannabis administration	Mode advantages	Mode Disadvantages	Quantity ² / Frequency of cannabis use	Cannabis used as a substitute for prescription medications
Ste-Marie et al. 2012[79]	Out of the 59 MC users: 80% smoked herbal cannabis; 24% used prescription cannabinoids; 3% used both.	NR	NR	72% used < 1 g/day [<i>< 7 g/week</i>].	NR
Ste-Marie et al. 2016[80]	86% smoking; 21% vaporizing; 18% ingestion; 4% topical.	NR	NR	For the 22 patients who recorded amounts used, most reported \leq 1.5 g/day [<i>$\leq 10.5g/week$</i>].	NR
Swift et al. 2005[34]	91% smoked. 74% considered smoking as the most helpful route.	Smoking: <ul style="list-style-type: none"> • Instant effect. • Ease of titration. • Cost-effectiveness. Edibles: <ul style="list-style-type: none"> • Healthier • Tasty when cooked in a recipe • Less obvious • Slow onset and long-lasting effects. 	Smoking: <ul style="list-style-type: none"> • Detrimental to respiratory function (and health) Edibles: <ul style="list-style-type: none"> • Availability of recipes • Difficulties with titration • expensive and ineffective for rapid relief. 	75% used at least weekly, 59% used almost daily, 22% used "as required".	62% of participants claimed they decreased or discontinued their use of other medicines with MC use.
Troutt & DiDonato 2015[70]	67% inhalation: ~ 42% smoking, ~ 25% vaporizing; ~ 27% edibles; ~4% tincture; ~2% oils.	NR	NR	84% used several times per week or more, 61% used daily. 78% used < 14 g/month [<i>3.2 g/week</i>].	90% of chronic pain, 81% of arthritis, 94% of fibromyalgia, and 84% of osteoarthritis patients report less frequent use of other medications.
Walsh et al. 2013[81]	57% smoking; 43% vaporizing; 28% orally.	NR	NR	53% used 2-3 times/day, 42 used \geq 4 times/day. 45% used >14 g/week.	

Article	Mode of cannabis administration	Mode advantages	Mode Disadvantages	Quantity ² / Frequency of cannabis use	Cannabis used as a substitute for prescription medications
Ware et al. 2003[82]	Among users for pain: 81% joint, 47% joint with tobacco, 34% pipe, 16% water pipe; 9% orally.	NR	NR	53% used ≤ 4 puffs/dosing interval, 25% smoked a whole cannabis cigarette, 12% smoked ≥ 1 joint. 22% of these participants used cannabis > 1 time/day, 16% used daily, 25% used weekly and 28% rarely used MC.	NR
Webb & Webb 2014[71]	NR	NR	NR	NR	6% wrote brief notes relating how cannabis helped them to decrease or to discontinue other medications.
Zaller et al. 2015[72]	74% smoking; 16.5% vaporizing; 7% orally.	NR	NR	60.5% used ≥ 3 times/day. 48.5% used 3-8 g/day, 34.5% used >8 g/day [21-56 g/week].	55% indicated they had used cannabis as a substitute for prescription medications.

2. [calculated amount of cannabis use in grams per week]

Abbreviations: MC: medical cannabis/cannabis for therapeutic purpose/medical marijuana; NR: not reported; THC: delta-9-tetrahydrocannabinol.

