

NARRATIVE REVIEW

Cannabis and pain: a scoping review



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Abstract For centuries, cannabis has been used with many different purposes, including medicinal use, usually bypassing any formal approval process. However, during the last decade, interest in cannabis in medicine has been increasing, and several countries, including the United States and Canada, have produced their own legislation about marihuana and cannabis-based medicines. Because of this, interest in research has been increasing and evidence about its medical effects is becoming necessary. We conducted a review examining the evidence of cannabis in pain. Cannabis had been shown to be useful in acute and chronic pain, however recently, these results have been controverted. Within the different types of chronic pain, it has a weak evidence for neuropathic, rheumatic pain, and headache, modest evidence for multiple sclerosis related pain, and as adjuvant therapy in cancer pain. There is no strong evidence to recommend cannabis in order to decrease opioids in patients with chronic use. Even though cannabis-based medications appear to be mostly safe, mild adverse effects are common; somnolence, sedation, amnesia, euphoric mood, hyperhidrosis, paranoia, and confusion may limit the use of cannabis in clinical practice. Risks have not been systematically analyzed. Special concern arises on how adverse effect might affect vulnerable population such as elderly patients. More research is needed in order to evaluate benefits and risks, as well as the ideal administration route and dosages. As cannabis use increases in several countries, answers to these questions might be coming soon.

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Introduction

For centuries, cannabis has been used with many different purposes, including medicinal use.¹ The Shennong Ben Cao Jing encyclopedia, which dates back to 2900 BC in China, recommended the seeds as treatment for pain, constipation and malaria.² Additionally, the plant was used along with wine to create an anesthetic effect for patients undergoing surgery.³ Around 1000 AC, cannabis flowers became popular in India, providing analgesia, hypnotic, antispasmodic, and anti-inflammatory effects.⁴ In the 21st century, cannabis began to be explored by Western medicine, however only plant extracts were used,¹ and active ingredients, both from leaves and flowers were isolated.⁵ During the 20th century, the endocannabinoid system was further understood and in the 3rd edition of the US Pharmacopoeia, in 1851, cannabis was included as a treatment for gout, rheumatism, tetanus, cholera, hysteria, depression, delirium tremens, and uterine bleedings.⁵ Cannabis was available in the US pharmacies since 1845 and was available in British pharmacies for over a century,⁶ however, because of the rise of concerns by its psychotropic effects, it was removed from the US Pharmacopoeia in 1941.⁷ In 1976, the United States Controlled Substances Act classified cannabis as a Schedule I drug, meaning it had no acceptable medical use and high potential for abuse.¹

During the last decade, interest in cannabis in medicine has been increasing, and several countries, including United States and Canada, have produced their own legislation about marijuana and cannabis-based medicines.⁸ In 2017, 38 states and the District of Columbia allowed medical use of cannabis, and 8 states and the District of Columbia have legalized its recreational use.⁹ Similarly, Health Canada has granted access to cannabis medical uses since 1999 and by 2013, more than 37,000 patients had been treated with cannabis for different conditions.¹⁰ In Germany, physicians may prescribe cannabinoids with costs covered by health insurances for patients with severe diseases, and no alternative treatment options.¹¹

During recent years, interest in the use of cannabis in clinical practice has been growing. Additionally, changes on the legislation of several countries have been made. Because of this, there is a current need for reviewing the evidence in order to keep practitioners with up-to-date knowledge. This review concentrates on its evidence for pain control.

Methods

On April 2nd, 2020, a search in PubMed was performed with the following terms: "Pain"[Mesh] OR "Pain" OR "Acute pain"[Mesh] OR "Pain management"[Mesh] OR "Chronic pain"[Mesh] OR "Cancer pain"[Mesh] OR "Pain, intractable"[Mesh] OR "Neuralgia"[Mesh] OR "Neuralgia" OR "Arthralgia"[Mesh] OR "Arthralgia" OR "Fibromyalgia"[Mesh] OR "Fibromyalgia"

AND

"Cannabis"[Mesh] OR "Hemp plant"[Mesh] OR "Marijuana Smoking"[Mesh] OR "Marijuana Abuse"[Mesh] OR "Hashish oil"[Supplementary Concept] OR "Cannabinoids"[Mesh] OR "Cannabinol"[Mesh] OR "Cannabidiol"[Mesh] OR "Dronabinol"[Mesh] OR "Tetrahydrocannabinol" OR "Cannabis" OR

"Marihuana" OR "Marijuana" OR "CBD" OR "THC" OR "Cannabinol" OR "Cannabinoids" OR "Cannabidiol" OR "Dronabinol" OR "Bhang" OR "Hemp" OR "Hashish" OR "Ganja".

