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CHRONIC PAIN (R STAUD, SECTION EDITOR)

Cannabis and Cannabinoids for Chronic Pain

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Abstract
Purpose of Review The purpose of this study was to provide the most up-to-date scientific evidence of the potential analgesic effects, or lack thereof, of the marijuana plant (cannabis) or cannabinoids, and of safety or tolerability of their long-term use.
Recent Findings We found that inhaled (smoked or vaporized) cannabis is consistently effective in reducing chronic non-cancer pain. Oral cannabinoids seem to improve some aspects of chronic pain (sleep and general quality of life), or cancer chronic pain, but they do not seem effective in acute postoperative pain, abdominal chronic pain, or rheumatoid pain. The available literature shows that inhaled cannabis seems to be more tolerable and predictable than oral cannabinoids.
Summary Cannabis or cannabinoids are not universally effective for pain. Continued research on cannabis constituents and improving bioavailability for oral cannabinoids is needed. Other aspects of pain management in patients using cannabis require further open discussion: concomitant opioid use, medical vs. recreational cannabis, abuse potential, etc.

This article is part of the Topical Collection on *Chronic Pain*

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Introduction

Cannabis, or marijuana, has become increasingly available over the last two decades in the USA for medical and recreational use. Although cannabis is still considered illegal under US federal law, 29 states and the District of Columbia (D.C.) have made policy changes allowing the use of marijuana for a variety of medical purposes ranging from chronic pain to nausea associated with chemotherapy [1]. Seven states and D.C. have approved the use of cannabis for recreational purposes. Cannabis contains two major active ingredients (cannabinoids), delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). The concentration of these ingredients within the cannabis plant is thought to be the underlying cause of the effects associated with different strains of cannabis.

Even though there is a clear need for further research within the field, there have been multiple advancements in basic science and clinical accomplishments using cannabis or cannabinoids for the treatment of pain [2]. Currently, and based on scientific evidence, there is a scientific consensus on the medicinal effects of cannabis for the treatment of chronic pain. These effects are believed to be mostly due to THC via activation or interactions with cannabinoid receptors type 1 and type 2 (CB1 and CB2). Cannabidiol does not directly interact with CB1 or CB2 receptor in a significant manner and, therefore, is devoid of psychotropic effects. In fact, it seems that CBD is an allosteric modulator of CB1 receptor and reduces the efficacy and potency of THC [3]. Additionally, CBD seems to act as an agonist for 5-TH1A receptor [4]. These

CBD actions could play a role in the efficacy of cannabis to treat pain [5].

Most Frequent Routes of Administration of Cannabis and Cannabinoids

Inhaled Administration (Smoked and Vaporized) of Cannabis

Cannabis is commonly used by inhalation via smoking the plant, oils, or resins, and at a lesser extent via vaporization. Among the 29 states plus the District of Columbia in which medicinal cannabis is legal in the USA, the vast majority allows the use of inhaled (smoked or vaporized) cannabis, but very few do not include pain (chronic, severe, intractable, or other types of pain) in the indications for which cannabis could be used [1]. In addition to the increased legalization of cannabis for medical purposes, the legalization of recreational use of marijuana makes it available at a broader spectrum.

Advantages and limitations of inhaled administration (Table 1) are as follows:

1. Advantages

   The pharmacokinetics of inhaled cannabis is one of its major advantages for the treatment of pain. After inhalation (smoked or vaporized), cannabis-related effects begin in general within a few minutes (15–45 min), peak at 1 h, and are maintained at steady state for 3–5 h, which is in accordance with the plasma levels of THC [6]. Interestingly, the inhaled cannabis PK profile is similar to (but with smaller areas under the curve) THC given intravenously [6]. The PK profile of CBD is very similar to THC orally, intravenously, or inhaled [6]. It is worth noting that the effects of cannabis could be experienced immediately after the first inhalation (puff) and these effects could increase within 1–10 min [15]. These pharmacokinetics (rapid onset, short time peak effect, and intermediate lasting effects), due to avoidance of first passage metabolism, allow for self-titration (which maximizes analgesic effects), reduces side effects or dysphoria, and drug exposure when pain is controlled. All of these advantages are virtually impossible with oral administration of cannabis or cannabinoids.
2. Limitations

