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

Daniela Furrer
Centre d'excellence sur le vieillissement de Québec, (CEVQ), Centre intégré Universitaire de Santé et de services sociaux de la Capitale-Nationale(CIUSSS)

Edeltraut Kröger (edeltraut.kroger.ciussscn@ssss.gouv.qc.ca)
Centre d'excellence sur le vieillissement de Québec, CR du CHU de Québec et CIUSSS-CN
https://orcid.org/0000-0002-5653-3979

Martine Marcotte
Centre d'excellence sur le vieillissement de Québec(CEVQ), Centre intégré de Santé et de services sociaux de la Capitale-Nationale(CIUSSS)

Nathalie Jauvin
Centre d'excellence sur le vieillissement de Québec(CEVQ), Centre intégré de Santé et de Services Sociaux de la Capitale-Nationale(CIUSSS)

Richard Bélanger
Faculty of Pharmacy, Université Laval

Mark Ware
Faculty of Medicine, McGill University

Guillaume Foldes-Busque
School of Psychology, Université Laval

Michèle Aubin
Faculty of Medicine, Université Laval

Pierre Pluye
McGill University Faculty of Medicine

Clermont E. Dionne
Centre d'excellence sur le vieillissement de Québec(CEVQ), Centre intégré Universitaire de Santé et de Services Sociaux de la Capitale-Nationale(CIUSSS)

Research article

Keywords: medical cannabis, musculoskeletal pain, chronic pain, non-cancer chronic pain, perceived effects, adverse effect.

DOI: https://doi.org/10.21203/rs.3.rs-19821/v1

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 mainly consist of pain management with 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.

Objectives Little is known about MC users suffering from CMP. We aimed to increase this knowledge, useful for health care professionals and policy makers 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 patients who had consumed MC to relieve chronic CMP and other non-cancer pain, as well as their demographic characteristics, patterns of MC use, and perceived positive and negative effects.

Conclusion Our review shows that MC users are frequently young or middle-aged men, and that the preferred form of use was smoking. Participants of the included studies reported that MC use was helpful in reducing CMP and other chronic non-cancer pain with only minor adverse effects; in addition, they reported improved psychological well-being.

Discussion The information from the included studies has several methodological limitations and is exploratory. MC use might, from the perspective of persistent users suffering from CMP and other chronic non-cancer pain, produce more benefits than harms. However, specific results for 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-psychotropic 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 identically 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 Unites 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 refers 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 reminder 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 patin, 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.

Acknowledgements

The authors are grateful to the pharmacists Norma Perez, MSc, and Rosa Martins, MSc., for their contribution during the screening of titles and abstracts and the review of eligible references.

Funding

This study received financial support from the Centre de recherche sur les soins et les services de première ligne de l'Université Laval (Edeltraut Kröger and study team), from the Réseau québécois de recherche sur le vieillissement – FRQS, and the Quebec Centre for Excellence in Aging of the Centre Intégré Universitaire de la Santé et de Services Sociaux de la Capitale Nationale (CIUSSSCN), as well as logistic support from the Centre de recherche du CHU de Québec – Université Laval (Edeltraut Kröger and part of the study team). None of the financial contributors participated in collection, analysis or interpretation of data or in writing the manuscript.

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.

References

1. Arthritis Society. Arthritis in Canada. Facts & Figures.: The Arthritis Society of Canada; 2015 February 2015.
2. Woolf AD, Erwin J, March L. The need to address the burden of musculoskeletal conditions. Best practice & research Clinical rheumatology. 2012;26(2):183-224.
3. Yelin E, Weinstein S, King T. The burden of musculoskeletal diseases in the United States. Seminars in arthritis and rheumatism. 2016;46(3):259-60.
4. Task Force on Taxonomy of the International Association for the Study of Pain. Classification of Chronic Pain. Descriptions of Chronic Pain Syndromes and Definition of Pain Terms. Seattle, USA: International Association for the Study of Pain (IASP); 1994.
5. Moore RA, Derry S, Taylor RS, Straube S, Phillips CJ. The costs and consequences of adequately managed chronic non-cancer pain and chronic neuropathic pain. Pain practice : the official journal of World Institute of Pain. 2014;14(1):79-94.
6. Fitzcharles MA, Baerwald C, Ablin J, Hauser W. Efficacy, tolerability and safety of cannabinoids in chronic pain associated with rheumatic diseases (fibromyalgia syndrome, back pain, osteoarthritis, rheumatoid arthritis) : A systematic review of randomized controlled trials. Schmerz. 2016;30(1):47-61.
7. Goldenberg DL, Clauw DJ, Fitzcharles MA. New concepts in pain research and pain management of the rheumatic diseases. Seminars in arthritis and rheumatism. 2011;41(3):319-34.
8. Petzke F, Enax-Krumova EK, Hauser W. [Efficacy, tolerability and safety of cannabinoids for chronic neuropathic pain: A systematic review of randomized controlled studies]. Schmerz. 2016;30(1):62-88.
9. Schaefert R, Welsch P, Klose P, Sommer C, Petzke F, Hauser W. [Opioids in chronic osteoarthritis pain. A systematic review and meta-analysis of efficacy, tolerability and safety in randomized placebo-controlled studies of at least 4 weeks duration]. Schmerz. 2015;29(1):47-59.
10. Atluri S, Sudarshan G, Manchikanti L. Assessment of the trends in medical use and misuse of opioid analgesics from 2004 to 2011. Pain physician. 2014;17(2):E119-28.
11. Ballantyne JC. Opioid therapy in chronic pain. Physical medicine and rehabilitation clinics of North America. 2015;26(2):201-18.
12. Hauser W, Petzke F, Radbruch L, Tolle TR. The opioid epidemic and the long-term opioid therapy for chronic noncancer pain revisited: a transatlantic perspective. Pain management. 2016.