No publication date or language limits were used. All the references retrieved were evaluated analyzing title and abstract, excluding irrelevant studies, and considering for further review those which dealt specifically with cannabis and any type of pain. The different topics of this review were distributed in the group, and each reviewer selected either systematic reviews, if available, or clinical trials. A central pre-designed Excel-based database was constructed, classifying studies according to research design, specific medical condition considered, outcomes measured, sample composition, comparator, dose, and administration route. All authors participated in structuring the review, selecting the subtopics, and drafting the manuscript.

Results

The initial search yielded 9,610 references. The title and abstract of all of them were reviewed by one author (CPR) looking for marijuana or cannabis-based drugs for the treatment of any type of pain on humans or animals; 5,742 articles were considered irrelevant and were excluded in this phase. Articles reviewing the use of marijuana or cannabis-based drugs for the treatment of any symptom different from pain were excluded. After this, 3,818 articles were retrieved on title and abstract, 111 articles were included for this review.

Cannabis and pain

The cannabis plant contains around 60 cannabinoids.¹² Cannabinoids are endogenous or exogenous compounds that have activity on the cannabinoid receptors¹³; there are three types of cannabinoids: phytocannabinoids (derived from plants such as nabiximols), endocannabinoids (endogenous compounds as anandamide and 2-arachidonulglycerol (2-AG)), and synthetic cannabinoids (dronabinol and nabilone).⁶ The principal cannabinoids found on the cannabis plant are delta-9-tetrahydrocannabinol (THC), cannabidiol (CBD) and cannabinol (CBN).^{14,15} There are three drugs now commercially available that can activate the cannabinoid system, and which are the focus of this review: Cesamet[®] (nabilone), Marinol[®] (THC + dronabinol) and Sativex[®] (THC + CBD). The half-life of cannabinoids on the distribution phase is about half an hour, however, the half-life of the terminal phase is longer, with an average of 30 hours.^{6,16} CBD alone was not included in the review.

Sativex[®] (or Nabiximols[®] in the US) is a cannabis-based spray that combines THC which acts as a partial agonist for the CB1 receptor with CBD, which acts as a cannabinoid system modulator.¹⁷ It has been approved for spasticity in multiple sclerosis (MS) in some European countries and in Canada, in where it has also been approved for neuropathic and cancer pain.¹⁸ Marinol[®] (Dronabinol) is a synthetic form of THC approved by the FDA for treating nausea and vomiting resulting from chemotherapy.¹⁷ Nabilone (Cesamet[®]) is a synthetic analogue of THC, approved in the US and the UK for chemotherapy or cancer pain-related vomiting. This review

examines the role of these cannabinoids in the treatment of different types of pain.

Pharmacology of cannabis

The endocannabinoid system is found throughout the human body, usually associated with neuronal tissue, but also expanded through other organs and systems as skin, bone, joints, and hematopoietic defense cells.¹² This lipid signaling system modulates pain, mood, appetite, promotion of sleep, emesis, memory, immunity, cell development, the cardiovascular system, and the “fight or flight” phenomenon.^{19–21} These are interesting targets for many therapeutic options, however, the understanding of the endocannabinoid system is very recent and started with the identification of the cannabinoid receptors CB1 and CB2 during the 1980s and the identification of its ligands.²² The best characterized endogenous ligands (endocannabinoids) are the 2-arachidonoyl glycerol (2-AG) and arachidonoyl ethanolamide (anandamide, AEA).²⁰ These are derived from the arachidonic acid and are produced during the inflammation triggered by tissue injury or following a pre-synaptic neuronal trigger.⁸ These ligands downregulate pain and inflammatory response.⁸ Exogenous ligands, such as phytocannabinoids and pharmaceutical preparations, can also bind to these receptors.^{23,24}