   The major limitation of inhaling cannabis is the intake of toxic combustion byproducts, such as carbon monoxide, following the smoking route and its subsequent effects within the respiratory tract [5]. Vaporization is a smoke-free alternative for the inhalation of cannabis or cannabinoids [7, 8]. Another disadvantage of inhalation is the variability in efficiency (inter-patient) due to differences in inhalation techniques (in some cases poor technique, especially in naïve-smoking or naïve-inhaling patients), potential discomfort of the inhalation process, respiratory tract irritation during inhalation, etc. In fact, a high inter-patient variability has been described in subjects smoking cannabis cigarettes under controlled conditions [15]. Thus, after smoking, plasma concentration of THC or its metabolites in active cannabis smokers are higher than that in ex-cannabis users [9].

Table 1 Comparison between inhaled and oral cannabis' PK and efficacy in chronic pain

Parameter	Inhaled	Oral (oromucosal)
Onset of effect	Minutes	Hours
Peak effect	1 h	Several hours (2–4 h)
Duration of effect	3–5 h	Variable, 8 to > 20 h
Self-titration to achieve desirable effects within tolerable ranges	Could be implemented relatively easy	Not recommended due to unpredictable appearance of side effects
Scientific evidence for chronic non-cancer neuropathic pain treatment	Conclusive or substantial for pain intensity	Moderate for short-term sleep improvement

Oral Pharmaceutical Cannabinoids

Currently, there are four available oral pharmaceutical preparations of cannabinoids. Dronabinol is a THC molecule extracted from the resin of cannabis, is available in capsule form, and has been approved by the U.S. Food and Drug Administration (FDA) for the treatment of chemotherapy-induced nausea and appetite stimulation in patients with AIDS [10]. Nabilone is a synthetic THC derivative, which is available in capsule form, and has been FDA approved for the treatment of chemotherapy-induced nausea, anorexia, and weight loss in patients with AIDS [10]. In addition, in Mexico, this drug has been approved as an adjuvant therapy for the treatment of chronic pain [11]. Nabiximols is an oromucosal spray that contains virtually equal concentrations of THC and CBD derived from the cannabis plant (plus minor quantities of other cannabis constituents) and currently has FDA investigational new drug (IND) status for the treatment of cancer pain. The first phase 3 clinical trial conducted by GW Pharmaceuticals (nabiximols manufacturer) failed to meet primary end points for the treatment of pain in patients with advanced cancer vs. placebo in 2015 (GW, 2015). Two other FDA phase 3 clinical trials for this condition are currently being conducted, and at the moment, they have shown similar negative results [12•]. Nabiximols is approved in Canada as an adjuvant treatment for multiple sclerosis

spasticity and, under certain conditions, for both multiple sclerosis neuropathic pain and opioid-resistant cancer pain. Epidolex is a liquid formulation of CBD derived from the cannabis plant with FDA IND status for the treatment of intractable seizure syndromes in children, and currently has not been studied for the treatment of chronic pain [13].

Advantages and limitations of oral administration (Table 1) are as follows:

1. Advantages

   The primary advantages with oral administration of cannabis or cannabinoids include pharmaceutical-grade compounds, standardized concentrations or doses, and a non-complicated route of administration.
2. Limitations

   The major limitation associated with the oral administration of cannabis or cannabinoids is its poor pharmacokinetic profile [14]. The bioavailability of THC (extract, synthetic, or cannabis) following oral administration is very low (6–20%), mostly due to its lipophilic nature. The absorption is slow, erratic, and variable, even in oil vehicles. The onset and peak plasma concentrations are low and delayed, and its metabolism produces psychoactive metabolites ("11-hydroxytetrahydrocannabinol" [11-OH-THC] and "11-nor-9-carboxy-tetrahydrocannabinol" [THC-COOH]) for which plasma concentrations are extended for several hours (8–12, in some cases 20–25 h) [15, 16]. This PK profile results in a late-onset, variable absorption, extended duration, and unpredictable psychotropic effects [15, 17]. Many aspects contribute to the fact that oral forms of pharmaceutical THC, namely nabilone, do not represent a matter of public and health concern from the abuse potential standpoint [18], for example: its oral PK profile, the higher frequency of side effects, and its higher price compared to herbal cannabis.