13. Tobin DG, Andrews R, Becker WC. Prescribing opioids in primary care: Safely starting, monitoring, and stopping. Cleveland Clinic journal of medicine. 2016;83(3):207-15.
14. Rowe J, Caprio AJ. Chronic pain: challenges and opportunities for relieving suffering. North Carolina Medical Journal. 2013;74(3):201-4.
15. Gereau RWt, Sluka KA, Maixner W, Savage SR, Price TJ, Murinson BB, et al. A pain research agenda for the 21st century. The journal of pain : official journal of the American Pain Society. 2014;15(12):1203-14.
16. Lynch ME, Ware MA. Cannabinoids for the Treatment of Chronic Non-Cancer Pain: An Updated Systematic Review of Randomized Controlled Trials. Journal of neuroimmune pharmacology : the official journal of the Society on NeuroImmune Pharmacology. 2015;10(2):293-301.
17. Elikottil J, Gupta P, Gupta K. The analgesic potential of cannabinoids. Journal of Opioid Management. 2009;5(6):341-57.
18. Boehnke KF, Litinas E, Clauw DJ. Medical Cannabis Use Is Associated With Decreased Opiate Medication Use in a Retrospective Cross-Sectional Survey of Patients With Chronic Pain. J Pain. 2016;17(6):739-44.
19. Hosking RD, Zajicek JP. Therapeutic potential of cannabis in pain medicine. British Journal of Anaesthesia. 2008;101(1):59-68.
20. D'Souza DC, Ranganathan M. Medical Marijuana: Is the Cart Before the Horse? JAMA. 2015;313(24):2431-2.
21. ElSohly MA, Gul W. Constituents of cannabis sativa. In: Pertwee RG, editor. Handbook of Cannabis. Oxford: Oxford University Press; 2014.
22. Ashton JC. Cannabinoids for the treatment of inflammation. Curr Opin Investig Drugs. 2007;8(5):373-84.
23. Niesink RJ, van Laar MW. Does Cannabidiol Protect Against Adverse Psychological Effects of THC? Frontiers in psychiatry. 2013;4:130.
24. Zhu HJ, Wang JS, Markowitz JS, Donovan JL, Gibson BB, Gefroh HA, et al. Characterization of P-glycoprotein inhibition by major cannabinoids from marijuana. The Journal of pharmacology and experimental therapeutics. 2006;317(2):850-7.
25. Burstein S. Cannabidiol (CBD) and its analogs: a review of their effects on inflammation. Bioorganic & medicinal chemistry. 2015;23(7):1377-85.
26. Costa B, Trovato AE, Comelli F, Giagnoni G, Colleoni M. The non-psychoactive cannabis constituent cannabidiol is an orally effective therapeutic agent in rat chronic inflammatory and neuropathic pain. European journal of pharmacology. 2007;556(1-3):75-83.
27. Maione S, Piscitelli F, Gatta L, Vita D, De Petrocellis L, Palazzo E, et al. Non-psychoactive cannabinoids modulate the descending pathway of antinociception in anaesthetized rats through several mechanisms of action. British journal of pharmacology. 2011;162(3):584-96.

28. Ashton CH. Pharmacology and effects of cannabis: a brief review. The British journal of psychiatry : the journal of mental science. 2001;178:101-6.
29. de Meijer E. The Chemical Phenotypes (Chemotypes) of Cannabis. In: Pertwee RG, editor. Handbook of Cannabis: Oxford University Press; 2014.
30. MacCallum CA, Russo EB. Practical considerations in medical cannabis administration and dosing. European journal of internal medicine. 2018;49:12-9.
31. Beaulieu P, Boulanger A, Desroches J, Clark AJ. Medical cannabis: considerations for the anesthesiologist and pain physician. Canadian journal of anaesthesia = Journal canadien d'anesthesie. 2016;63(5):608-24.
32. Ko GD, Bober SL, Mindra S, Moreau JM. Medical cannabis - the Canadian perspective. Journal of Pain Research. 2016;9:735-44.
33. Abuhasira R, Shbiro L, Landschaft Y. Medical use of cannabis and cannabinoids containing products - Regulations in Europe and North America. European journal of internal medicine. 2018;49:2-6.
34. Swift W, Gates P, Dillon P. Survey of Australians using cannabis for medical purposes. Harm Reduct J. 2005;2:18.
35. Ware MA, Adams H, Guy GW. The medicinal use of cannabis in the UK: results of a nationwide survey. International journal of clinical practice. 2005;59(3):291-5.
36. Aggarwal SK, Carter GT, Sullivan MD, ZumBrunnen C, Morrill R, Mayer JD. Characteristics of patients with chronic pain accessing treatment with medical cannabis in Washington State. Journal of Opioid Management. 2009;5(5):257-86.
37. Arthritis Society. Research: Medical Cannabis. Canada: The Arthritis Society; 2015. p. 1-5.
38. Whiting PF, Wolff RF, Deshpande S, Di Nisio M, Duffy S, Hernandez AV, et al. Cannabinoids for Medical Use: A Systematic Review and Meta-analysis. JAMA. 2015;313(24):2456-73.
39. National Academies of Sciences E, and Medicine,. The Health Effects of Cannabis and Cannabinoids. The Current State of Evidence and Recommendations for Research. Washington DC: National Academies Press; 2017.
40. Stockings E, Campbell G, Hall WD, Nielsen S, Zagic D, Rahman R, et al. Cannabis and cannabinoids for the treatment of people with chronic noncancer pain conditions: a systematic review and meta-analysis of controlled and observational studies. Pain. 2018;159(10):1932-54.
41. Nugent SM, Morasco BJ, O'Neil ME, Freeman M, Low A, Kondo K, et al. The Effects of Cannabis Among Adults With Chronic Pain and an Overview of General Harms: A Systematic Review. Annals of internal medicine. 2017;167(5):319-31.
42. Skrabek RQ, Galimova L, Ethans K, Perry D. Nabilone for the treatment of pain in fibromyalgia. The journal of pain : official journal of the American Pain Society. 2008;9(2):164-73.
43. Blake DR, Robson P, Ho M, Jubb RW, McCabe CS. Preliminary assessment of the efficacy, tolerability and safety of a cannabis-based medicine (Sativex) in the treatment of pain caused by rheumatoid arthritis. Rheumatology. 2006;45(1):50-2.