Figures

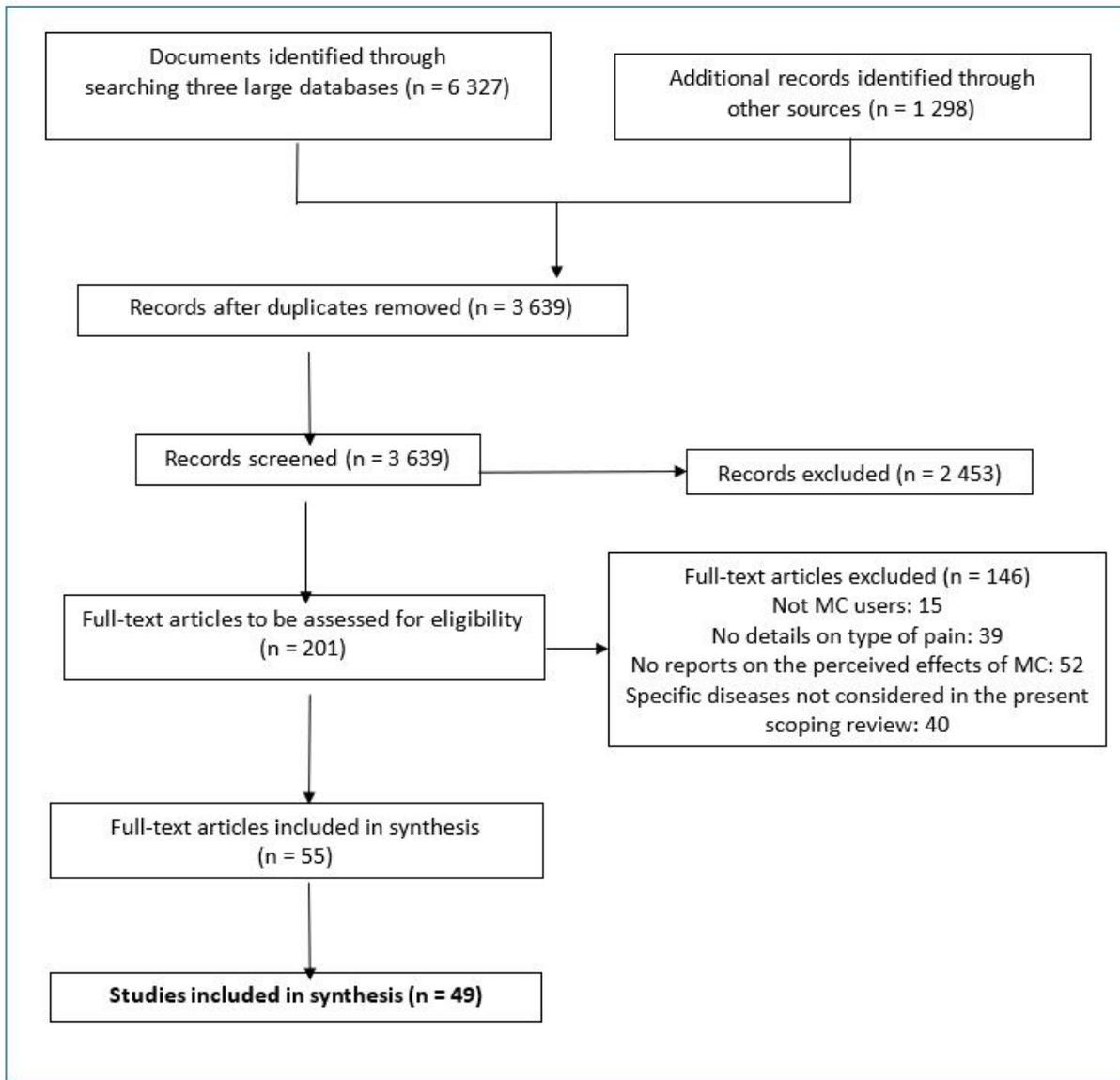
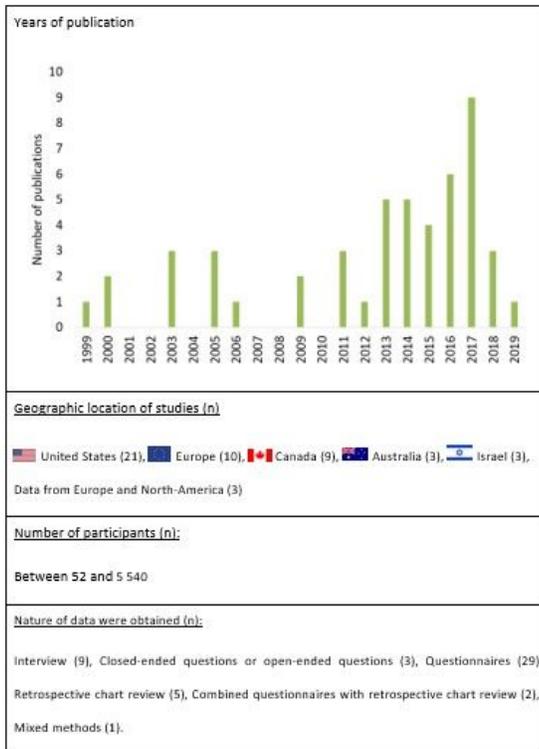


Figure 1

Flowchart of the scoping review



Location of participants recruitment (n):

MC or cannabis dispensaries, MC associations or MC advocacy groups (20), MC clinics (4), Pain or health-care clinics (13), Pharmacies specialized in MC distribution (2), Other pharmacies (2), Newspapers, university websites, mass media, restaurants or bookstores (4), Social media or social networks (4), Online forum or websites of MC association (3), Public Health Agency (2), Industry-based consumers directed organizations or consumers/patients' organizations (2).

Figure 2

Characteristics of included studies

Supplementary Files

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- [ScopingreviewsupplementstablesBMC.pdf](#)