What Is the Evidence for Cannabis or Cannabinoids for Pain Treatment Efficacy?

According to the 2017 National Academies of Sciences Engineering Medicine report [19••], there is conclusive or substantial evidence to support cannabis being effective for the treatment of chronic pain in adults and moderate evidence that cannabinoids, primarily nabiximols, are effective for improving short-term sleep outcomes in individuals with chronic pain.

This notion has been replicated in a recent meta-analysis that included orally administered cannabinoids and inhaled cannabis for multiple medical conditions, which found moderate-quality evidence in favor of cannabinoid efficacy to treat chronic pain (and spasticity) due to neuropathy or cancer [20•]. This study also found that both cannabinoids and cannabis possess a higher risk of short-term side effects, but these side effects were mostly tolerable.

Inhaled Cannabis for Pain Treatment

The most up-to-date meta-analysis (individual patient data meta-analysis using a Bayesian probability analysis) of inhaled cannabis in chronic painful neuropathy (not including multiple sclerosis) presents evidence that supports inhaled (smoked or vaporized) cannabis reduces pain in chronic neuropathic pain. This study shows that the number needed to treat (> 30% reduction in pain scores) of inhaled cannabis is 1 out of every 5–6 patients [21]. Interestingly, the studies that evaluated more than one THC concentration and were included in this meta-analysis showed a dose-related effect of cannabis [22–24]. Of particular relevance is the fact that one of these studies showed that low concentrations of cannabis THC, 1.29% (vaporized), provided pain relief in neuropathic pain patients [23]. In the five randomized studies included in this meta-analysis, the cannabis used contained THC concentrations that ranged from 0 to 1.29% to 9.4% (0–5.85 to 96 mg/day) [22–26]. In these published studies, the reported side effects were mild to moderate and tolerable. Side effects included anxiety, disorientation, difficulty concentrating, headache, dry eyes, burning sensation, dizziness, numbness, memory impairment, and reduced psychomotor performance and attention. Withdrawals due to adverse effects were reported to be 3 (1 in the placebo [psychosis] and 2 in the cannabis-treated cohort [hypertension and increased pain]) in a total of 178 patients. Euphoric effects ("high") were found to be rare and mild in intensity in this meta-analysis.

In accordance with these conclusions, in a more recent small randomized, double-blinded, placebo-controlled crossover clinical study in patients (16 subjects) suffering from painful diabetic neuropathy (4 or higher on a 0–10 numerical rating scale), vaporized cannabis reduced spontaneous pain and reduced evoked pain induced by a foam brush or von Frey filaments in a dose-dependent fashion [27•]. In this study, the maximum and consistent effect observed was in the group receiving the highest dose, 7% THC (28 mg), which produced a reduction of 1.2 points in pain intensity when compared to placebo. Interestingly, the low- and medium-dose groups (1 and 4%, 4 and 16 mg, respectively) also reported a significant reduction in pain intensity average scores when compared to the placebo's effect (0.44 and 0.42 for low and medium doses, respectively). All THC groups had < 1% of CBD. In accordance with the PK of inhaled cannabis, pain reduction was observed as early as 15 min after cannabis inhalation, and these effects were sustained for at least 4 h. In terms of side effects, modest effects were observed when compared to placebo and included euphoria ("high"), somnolence, and decline in cognitive tests [27•].

In another randomized, placebo-controlled, double-blind, crossover study (38–41 subjects per group) using vaporized cannabis, a THC dose-related analgesic effect was observed in pain intensity of patients with chronic neuropathic pain due to spinal cord injury or disease [28•]. Vaporized cannabis was effective in reducing pain at the low and high THC concentrations (2.9 and 6.7% THC, average 45.9 and 56.3 mg, respectively) and the estimated patient number needed to treat to achieve 30% pain reduction was found to be four for 2.9% THC (70% of patients vs. 45% in placebo group) and three for 6.7% THC (88% of patients). Regarding cannabis-related side effects, both THC concentrations produced more side effects when compared to placebo, and the group containing higher THC concentration produced more side effects than the group with lower THC concentration. These effects were: "high" (euphoria), sedation, confusion, and distortion in space and time perception. In this patient population (37 subjects), higher plasma levels of THC and/or THC-COOH (a THC metabolite) significantly correlated with improvements in itching, burning, and deep pain [9].