44. Aguilar S, Gutierrez V SL, Nougier M. Medicinal cannabis policies and practices around the world. London, UK; 2018.
45. Kosiba JD, Maisto SA, Ditre JW. Patient-reported use of medical cannabis for pain, anxiety, and depression symptoms: Systematic review and meta-analysis. Social science & medicine. 2019;233:181-92.
46. Park JY, Wu LT. Prevalence, reasons, perceived effects, and correlates of medical marijuana use: A review. Drug Alcohol Depend. 2017;177:1-13.
47. Arksey H, O'Malley L. Scoping studies: towards a methodological framework. Int J Social Research Methodology. 2005;8(1):19-32.
48. Levac D, Colquhoun H, O'Brien KK. Scoping studies: advancing the methodology. Implement Sci. 2010;5(69):69.
49. Colquhoun HL, Levac D, O'Brien KK, Straus S, Tricco AC, Perrier L, et al. Scoping reviews: time for clarity in definition, methods, and reporting. Journal of clinical epidemiology. 2014;67(12):1291-4.
50. Podichetty VK, Mazanec DJ, Biscup RS. Chronic non-malignant musculoskeletal pain in older adults: clinical issues and opioid intervention. Postgrad Med J. 2003;79(937):627-33.
51. Hazekamp A, Ware MA, Muller-Vahl KR, Abrams D, Grotenhermen F. The medicinal use of cannabis and cannabinoids--an international cross-sectional survey on administration forms. Journal of psychoactive drugs. 2013;45(3):199-210.
52. Perron BE, Bohnert K, Perone AK, Bonn-Miller MO, Ilgen M. Use of prescription pain medications among medical cannabis patients: comparisons of pain levels, functioning, and patterns of alcohol and other drug use. Journal of Studies on Alcohol & Drugs. 2015;76(3):406-13.
53. Ilgen MA, Bohnert K, Kleinberg F, Jannausch M, Bohnert AS, Walton M, et al. Characteristics of adults seeking medical marijuana certification. Drug & Alcohol Dependence. 2013;132(3):654-9.
54. Aggarwal SK, Carter G, Sullivan M, Morrill R, Zumbrunnen C, Mayer J. Distress, coping, and drug law enforcement in a series of patients using medical cannabis. J Nerv Ment Dis. 2013;201(4):292-303.
55. Aggarwal SK, Carter GT, Sullivan MD, Zumbrunnen C, Morrill R, Mayer JD. Prospectively surveying health-related quality of life and symptom relief in a lot-based sample of medical cannabis-using patients in urban Washington State reveals managed chronic illness and debility. Am J Hosp Palliat Care. 2013;30(6):523-31.
56. Alexandre CR. The Rhode Island medical marijuana program: an exploratory study. Policy Polit Nurs Pract. 2011;12(2):104-13.
57. Bonn-Miller MO, Boden MT, Bucossi MM, Babson KA. Self-reported cannabis use characteristics, patterns and helpfulness among medical cannabis users. Am J Drug Alcohol Abuse. 2014;40(1):23-30.
58. Bruce D, Brady JP, Foster E, Shattell M. Preferences for Medical Marijuana over Prescription Medications Among Persons Living with Chronic Conditions: Alternative, Complementary, and Tapering Uses. Journal of alternative and complementary medicine. 2018;24(2):146-53.

59. Cranford JA, Bohnert KM, Perron BE, Bourque C, Ilgen M. Prevalence and correlates of "Vaping" as a route of cannabis administration in medical cannabis patients. Drug & Alcohol Dependence. 2016;169:41-7.
60. Crowell TL. Therapeutic Value of Medical Marijuana in New Jersey Patients: A Community Partnership Research Endeavor. J Allied Health. 2017;46(4):232-8.
61. Grella CE, Rodriguez L, Kim T. Patterns of medical marijuana use among individuals sampled from medical marijuana dispensaries in los angeles. Journal of Psychoactive Drugs. 2014;46(4):267-75.
62. Harris D, Jones RT, Shank R, Nath R, Fernandez E, Goldstein K, et al. Self-reported marijuana effects and characteristics of 100 San Francisco Medical Marijuana Club members. J Addict Dis. 2000;19(3):89-103.
63. Hoffman KA, Ponce Terashima J, McCarty D, Muench J. Toward a Patient Registry for Cannabis Use: An Exploratory Study of Patient Use in an Outpatient Health-Care Clinic in Oregon. World Medical and Health Policy. 2017;9(3):307-17.
64. Nunberg H, Kilmer B, Pacula RL, Burgdorf J. An Analysis of Applicants Presenting to a Medical Marijuana Specialty Practice in California. Journal of drug policy analysis. 2011;4(1).
65. Piper BJ, Beals ML, Abess AT, Nichols SD, Martin MW, Cobb CM, et al. Chronic pain patients' perspectives of medical cannabis. Pain. 2017;158(7):1373-9.
66. Reiman A. Cannabis as a substitute for alcohol and other drugs. Harm Reduct J. 2009;6:35.
67. Reiman A, Welty M, Solomon P. Cannabis as a Substitute for Opioid-Based Pain Medication: Patient Self-Report. Cannabis and cannabinoid research. 2017;2(1):160-6.
68. Reinarman C, Nunberg H, Lanthier F, Heddleston T. Who are medical marijuana patients? Population characteristics from nine California assessment clinics. Journal of Psychoactive Drugs. 2011;43(2):128-35.
69. Shah A, Craner J, Cunningham JL. Medical cannabis use among patients with chronic pain in an interdisciplinary pain rehabilitation program: Characterization and treatment outcomes. Journal of substance abuse treatment. 2017;77:95-100.
70. Troutt WD, DiDonato MD. Medical Cannabis in Arizona: Patient Characteristics, Perceptions, and Impressions of Medical Cannabis Legalization. Journal of Psychoactive Drugs. 2015;47(4):259-66.
71. Webb CW, Webb SM. Therapeutic benefits of cannabis: a patient survey. Hawaii J Med Public Health. 2014;73(4):109-11.
72. Zaller N, Topletz A, Frater S, Yates G, Lally M. Profiles of Medicinal Cannabis Patients Attending Compassion Centers in Rhode Island. Journal of Psychoactive Drugs. 2015;47(1):18-23.
73. Belle-Isle L, Walsh Z, Callaway R, Lucas P, Capler R, Kay R, et al. Barriers to access for Canadians who use cannabis for therapeutic purposes. The International journal on drug policy. 2014;25(4):691-9.
74. Bottorff JL, Bissell LJ, Balneaves LG, Oliffe JL, Kang HB, Capler NR, et al. Health effects of using cannabis for therapeutic purposes: a gender analysis of users' perspectives. Substance Use & Misuse. 2011;46(6):769-80.