Pain is a subjective experience that is composed by sensory, physiological, motivational, cognitive, and affective factors.²⁵ The three main pain systems are nociceptive, neuropathic, and central.¹ Nociceptive pain is due to tissue damage, and is usually described as throbbing, aching, or sharp pain. It is usually related with immune cells secreting cytokines such as histamine, serotonin, prostaglandin, and bradykinin on the lesion and injury signals carried by C and A gamma peripheral nerve fibers to dorsal root ganglia, up to the thalamus, and then to the cerebral cortex.²⁶ Nociceptive pain has the importance of warning the individual about danger.¹ Neuropathic pain is caused by damage to the nerves, which trigger inaccurate pain messages to the thalamus and the cortex,²⁷ and centralized pain results as amplification of peripheral system due to persistent central nervous dysfunction.²⁸

Pain is a complex process modulated by many subjective factors, which makes it difficult to create simple pharmaceutical targets. Cannabis is rarely the first drug used to treat pain, as patients usually start with nonsteroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase inhibitors (COX), and opioids.¹ The two major ascending pathways in mammals that are devoted to pain, the spinothalamic pathway, and the spinoparabrachial pathway are responsible for the discriminatory and the affective aspects of pain, respectively.²⁹ The descending control of pain can be inhibitory or facilitatory, originates in higher cortical regions, amygdala and hypothalamus, and projects to the lower brain stem and the spinal cord.²⁹ The endocannabinoid system is expressed throughout the ascending and the descending pathway. The cannabinoid receptors 1 and 2 (CB1 and CB2) have been extensively studied as antinociceptive receptors, either singly or in combination.³⁰ The CB1 receptors are located on the peripheral endings and central terminals of the primary afferent neurons,³¹ as well as

the dorsal root ganglion,³² however, the clinical utility of cannabinoids acting at the CB1 receptor can be limited due to the development of tolerance and the high rate of central adverse effects.³³

The CB2 receptor is the classical peripheral cannabinoid receptor and is present in immune cells and in the reproductive, cardiovascular, gastrointestinal, and respiratory systems.³⁴ It is also present in cerebral cortex, hippocampus, striatum, amygdala, thalamic nuclei, cerebellum, and brain stem, in particular inflammatory or pathologic conditions.³⁵ It has been seen shown that inflammatory effects can be modulated by an increased production of endocannabinoids, or by the upregulation of the cannabinoid receptor activity.³⁶ Additionally, the endocannabinoid system plays a role in neuronal development affecting the growth and pruning of axons,³⁷ which could represent an impact on brain development; this should be considered during neuronal development.⁸

Animal models

Cannabinoids have been used in animal models to study inflammatory and neuropathic pain. These studies suggest that CB1 and CB2 agonists reverse allodynia induced by inflammation, even at doses that have not shown analgesic effects.³⁸ It has been seen that the CB2 receptor is upregulated on the spinal cord in rats under inflammatory conditions, which may suggest that it plays an analgesic effect on peripheral sites, but also at central levels of the spinal cord.^{35,39}

The effects of intracerebral administration of cannabinoids have also studied, specifically in the nucleus reticularis, which is known to be an important source of descending modulation of pain.⁴⁰ Additionally, the intracerebral injection of a CB1 antagonist on rats reverses the analgesia in rat models.⁴¹ It was also seen that the intra-articular injection of cannabinoids in an animal model of arthritis and activation of the CB1 receptor increases the activity of the prefrontal cortex and inhibits neuronal activity related with pain in the central nucleus of the amygdala.⁴²

On the other hand, cannabinoids have been shown to suppress C-fiber evoked potentials on neurons of the dorsal horn of rats with neuropathic pain,⁴³ and also inhibit the activity-dependent facilitation of nociceptive stimuli on the spinal cord.²⁹ Strangman and Walker suggested that the inhibition of nociceptive facilitation was explained by general inhibitors of the central sensitization, through inhibition of calcium entry.⁴⁴ Additionally, increased levels of AEA and 2-AG had been seen on the periaqueductal grey (PAG) and the rostral ventromedial medulla (RVM) of rats, after 7 days of chronic injury of the sciatic nerve.⁴⁵

However, the effectiveness of cannabinoids in pre-clinical models of neuropathic pain is contradictory.²⁹ While some authors suggest that systemic administration of cannabinoids mitigates allodynia,⁴⁶ other studies have shown that upregulation and activation of CB1 receptor can be maladaptive and contribute to hypersensitivity.⁴⁷ However, it is clear that the endocannabinoid system modulates pain, and these receptors might be interesting targets for future therapeutic options.