Oral Cannabinoids for Pain Treatment

A recent meta-analysis that included randomized controlled trials for cannabinoids, namely dronabinol, nabilone, or nabiximols in patients with moderate to severe (4 or higher on a 0–10 numerical pain rating scale) chronic neuropathic pain of peripheral or central origin (including multiple sclerosis) concluded that cannabinoids produced a significant reduction of pain intensity after a minimum of 2 weeks following initiation of treatment with the cannabinoid [29•]. This beneficial effect was reported to be clinically small (0.65 points in a 0–10 pain intensity scale). Interestingly, the meta-analysis also found that cannabinoids improved quality of life and sleep in patients with chronic neuropathic pain. In the 11 randomized studies that were included in this meta-analysis, the doses for dronabinol were 2.5–10 mg/day, for nabilone were 1–4 mg/day, and for nabiximols were approximately 10–29 mg/day [30–40]. The reported side effects were mild to moderate, transient, and tolerable (dizziness/lightheadedness, somnolence, and dry mouth). A number of withdrawals occurred in some of the analyzed trials in this meta-analysis: 3 out of 13 patients with nabilone [39], 4 out of 96 [31] patients with nabilone, and 11 out of 63 patients with nabiximols (vs. 2 out of 62 in placebo) [34].

Are Cannabinoids Effective in All Types of Pain?

Due to the different pathophysiological mechanisms of chronic and acute pain, and among different types of chronic pain (peripheral, central, metabolic, chemotherapy toxic, cancer, amputation, etc.), it would be surprising if cannabis or cannabinoids were effective in treating any type of pain. Accordingly, some reviews have found conflicting results when the effectiveness of cannabinoids has been evaluated for cancer pain and neuropathic pain. A recent review with critical appraisal conducted by the Canadian Agency for Drugs and Technologies in Health [41•] analyzed five systematic reviews and two meta-analyses of nabiximols (THC and CBD in oromucosal spray) for the treatment of chronic cancer and non-cancer neuropathic pain. This review found mixed results (effective and non-effective studies) and concluded that there is not a sufficient amount of evidence to support nabiximols having a clinical advantage when compared to placebo in the treatment of chronic pain. In terms of side effects, the following were found to be mild and in accordance with a cannabinoid-associated action: dizziness, drowsiness, fatigue, vertigo, headache; or related to the route of administration: mouth ulcers, dysgeusia, sore throat [41•].

Cancer Pain

Nabiximols has been extensively studied in cancer pain patients. In an early study of cancer patients with chronic pain non-responsive to opioids (multicenter, double-blind, randomized, placebo-controlled, parallel-group, 58–60 subjects per group), nabiximols was given for 2 weeks and showed a reduction in pain intensity (effect of 30% or more) in a larger proportion of patients than placebo (approximately 40 vs. 20%, respectively), while the proportion of patients with reduced pain was similar between the THC-alone and placebo groups [42]. Regarding side effects, nabiximols produced more nausea and vomiting than placebo, while these side effects were similar between the THC and placebo groups. A decline in cognitive function was observed in both the nabiximols group and the THC-alone groups when compared to the placebo. Somnolence, dizziness, and nausea were also frequent, but mild, in the nabiximols group [42].

In a subsequent study (multicenter, randomized, double-blind, placebo-controlled, graded-dose) in cancer patients with moderate to severe pain despite active stable opioid treatment (88–91 subjects per group, placebo, low, medium, and high doses), it was shown that following 35 days of treatment, the proportion of patients reporting 30% relief (primary endpoint) was not different between the nabiximols groups and placebo. However, a secondary endpoint that evaluated the proportion of continuous response throughout the duration of the study showed that the low and medium doses (but not the high dose) of nabiximols were favorable when compared to placebo [43]. The number of patients that withdrew and the side effects were more frequently associated with the high-dose nabiximols group when compared to the placebo, and these side effects were consistent with cannabinoid-related effects: dizziness, somnolence, disorientation, nausea, etc. [43].