75. Lucas P, Walsh Z. Medical cannabis access, use, and substitution for prescription opioids and other substances: A survey of authorized medical cannabis patients. Int J Drug Policy. 2017;42:30-5.
76. Lynch ME, Young J, Clark AJ. A case series of patients using medicinal marihuana for management of chronic pain under the Canadian Marihuana Medical Access Regulations. Journal of Pain & Symptom Management. 2006;32(5):497-501.
77. Ogborne AC, Smart RG, Weber T, Birchmore-Timney C. Who is using cannabis as a medicine and why: an exploratory study. Journal of Psychoactive Drugs. 2000;32(4):435-43.
78. Shiplo S, Asbridge M, Leatherdale ST, Hammond D. Medical cannabis use in Canada: vapourization and modes of delivery. Harm reduction journal. 2016;13(1):30.
79. Ste-Marie PA, Fitzcharles MA, Gamsa A, Panopalis P, Shir Y. Cannabinoid use in fibromyalgia is associated with male gender, opioid use and drug seeking behaviour. Pain Research and Management. 2012;17(3):224.
80. Ste-Marie PA, Shir Y, Rampakakis E, Sampalis JS, Karellis A, Cohen M, et al. Survey of herbal cannabis (marijuana) use in rheumatology clinic attenders with a rheumatologist confirmed diagnosis. Pain. 2016;157(12):2792-7.
81. Walsh Z, Callaway R, Belle-Isle L, Capler R, Kay R, Lucas P, et al. Cannabis for therapeutic purposes: patient characteristics, access, and reasons for use. The International journal on drug policy. 2013;24(6):511-6.
82. Ware MA, Doyle CR, Woods R, Lynch ME, Clark AJ. Cannabis use for chronic non-cancer pain: results of a prospective survey. Pain. 2003;102(1-2):211-6.
83. Brunt TM, van Genugten M, Honer-Snoeken K, van de Velde MJ, Niesink RJM. Therapeutic Satisfaction and Subjective Effects of Different Strains of Pharmaceutical-Grade Cannabis. J Clin Psychopharmacol. 2014;34(3):344-9.
84. Coomber R, Oliver M, Morris C. Using Cannabis Therapeutically in the UK: A Qualitative Analysis. Journal of Drug Issues. 2003;33(2):325-56.
85. Erkens JA, Janse AF, Herings RM. Limited use of medicinal cannabis but for labeled indications after legalization. Pharmacoepidemiology & Drug Safety. 2005;14(11):821-2.
86. Fanelli G, De Carolis G, Leonardi C, Longobardi A, Sarli E, Allegri M, et al. Cannabis and intractable chronic pain: an explorative retrospective analysis of Italian cohort of 614 patients. Journal of pain research. 2017;10:1217-24.
87. Gorter RW, Butorac M, Cobian EP, van der Sluis W. Medical use of cannabis in the Netherlands. Neurology. 2005;64(5):917-9.
88. Grotenhermen F, Schnelle M. Survey on the medical use of Cannabis and THC in Germany. Journal of Cannabis Therapeutics. 2003;3(2):17-40.
89. Hazekamp A, Heerdink ER. The prevalence and incidence of medicinal cannabis on prescription in The Netherlands. European Journal of Clinical Pharmacology. 2013;69(8):1575-80.

90. Kilcher G, Zwahlen M, Ritter C, Fenner L, Egger M. Medical use of cannabis in Switzerland: analysis of approved exceptional licences. Swiss Med Wkly. 2017;147:w14463.
91. Pedersen W, Sandberg S. The medicalisation of revolt: a sociological analysis of medical cannabis users. Sociol Health Ill. 2013;35(1):17-32.
92. Schnelle M, Grotenhermen F, Reif M, Gorter RW. [Results of a standardized survey on the medical use of cannabis products in the German-speaking area]. Forschende Komplementarmedizin. 1999;6(Suppl 3):28-36.
93. Degenhardt L, Lintzeris N, Campbell G, Bruno R, Cohen M, Farrell M, et al. Experience of adjunctive cannabis use for chronic non-cancer pain: findings from the Pain and Opioids IN Treatment (POINT) study. Drug & Alcohol Dependence. 2015;147:144-50.
94. Lintzeris N, Driels J, Elias N, Arnold JC, McGregor IS, Allsop DJ. Medicinal cannabis in Australia, 2016: the Cannabis as Medicine Survey (CAMS-16). The Medical journal of Australia. 2018;209(5):211-6.
95. Haroutounian S, Ratz Y, Ginosar Y, Furmanov K, Saifi F, Meidan R, et al. The Effect of Medicinal Cannabis on Pain and Quality of Life Outcomes in Chronic Pain: A Prospective Open-label Study. The Clinical journal of pain. 2016.
96. Lavie-Ajayi M, Shvartzman P. Restored Self: A Phenomenological Study of Pain Relief by Cannabis. Pain medicine. 2018.
97. Sagy I, Bar-Lev Schleider L, Abu-Shakra M, Novack V. Safety and Efficacy of Medical Cannabis in Fibromyalgia. Journal of clinical medicine. 2019;8(6).
98. Corroon JM, Jr., Mischley LK, Sexton M. Cannabis as a substitute for prescription drugs - a cross-sectional study. Journal of pain research. 2017;10:989-98.
99. Sexton M, Cuttler C, Finnell JS, Mischley LK. A Cross-Sectional Survey of Medical Cannabis Users: Patterns of Use and Perceived Efficacy. Cannabis Cannabinoid Res. 2016;1(1):131-8.
100. Ware MA, Fitzcharles MA, Joseph L, Shir Y. The effects of nabilone on sleep in fibromyalgia: results of a randomized controlled trial. Anesthesia and analgesia. 2010;110(2):604-10.
101. Reiman A. Medical Cannabis Patients: Patient Profiles and Health Care Utilization Patterns. Complementary Health Practice Review. 2007;12(1):31-50.
102. Bigand T, Anderson CL, Roberts ML, Shaw MR, Wilson M. Benefits and adverse effects of cannabis use among adults with persistent pain. Nursing outlook. 2019;67(3):223-31.
103. Lum HD, Arora K, Croker JA, Qualls SH, Schuchman M, Bobitt J, et al. Patterns of Marijuana Use and Health Impact: A Survey Among Older Coloradans. Gerontology & geriatric medicine. 2019;5:2333721419843707.
104. Carliner H, Mauro PM, Brown QL, Shmulewitz D, Rahim-Juwel R, Sarvet AL, et al. The widening gender gap in marijuana use prevalence in the U.S. during a period of economic change, 2002-2014. Drug Alcohol Depend. 2017;170:51-8.