Clinical studies with cannabis

Acute pain

Cannador® has been studied for postoperative pain at doses of 5, 10 and 15 mg,⁴⁸ finding a dose dependent reduction in pain overall, with the 10mg dose the optimal to provide pain-relief without serious adverse effects.⁴⁸ However, in other studies, dronabinol and nabilone were not able to prove benefits on postoperative pain of women with abdominal hysterectomy, with some patients showing an increase on pain scores.^{49,50}

In another study, in which intravenous THC was studied during dental extraction, low dose THC proved to be superior providing analgesia compared with placebo, but less than diazepam. High dose THC, however, was better analgesic than placebo or diazepam.⁵¹ Another study on the effect of levonantradol administered intramuscularly vs placebo on postoperative or trauma pain, showed that levonantradol was better providing analgesia than placebo, without a dose-dependent curve.⁵²

However, recently studies have disputed this evidence. In 2020, vaporized cannabis did not show any beneficial effect over placebo over pain caused by sickle cell anemia.⁵³ A recent meta-analysis comparing cannabis vs analgesics for acute pain did not show any additional benefit from cannabis over common analgesics for acute pain.⁵⁴

Chronic non-cancer pain

Chronic pain is defined as pain that persists after the normal healing time, or when it persists after 3 to 6 months.⁵⁵ There are many conditions that cause chronic pain; it is estimated that 1 in 5 people experience this problem sometime in their lives, and the figure is expected to grow due to an aging population and increasing rates of survival to cancer, and other chronic conditions.¹⁰ Several studies have evaluated the use of cannabis-derivates to treat chronic pain. The causes of chronic pain in these studies are heterogeneous, and include different combinations of neuropathic pain, cancer, diabetes or HIV-associated neuropathy, and fibromyalgia.⁵⁶ The evidence needs to be reviewed separately for each of these conditions.

Neuropathic pain

Neuropathic pain is caused by damage to the somatosensory system⁵⁷ and is a consequence of direct damage to neuronal tissue.⁵⁸ Some of the most common causes are diabetic neuropathy, postherpetic neuralgia, phantom limb pain, trauma, spinal cord injury, trigeminal neuralgia and HIV infection. Many times, however, the cause of the pain remains unknown.⁵⁸ It is difficult to treat, and NSAIDs are not very effective, if at all, and patients require opioids, antidepressants, or antiepileptics.^{59,60}

Abrams et al. evaluated the subjective report of 24-hour pain (on a 1–100mm scale) of patients with HIV-induced neuropathy who were randomized to 3.56% THC smoked cannabis vs placebo cannabis cigarettes, limiting the study to those patients who had prior exposure to THC.⁶¹ In this

study, 52% of the patients in the intervention arm and 24% of the control showed greater than 30% reduction in pain.⁶¹ The number of adverse effects was low, however it was significantly higher on the cannabis arm including sedation, disorientation, confusion, dizziness, and anxiety.⁶¹ Ellis et al. also explored the treatment of HIV neuropathy with smoked cannabis using the Descriptor Differential Scale as a primary measure⁶²; patients were exposed to both arms (THC-free-cannabis and THC-cannabis) and were able to titrate the dose between 1 and 8%.⁶² Participants titrated to 8% while using the THC-free-cannabis but remained at 2 and 4% with the THC-cannabis ($p = 0.016$), however, the use of analgesics did not decrease during the THC-cannabis phase.⁶²

On another study, different concentrations of THC smoked cannabis (0%, 2.5%, 6%, and 9.4%) were used as treatment for post-traumatic or post-surgical neuropathic pain,⁶³ patients reported difference in average daily pain, additionally to improved perceptions of time to sleep while being on the highest doses.⁶³ However, the study did not report improvement in mood, quality of life or mobility.⁶³

Wilsey et al. compared smoked cannabis for neuropathic pain by randomizing patients between THC 0%, 3.5%, and 7% with previous cannabis exposure was required for inclusion.⁶⁴ Both THC treatments (on concentrations of 3.5% and 7%) decreased pain intensity compared to placebo, but there was no difference of the effect between both.⁶⁵ Additionally, cannabinoid blood levels did not correlate with analgesia.⁶⁵