More recently (October 27, 2015), GW Pharmaceuticals, the manufacturer of nabiximols (sativex) made a public announcement through its website regarding two phase 3 clinical trials (randomized, double-blind, placebo-controlled, parallel-group) conducted in different countries (Europe, USA, and Mexico) comparing nabiximols and the placebo in cancer patients with chronic pain that were non-responsive to established opioid therapy [12•]. In this announcement, GW Pharmaceuticals communicated that nabiximols failed to show superiority over the placebo in both of the clinical trials. They reported that in one of the studies, nabiximols was found to be significantly superior than the placebo in the patient sub-population studied in the US sites, and this significance was lost when patients from Europe and Mexico were added to the analysis. In the other clinical trial conducted outside the USA, the effects of nabiximols were not different from the placebo [12•].

Based on these studies, the general effectiveness of cannabinoids for chronic cancer pain is questionable. However, whether the benefits of cannabinoids for some clinical aspects in this patient population result in a significant improvement in their quality of life remains to be elucidated. It is possible that this notion could be clarified when these clinical trial results are published.

Rheumatoid Pain

A systematic review of cannabinoids (nabiximols, nabilone, and a fatty acid amide hydrolase inhibitor—which enhances the endocannabinoid anandamide) for the treatment of rheumatoid conditions, including rheumatoid arthritis, fibromyalgia, or osteoarthritis, included four studies that were identified to have a high risk of bias [44•]. This systematic review found that none of these studies had a beneficial effect for pain, and the cannabinoid treatment groups experienced more frequent side effects and withdrawals due to side effects than their comparator groups [45–48]. These data seem to be in accordance with the use of cannabis among patients with rheumatologic conditions. For example, one survey study shows that inhaled cannabis does not seem to be popular among rheumatology patients in areas in which medicinal cannabis is legal. In Canada, cannabis is used by a very low proportion (3.8%) of rheumatology patients, despite the fact that two thirds of the 40,000 patients authorized to possess cannabis for medicinal purposes in Canada are identified with severe arthritis [49].

Chronic Abdominal Pain

In a randomized, double-blind, placebo-control, parallel-design clinical study, using oral THC, incremental 3–8 mg (in a dose escalation fashion) three times a day given for 50 days, failed to reduce pain intensity in patients with chronic abdominal pain (3 or more points in a 0–10 pain intensity scale) due to surgery or chronic pancreatitis [50•]. This study confirmed plasma levels of THC and 11-OH-THC, indicating adequate absorption of the drug. Seven patients did not tolerate THC (5 mg) and they discontinued treatment in comparison to two patients that withdrew in the placebo group. In addition, five patients in the THC group (vs. two in the placebo group) reduced their dose from 8 mg to 5 mg due to tolerability issues. Side effects were more frequent in the THC group and they were mild to moderate, tolerable, and cannabinoid-related: dizziness, somnolence, euphoria, etc. [50•].

Acute Postoperative Pain

A multicenter study has shown that a cannabis extract containing mostly THC (1:0.3–0.5 THC/CBD ratio) given orally reduces acute pain intensity in postoperative patients (20 subjects) in a dose-dependent manner (5, 10, and 15 mg). In this study, side effects were consistent with cannabis-related effects and they were also observed in a dose-dependent fashion. The results of this study should be taken cautiously since this study was not placebo-controlled and not performed in a blind fashion [51].

A study (randomized, double-blind, placebo-controlled, single-dose) using 5 mg of oral THC (dronabinol) in patients that underwent abdominal hysterectomies (20 subjects) showed no significant differences in pain intensity on movement or at rest when compared to the placebo group (20 subjects). There were minimal side effects reported in the THC group [52].

A pilot study (double-blind, randomized, placebo-controlled, parallel-group) using two doses of nabilone (oral, 1 and 2 mg, 11 and 9 subjects, respectively) found that oral THC did not change opioid consumption following surgery, and furthermore, 2 mg of nabilone produced higher pain scores with movement and at rest when compared to either placebo (10 subjects) or ketoprofen (11 subjects). This study did not show any significant difference in side effects among groups [53]. Similarly, another study found that intravenous THC was not effective in reducing pain in patients with tooth extraction pain when compared to placebo, and moreover, some patients preferred placebo over a lower dose of THC [54].

The results of these various studies indicated that cannabinoids are not effective to treat acute postoperative pain that resulted from different types of surgeries.

Are Oral Cannabinoids or Inhaled Cannabis Safe for Long-Term Use?