105. McMahon SB, Koltzenburg M TI, Turk D. Wall & Melzack's Textbook of Pain, 6th Edition. @Saunders: Elsevier; 2013. 1184 p.
106. Zolotov Y, Baruch Y, Reuveni H, Magnezi R. Adherence to Medical Cannabis Among Licensed Patients in Israel. Cannabis and cannabinoid research. 2016;1(1):16-21.
107. Caulley L, Caplan B, Ross E. Medical Marijuana for Chronic Pain. N Engl J Med. 2018;379(16):1575-7.
108. Allan GM, Ramji J, Perry D, Ton J, Beahm NP, Crisp N, et al. Simplified guideline for prescribing medical cannabinoids in primary care. Can Fam Physician. 2018;64(2):111-20.

Tables

Table 1: Brief summary of included studies

Article	Study		Participants Number / Age / Sex	Reasons for using cannabis medically	Reported effects and perceptions of MC	Funding
	Objectives / Design: data source; Recruitment	Location /Period, legality [1]				
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*
Alexandre 2011[56]	To identify patient's expectations and experience of	Rhode Island, US. 2009-2010, legal MC use.	15 MC qualified users enrolled in the MC program. 23-60 y.	Not reported for the study sample (67% of registered	Reports of significant relief from pain.	No funding

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	67% men.	users diagnosed with chronic or debilitating disease or treatment, including chronic pain not related to cancer).

	Rhode Island Patient Advocacy Coalition (RIPAC), supporting patients in the use of MC.					
Boehnke et al. 2016[18]	To examine whether using MC for chronic pain changed individual patterns of opioid use.	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 medicat	N/A

	Quantitative: Retrospective cross-sectional survey (online questionnaire carried out in collaboration with an MC dispensary)				ions, and an improved quality of life (45%).	
Bonn-Miller et al. 2014[57]	To describe population; To examine association psychological	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% depress	Regardless of condition, MC reported as moderately to mostly helpful.	(Mixed) Research grant *VA Clinical Science Research and Development (CSR&D) Career*

& pain sympto ms vs. MC use motives . Quantit ative: Cross- section al questio nnaires; recruit ment via an MC dispens ary.	ion, 30% appetit e, 26% headac hes, 22% nausea, 20% muscle spasms, 19% PTSD; less than 10% of the sample reporte d to use MC against cancer.	*Develop ment Award-2* Local resourc e funding *San Francis co Patient and Resourc e Center*	

Bottorf f et al. 2011[74]	To describ e perceiv ed MC health effects. Qualitat ive: Semi-structur ed, individu al face-to-face or telepho ne intervie ws; recruit ment through an online forum and through compas sion centers.	British Columb ia, Canada . 2007-2008, MMAR* but adults recruite d from tolerate d but illegal dispens aries.	23 self-reportin g MC users. 45 (25-66) y. 43% men.	26% HIV/AI DS 22% fibromy algia 17% arthritis 13% mood/a nxiety disorde rs.	Reports of immedi ate effects and, for the first time in many years, particip ants “could manage life again.”	N/A

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 questio	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 *Provost's Collaborative Research Fellowship, DePaul University*

	ns; recruitment through flyers at MC dispensaries.					
Brunt et al. 2014[83]	To assess therapeutic satisfaction with pharmaceutical-grade cannabis. To compare the subjective effects among the availabl	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 *Ministry of Health, Welfare and Sport*

e

strains.

Quantit

ative:

questio

nnaires;

recruit

ment

through

pharma

cies

speciali

zed in

MC

distribu

tion.

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
Corroo	To	83% US	Conveni	1040/2	46%	Researc

n et al. 2017[98]	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.	(all 50 states represented) and over 42 countries represented. 2013-2016 Legality differed between US states and countries.	ence sample of 2 774 cannabis users. 63% were under 36 y, 56% men. 60% identified themselves as MC users.	774 (37%) of respondents reported pain and/or intractable pain.	have substituted cannabis for prescription drugs.	h grant *NIH NCCAM K01ATTA*

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 *National Institute on Drug Abuse (NIDA), National Institutes of Health*

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.	To investigate	Australia.	242 patients prescri	Chronic non-cancer	Among those using	Research grant

2015[93]	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	Legal MC use.	bed opioids for chronic non-cancer pain which had used cannabis for pain. 48.7 ± 10.1 y. 62.5% men.	pain, including: 84% back/neck problems 57% arthritis / rheumatism.	cannabis for pain, the average pain relief was 70% while the average pain relief from prescribed opioids was 50%.	*Australian National Health and Medical Research Council*

	across Australia.					
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 *Ministry of Health, Welfare and Sports, The Netherlands*
Fanelli et al. 2017[86]	To present the first snapshot of	Pisa, Italy. 2015-2016, initial	614 qualified MC users.	91% chronic pain.	49% reported an improvement	N/A

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	year of authorized MC use for chronic pain. Legal MC use.	61.3 ± 15.3 y. 29% men.	associated with the therapy. 15% stopped the treatment due to side effects (none of which were severe).

	pain clinics.					
Gorter et al. 2005[87]	To investigate indications for cannabis prescription. To assess cannabis efficacy and side effects. Quantitative: standardized questionnaire; recruitment via questionnaires	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 *Mariph arm*

accomp
anying
shipme
nt of
medical
-grade
cannabi
s
directe
d to
both
patient
and
prescri
bing
physicia
n.

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 *Los Angeles County Department of Public Health, Substance Abuse Prevention and Control Programs*

Groten-herme n & Schne lle 2003[88]	To investig ate indicati ons for cannabi s prescri ption. To assess cannabi s efficacy and side effects. Quantit ative: questio nnaires; recruit ment via an MC associa tion.	German speech area of Europe. 2001: illegal use of natural cannabi s product s but THC could be prescri bed.	143 particip ants with cannabi s or THC experie nce. Median 40.3 (16-87) y. 61% men.	28% neurolo gical sympto ms 25% painful conditio ns.	75% reporte d their conditio ns much improve d by cannabi s or THC. 73% reporte d no side effects.	N\A
Harout ounia n et	To determi ne the	Jerusal em, Israel.	206 qualifie	93% chronic non-	Pain sympto m score	Researc h grant

al. 2016[95]	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 (questionnaire	2010-2013, legal MC use.	d MC users. 51.2 ± 15.4 years 62% men.	cancer pain, including: 37% musculoskeletal pain 34% peripheral neuropathic pain 19% radicular low back pain.	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 transa	Support from the Hadassah-Hebrew University Pain Relief Unit

	s); recruitment via an ambulatory pain clinic.				minases, 1 elderly admitted to ED in a confusional state).	
Harris et al. 2000[62]	To better understand relationships between past experience with drugs and reasons for cannabis use; perceived effectiveness of cannabi	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)	66% rated effectiveness as 80% compared with 52% for other medications. 56% reported no side effects. ess severe side effects than other treatme	Research grant *US Public Health Service grants, National Institute on Drug Abuse*

	s as a therapeutic agent. Quantitative: questionnaires; recruitment via advertisements posted at the Cannabis Cultivator's Club.			13% neurologic and non-musculoskeletal pain syndromes.	nts. Anxiety effects frequently reported on the checklist but not listed as side effects.	
Hazekamp & Heerdink, 2013[89]	To analyse the incidence and prevalence of MC use and characteristics	Netherlands, 2003–2010, pharmaceutical-grade cannabis distributed for medicin	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-	NR	N/A

	of users. Quantitative: Retrospective database study; recruitment through the Dutch Foundation for Pharmaceutical Statistics and the only Dutch pharmacy specialized in MC dispensing.	al purposes since 2003.		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.		
Hazekamp et al.	To compare differen	31 countries includin	953 adults self-reportin	Top 5 conditions:	Herbal MC received	Non-governmental organiz

2013[51]	t 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	g US (40 states represented), Germany, France, Canada, Netherlands & Spain. 2009-2010, legality differed by country.	g experience with ≥ 2 different cannabinoid-based medicines or administration forms, 87% current MC users. 40.7 (14–76) y. 64% men.	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	higher appreciation than pharmaceutical cannabinoids. Side effects: irritation of the lungs (inhalation), drowsiness, uncontrollable appetite, “getting high”.	ation funding *Dutch Association for Legal Cannabis and its Constituents as Medicine (NCSM foundation)*

website of the International Association for Cannabinoid Medicines.

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 *National Institute of Drug Abuse supported this study*

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 cannabi	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

	noids; recruitment via formal requests of MC use.					
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%)	Research grant *Ben Gurion University of the Negev, Faculty of Humanities and Social Sciences.*

					, ocular irritation (40.7%), lack of energy (37.5%), memory impairment (31.6%), palpitations (15.4%), and paranoia (15.2%) or confusion (12.4%).	
Lintzeris et al., 2018 [94]	To explore patterns of MC use.	Australia. 2016, illegal MC use.	1748 MC users. 37.9 y. 68% men.	51% anxiety, 50% back pain, 49%	Most participants reported that MC	Mixed Research grant *Australian Researc*

Quantitative: online survey; recruitment trough online media, consumer group webpages, and MC consumer forums.	depression, 44% sleep problems, 26% neck pain, 23% PTSD. 69.4% of respondents used MC to manage pain.	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	*h Council and the National Health and Medical Research council (NHMRC)* Local research grant *Lambert Initiative for Cannabinoid Therapeutics*	

					confusion (12%).	
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	Canada. July 2015, legal MC use (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,	95% reported that cannabis often or always helped alleviate their symptoms.	Research grant *Institute for Healthy Living and Chronic Disease*

	a license d produce r of cannabi s.			32% headac he.		
Lynch et al. 2006[76]	To describ e MC users. Quantit ative: structur ed follow-up questio nnaire; recruit ment of patients followe d at a tertiary care pain manage ment center.	Nova Scotia, Canada . 2001-2005, legal MC use (MMAR *).	30 qualifie d MC users (MMAR). 45 (31-61) y. 60% men.	Chronic severe pain that had not respond ed to traditio nal approac hes: 47% neurop athic pain 13% low back pain 10% arthritis .	93% reporte d modera te or greater pain relief. 95% reporte d subjecti ve improve ment in function . No serious adverse events reporte d.	N/A
Nunber	To	Californ	1 746	82.6%	Patient	Mixed

g et al. 2011 and Reinarman et al. 2011[64, 68]	describe MC users: demographics; symptoms; physician evaluations; conventional treatments tried; use practices. Quantitative: Physician records and patients’ questionnaire; recruitment	ia, US. June-August 2006, legal MC use.	MC applicants. 33% ≥ 45 y. 75% men.	report using MC to relieve pain. 58.2% diagnosed with chronic pain disorders, including: 26% low back pain 18% arthritis 2% fibromyalgia.	s typically report at least one therapeutic benefit: 83% relief of pain 41% muscle spasms 41% headache 38% anxiety 28% nausea and vomiting 26% depression.	funding Research grant *RAND Corporation;* Non-governmental organization funding Cannabis “industry” *MediCann;* Private Foundation *Rosenbaum Foundation*

	through nine MC clinics.					
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 advertis	Toronto, Canada. Before the 2001 *Marihuana Medical Access Program*.	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,	N/A

	ements in newspapers and on bulletin boards at an Addiction Research Foundation and at different town locations (bookstores, grocery stores, restaurants, laundromats, etc).				paranoia, and depression.	
Pedersen & Sandberg	To investigate the medical	Norway. 2006-2010,	100 long-term cannabi	Cannabis was used therape	Cannabis is typically	Research grant *Research*

2013[91]	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	illegal.	s users (25 stated explicitly they used cannabis s medically). 20-62 y. 88% men.	utically 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.	described as useful for treating stress, insomnia and pain, as well as for relaxation.	*Council of Norway*

	organisations such as the National Organisation for the Reform of Marijuana Laws.					
Perron et al. 2015[52]	To better elucidate, among MC users with and without concurrent use of prescription pain medicat	Michigan, US. Legal MC use.	273 adults reporting past-month cannabis use for pain-related purposes (subsample of Ilgen et al.. 2013 study).	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 *National Institute on Drug Abuse grant*

ion (PPM): pattern s of alcohol and other drug use; function ing; perceiv ed efficacy of pain treatme nts. Quantit ative: questio nnaires; recruit ment via a survey conduct ed among persons seeking MC	40.3 ± 12.5 y. 69% men.