Since scientific evidence shows that chronic pain is one of the few validated conditions for medicinal cannabis, it is, therefore, expected that patients who find pain relief with cannabis or cannabinoids will use it for extended periods of time. One concern regarding the use of cannabis for chronic pain is the

potential undesirable effects when used for months or years. Even though there are few randomized, blind, controlled clinical trials for long-term cannabis use looking at safety and tolerability (mostly in multiple sclerosis patients and using oral cannabinoids), the following section discusses studies that provide valuable information. However, due to the limitations of these studies, these data should be taken into consideration cautiously.

Cannabis Studies Evaluating Long-Term Use Safety and Tolerability

A prospective multicenter cohort study (open label) was conducted to primarily assess the risk of adverse events, secondarily neurocognitive function, pulmonary function, and effectiveness on pain in patients (215 subjects in cannabis group, 216 subjects in control non-cannabis group) using cannabis long-term for chronic non-cancer pain [55••]. The cannabis that was provided to patients contained 12.5 ± 1.5% THC, and the median daily amount of cannabis consumed by patients was 2.8, 1.8, or 2.0 g/day, for current users, ex-users, and cannabis-naïve patients, respectively. The participants in the cannabis group used different modes of administration: smoking only (27%), orally and vaporization (61%), and orally only (8%). The median duration of follow-up for patients within the cannabis group was 11.9 months (7–551 days) and 12.1 months (28–567 days) for patients in the control group (non-cannabis users from the same clinics of cannabis users). Ten patients (5%) within the cannabis group withdrew due to adverse events. Most adverse events were mild to moderate in the control and cannabis groups, and serious adverse events were similar in both groups. The incidence rate of non-serious adverse events was higher in the cannabis groups than in the control group. The most frequent (occur more than once) adverse events related to cannabis were somnolence, amnesia, cough, euphoric mood, hyperhidrosis, and paranoia (0.2–0.6%). Only one cannabis-related serious adverse event was reported. Lack of efficacy was the cause of withdrawal for 18 patients (8%). Five patients (2%) withdrew due to adverse events and lack of efficacy, and four patients (2%) withdrew due to dislike of the product. Interestingly, ex-cannabis users and cannabis-naïve users were more likely to withdraw than current cannabis users. All neurocognitive tests performed for both cannabis and control groups showed improvement over time. Regarding pulmonary function with prolonged cannabis use, it was found that there was a decrease in residual volume, diffusion capacity, forced expiratory volume, forced expiratory volume/forced vital capacity, and forced expiratory $flow_{25–75\%}$. Pain scores decreased and physical function, mood, and distress improved over 1 year in the cannabis group. This was not observed in the control group, which suggests that the use of cannabis over 1 year does not induce analgesic tolerance [55••].

Oral Cannabinoid Studies Evaluating Long-Term Use Safety and Tolerability

A 12-month randomized, double-blind, placebo-controlled trial continuation of a randomized parent study measured the safety and efficacy of oral cannabinoids (capsules) in patients with multiple sclerosis [56]. These studies included two active arm treatments, 2.5 mg dronabinol (THC, 216 subjects), and a cannabis extract containing 2.5 mg THC, 1.25 mg CBD, and < 5% other cannabinoids in each capsule (219 subjects). Each active arm group was run in parallel with their respective placebo (114 and 108 for dronabinol and cannabis extract, respectively). Patients were titrated to a maximum of 25 mg THC daily depending on tolerability and patient weight. During the main parent study, 27 patients withdrew due to side effects in the cannabis extract group, 28 patients withdrew in the dronabinol group, and 10 patients withdrew in the placebo group due to side effects. During that phase of the study, 31 patients withdrew due to lack of efficacy in the cannabis extract group, 30 patients withdrew in the dronabinol group, and 64 patients withdrew in the placebo group due to lack of efficacy. From the remaining patients who continued into the follow-up study, the number of patients who withdrew due to lack of efficacy or side effects was similar in the active arm groups (1–2 patients); however, in the placebo group, five withdrew due to lack of efficacy, and one due to side effects. For the patients that completed the follow-up study (383 subjects), serious side effects were similar between placebo and active groups and were related to the medical condition. Adverse events occurred in 125 patients on cannabis extract, 109 patients on dronabinol, and 127 patients on placebo. Regarding efficacy, improvements (statistical significance) were seen in pain, shaking, spasms, spasticity, sleep, energy, and tiredness. The Ashworth scale, which measures spasticity, showed a 2-point improvement from the mean baseline score of 22. Overall, there were no safety concerns associated with patients during treatment in the follow-up study [56].