	certification or recertification at an MC certification clinic.					
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 questio	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	75% relief of symptoms. Reported benefits: pain relief, better sleep, safe/natural (limited addictive potential), quality of life, functionality.	(Mixed) Nonprofit organization funding *Center for Wellness Leadership* Local resource funding *Wellness Connection of Maine;* Research grant

	ns; recruitment via MC dispensaries.			pain after trauma/ injury.	Negative themes: respiratory effects, increased appetite, cognitive (decrease ability to concentrate, non-alert feeling ...).	*National Institute of Drug Abuse*
Reiman 2009[66]	To examine drug and alcohol use, and the occurrence of substitu	California, US. Legal MC use.	350 MC users 39 (18-81) y. 68% men.	52% use cannabis for a pain related condition, includin	65% use MC as a substitute for alcohol, illicit or licit drugs with	N/A

	tion among MC users. Quantitative: Survey data collected at a MC dispensing collective; recruitment through an MC dispensing collective.			g 45% who used it against pain resulting from an alcohol related accident. 75% use cannabis for a mental health issue.	less adverse side effects.	
Reiman et al. 2017[67]	To gather the impressions of patients who have used	California, US.	2 897 MC respondents seeking MC certification. ≥ 20 y.	63% pain-related conditions including back pain and	Respondents overwhelmingly reported that cannabis	N/A

	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).		55% men.	arthritis.	provided relief on par with their other medications, but without the unwanted side effects.	
Sagy et	To	Israel.	367	100%	Overall	N/A

al. 2019 [97]	investigate the characteristics, safety and effectiveness of MC in fibromyalgia over a period of 6 months. Quantitative: Questionnaire; recruitment via MC provider.	2015-2017, legal MC use.	fibromyalgia patients, qualified MC users. 52.9 (± 15.1) y. 18% men.	fibromyalgia.	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%).	
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

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.	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 *NIH NCCAM K01ATTA*

	quantitative: Cross-sectional online survey); recruitment through links posted on University (Bastyr University California (US)) websites, social media and cannabis dispensaries.					
Shah et al.	To examine	US. March-Decemb	24 patients with	Chronic pain.	NR	N/A

2017[69]	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;	er 2015. NR	THC positive urine test participating to a pain rehabilitation program. 45.4 ± 15.3 y. 42% men.

recruit
ment of
patients
admitte
d to a 3-
week
outpati
ent
inter-
discipli
nary
chronic
pain
rehabili
tation
progra
m.

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 *Canadian Institute of Health Research (CIHR) Training Grant Program in Population Intervention for Chronic Disease Prevention*
Ste-Marie	To docume	Montreal,	59 MC users	Fibromyalgia	NR	Research grant

et al. 2012[79]	nt 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.	Canada. 2005-2010. Legal MC use.	with a diagnosis of fibromyalgia. 24% used prescription cannabinoids. 45 ± 10 y 33% men.	(61%) or regional pain syndrome and spinal pain, rheumatic disease, neurologic condition.		*Louise and Alan Edwards Foundation*
Ste-Marie	To	Ontario,	28 current	Specific rheuma	MC reporte	Research grant

et al. 2016[80]	examine the prevalence of cannabis use among rheumatology patients; To compare the clinical characteristics of MC users and nonusers. Quantitative: Cross-sectional survey (questionnaire	Canada. April-May 2014. Legal MC use.	MC users. 52.7 ±13.6 y. 43% men. 15 previous MC users, 62.8 ± 14.4 y, 26% men.	tic disease: 54% osteoarthritis or spinal pain 32% inflammatory arthritis 18% fibromyalgia.	d to relieve pain, anxiety, nausea, improve sleep and appetite.	*Louise and Alan Edwards Foundation*

	s); recruitment via an university-affiliated community rheumatology clinic.					
Swift et al. 2005[34]	To learn more about: patterns of use; experiences and concerns; interest in participating in a MC trial.	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 undesir	N/A

	Quantitative: mailed questionnaires; recruitment through opportunistic media stories in newspapers, on radio and television.				able effects, and the extent of relief provided. 15% had stopped, 16% disliked the side effects or route of use (each 3/19).	
Troutt & DiDonato, 2015[70]	To examine MC users': characteristics; perceptions; behaviors. To learn	Arizona, US. After the 2012 Arizona Department of Health Services Medical Marijua	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

	about experiences with cannabis before legalization. Quantitative: anonymous online survey; recruitment: via four MC dispensaries.	na Rules.				
Walsh et al. 2013 and Belle-Isle et al. 2014[73, 81]	To examine: cannabis use history; medical conditions and	British Columbia, Canada. 2011-2012. Legal MC use.	628 self-identified current MC users. 39.1 ± 13.1 y.	Pain, including chronic, spinal and non-spinal pain, arthritis	Cannabis perceived to provide effective symptoms relief:	Research grant *UBC Institute for Healthy Living and Chronic Disease*

sympto ms; pattern s of use; modes of access; perceiv ed effectiv eness. Quantit ative: survey (online or at a cannabi s dispens ary); recruit ment through local MC dispens aries and national organiz	71% men.	(82%), anxiety, and sleep proble ms.	72% reporte d MC always helpful, 24% often helpful.	*Prevent ion*

	ations that assist MC users.					
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	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	(Mixed) University funding **Faculty of Medicine* **Department of Anesthesia;* Non-governmental organization funding *Research-based pharmaceutical companies*

	was sought. Quantitative: Cross-sectional survey; recruitment of all patients entering the ambulatory pain management unit of the Queen Elizabeth II Health Sciences Center.				effects, no severe side effects.	
Webb & Webb 2014[71]	To discover the benefits and	Hawaii, US. 2010-2011.	94 patients re-applying for	97% used cannabis primaril	64% relative decrease in	N/A

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	Legal MC use.	MC certification. 49.3 y.	y for chronic pain.	average pain. 71% reported no adverse effects, 6% reported a cough or throat irritation.

	certific ation.					
Zaller et al. 2015[72]	To charact erize socio-demogr aphics and reasons for MC use among dispens ary patients . Quantit ative: cross-section al survey (questi onnaire s); recruit ment through Compas sion Centers	Rhode Island, US. After the 2013 authori zation for MC dispens aries.	200 qualifie d MC users. Median 41 (18-76) y. 73% men.	The most commo n reason for MC use was chronic pain manage ment.	Most particip ants report that MC improve s their pain sympto mology. 91.5% report less unwant ed side effects than with prescri ption medicat ions.	N/A

	of the Department of Health.

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 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: • convenient • affordable • more effective regulation of dosing.	Smoking-related concerns: • 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: • alternative to prescription (opioids, anticonvulsants, anti-inflammatories) or OTC medications; • complementary, with

					prescription medications; • a means for tapering off 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

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 tranquillizers.
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

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 tranquillizers.

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

Hazekamp et al. 2013[51]	63% preferred smoking; 24% vaporizing; 8% food/tincture; 2.4% tea. Fewer participants had experience with dronabinol 11.3%, nabilone 2.1%, nabiximols 1.1%.	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

Hoffman et al. 2017[63]	73% smoking; 32% ingestion; 23% vaporizing; 9% topical use.	• 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]	Inhalation (83.4%)	NR	NR	Participants used 3 times/day	NR
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,	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%).

	1% topicals. Preferred method: 44% vaporization, 23% edibles.				
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 & Reinarman et al. 2011[64, 68]	NR	NR	NR	NR	51% reported using cannabis as a substitute for prescription medications.
Ogborne et al. 2000[77]	Mainly smoking.	Smoking: • enjoyable • immediate, effective • less expensive Eating/drinking: • “less of a head stone...” • longer lasting • no smell	Smoking: • Respiratory side effects (cough, throat irritation) Eating/drinking: • 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: • not always convenient • gross • bad taste. Vaporizing: • cumbersome • too expensive. Edibles: • Lack of availability. Tincture: • 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.

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
Sexton et al. 2016[99]	84% inhalation: 32% pipes, 19% bongs, 16.5% joints/blunts, 16% vaporizer; 8% oral (edibles, tincture	NR	NR	61% reported using 1–5 hits per smoking session, 21.3% reported 6–10 hits, 18% reported >10 hits/session.	60% reported substitute MC for prescription drugs, 25% for pain medications, including opiates.

s, capsules); 6% concentrates (oil, keif, hash); 0.6% topical; 0.5% fresh juice.		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%).	
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.	• Time to onset of effect. • Ability to find correct dose. • Smoking lower cost and more accessible. • Eating/drinking had more durable effect.	• 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

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 *[< 7 g/week]*.	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 ≤ 1.5 g/day *[≤10.5g/week]*.	NR

Swift et al. 2005[34]	91% smoked. 74% considered smoking as the most helpful route.	Smoking: • Instant effect. • Ease of titration. • Cost-effectiveness. Edibles: • Healthier • Tasty when cooked in a recipe • Less obvious • Slow onset and long-lasting effects.	Smoking: • Detrimental to respiratory function (and health) Edibles: • 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 *[3.2 g/week]*.	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 ≥ 4 times/day. 45% used >14 g/week.	
Ware et	Among	NR	NR	53% used	NR

al. 2003[82]	users for pain: 81% joint, 47% joint with tobacco, 34% pipe, 16% water pipe; 9% orally.		≤ 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.

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

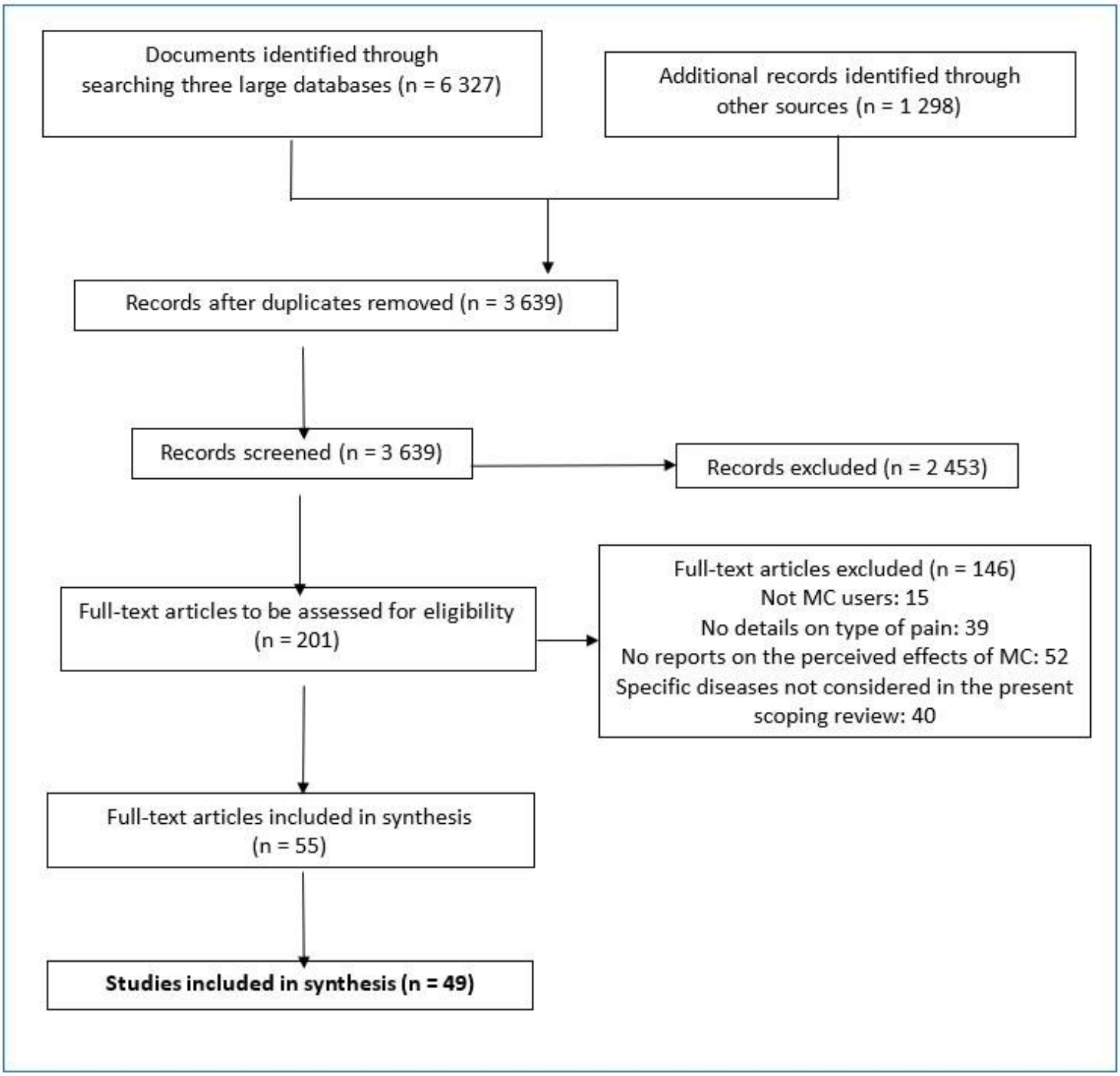

Figure 1

Flowchart of the scoping review

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- ScopingreviewsupplementstablesBMC.pdf