A series of trials have used nabiximols long-term in different conditions to study its safety and tolerability. These were open-label extension studies from previous trials that did not include a control group. They present interesting information including a patient withdrawing due to treatment related adverse events or lack of efficacy. The majority of adverse effects reported in these studies were mild to moderate. These studies are summarized in Table 2 [57–60].

In an open-label, non-controlled trial, nabiximols was studied for potential withdrawal syndrome-related effects in multiple sclerosis patients [60]. Twenty-five patients that used nabiximols for 1 year gave their consent to abruptly discontinue their treatment for 2 weeks. Eleven of these patients (44%) reported withdrawal-type symptoms such as interrupted sleep, hot and cold flashes, tiredness, low mood, and decreased appetite [60]. Conversely, in another open-label

Table 2 Summary of safety and tolerability studies using oromucosal cannabinoids (THC/CBD). All studies are open-label and uncontrolled. Adverse events and serious adverse events reported are treatment (cannabinoid)-related

Reference	Condition	Duration of study	Duration of treatment (median or mean)	Withdraws due to (no. patients/total no. of patients)		Serious adverse events[b]
				Lack of efficacy	Adverse events	
57[a]	Cancer pain	> 1 year	25 days (median, range = 2–579)	23/39	3/39	3/39
58	Neuropathic pain and MS	2 years	638 days (median, range = 3–917)	17/63	3/63	1/63
59	MS	> 2 years	334 days (mean, SD = 209)	20/146 1st year; 3/59 2nd year	14/146	2/146
60	MS	> 2 years	329.5 days (mean, range = 21–814)	24/137	17/137	3/137

[a] This study included a very small group of patients receiving only THC (4 subjects); therefore, the data interpretation from this group may not be compelling

[b] Data are presented as no. of patients/total no. of patients

MS multiple sclerosis

uncontrolled trial that used nabiximols in multiple sclerosis patients, the investigators did not find signs or symptoms of withdrawal syndrome in patients who stopped their treatment [59].

Taking all these studies together (time that patients remained using the treatment, number of withdrawals due to adverse events related to treatment or lack of efficacy, serious adverse events, and other tolerability or efficacy parameters), it seems that, in general, cannabis appears more tolerable than oral cannabinoids. This interpretation is based on a single trial for cannabis [55••] and, hence, should be taken cautiously.

The potential safety regarding misuse or abuse of cannabis when used for long-term and for medicinal purposes requires further discussion. It is well documented that the use of cannabis at young ages, or the regular daily use of cannabis enhances the changes to develop problems in cannabis use [19••].

Summary and Conclusions

In summary, we conclude that the scientific evidence presented demonstrates that inhaled cannabis is clinically useful for the treatment of chronic (neuropathic) pain, and seems to be safe and tolerable for long-term use under medical supervision. The effects seem to be modest and variable. However, clear monitoring parameters and extreme caution are required to standardize its extended use. Oral cannabinoids seem to be less effective and less tolerable than inhaled cannabis to reduce pain intensity. With the current evidence, it is not clear whether oral cannabinoids could improve certain aspects of pain in patients with cancer. The scarce available literature shows that cannabinoids have limited efficacy in rheumatologic-associated pain conditions. Similarly, oral cannabinoids do not reduce acute postoperative pain or chronic abdominal pain. The use of inhaled cannabis or cannabinoids for the treatment of chronic pain entails multiple considerations that the health care professionals should take into consideration, such as the concentration of THC required to manage pain. For example, the majority of the studies showing efficacy to treat chronic pain used cannabis with a THC concentration close or lower than 10%, and some studies show efficacy with very low THC concentration strains. This is in contrast with the high concentrations of THC found in cannabis for recreations use (> 15%). Health care professionals should monitor these patients more closely for potential concomitant use with opioids. Having a comprehensive approach using non-pharmacological strategies to treat chronic pain should be part of the pain management plan. These strategies could help reduce the use cannabis or other medications and restore functional activity in patients that suffer some pain-related disabilities.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

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