Even though these results sound promising, studies have limitations and results are inconsistent. Therefore, there is no high-quality evidence that supports the use of cannabis on neuropathic pain.⁵⁸ Furthermore, recently published systematic analysis by Stockings et al showed limited benefit for cannabinoids in chronic neuropathic pain.⁶⁶ Additionally, some adverse effects (such as somnolence, sedation, or confusion) may limit even more the use of cannabis in clinical practice.⁵⁸ The Special Interest Group on Neuropathic Pain proposed the evidence of the use of cannabis is weak,⁶⁷ nevertheless, the Canadian Pain Society recommended cannabis as a third line of treatment when the previous lines have been used with limited effectiveness.⁶⁸

Multiple sclerosis (MS)-related pain

MS is the leading non-traumatic cause of neurologic disability in young adults.⁶⁹ People with MS can experience pain, muscle spasms, headaches, fatigue and depression, depending where the plaques are located.^{69,70} In 2017, a survey revealed that 47% of respondents had considered using cannabis to treat symptoms caused by MS, 26% have actually use it, 20% have spoken to the clinician about cannabis and 16% were currently using cannabis.⁷¹ Cannabis has been studied for other symptoms, like spasticity or fatigue, but this review focuses on MS-related pain, which affects two thirds of people with MS⁶⁹ and can present itself as headache (43% of patients), neuropathic pain on arms or legs (26%), back pain (20%), painful spasms (15%) or trigeminal neuralgia (4%).⁷²

One trial assessed the role of THC:CBD as an oromucosal spray for the treatment of central pain in MS.⁷³ Patients

were randomized to THC:CBD on one arm and to placebo on the other, showing that THC:CBD as superior for reducing pain and improving sleep.⁷³ The CAMS study, which enrolled 630 patients with muscle spasticity to receive THC cannabis extract⁷³ and the MUSEC trial, which enrolled patients with MS from 22 UK centers and was focused on stiffness,⁷⁴ measured effectiveness of cannabinoids on pain as secondary outcomes, finding both a reduction in pain when compared with placebo.^{73,74}

Another trial studied Nabilone as an adjunctive treatment to gabapentin for neuropathic pain induced by MS, finding that the reduction of pain was greater in patients that used nabilone than in patients who were treated with placebo.⁷⁵ No trials were found evaluating the role of smoked cannabinoids for the treatment of MS-related pain.

Two systematic reviews were included; on one of them, 15 of 18 trials found at least modest pain relief,⁷⁶ on the other one, cannabis preparations were also found effective in reducing pain scores for the treatment of MS-related pain, however the authors did not state implications for clinical practice.⁷⁷ Therefore, there is modest evidence of the role that cannabis-based medicines can play on MS-related pain; however, research should be enhanced as evidence suggest there are benefits for these patients.

Rheumatic diseases

Rheumatic diseases are an important cause of chronic pain, usually difficult to treat with current analgesic treatments,⁷⁸ and in the absence of a cure for the disease, the treatment of pain should be an important part of the integral management.^{79,80} Analgesic treatment consisting on NSAID, antidepressants and opioids are effective only in 10 to 25% of patients,⁷⁸ and new treatment options are required. Endocannabinoids are present in synovial fluid of joints of people with inflammatory arthritis (IA) and osteoarthritis (OA), but not in normal controls, suggesting that synthesis of receptors follows inflammation and tissue injury.⁸¹

Blake et al. studied the effect of cannabis-based medicine (Sativex) vs. placebo for pain on movement, pain at rest, morning stiffness and sleep quality in patients with rheumatoid arthritis (RA).⁸² On this study, cannabis-based treatment improved significantly pain during movement, pain at rest and quality of sleep, however, it showed no effect on morning stiffness.⁸² There were no serious adverse effects in the active treatment group.⁸²

Nabilone was studied for pain management and quality of life in 40 patients with fibromyalgia.⁸³ Nabilone was used on doses titrated up from 0.5 mg daily to 1 mg BID over 4 weeks vs. placebo. Patients were evaluated at the 2nd and at the 4th week with visual analogue scale (VAS) for pain as main outcome, and a number of tender points; Fibromyalgia Impact Questionnaire (FIQ) and average tender point pain threshold were secondary endpoints.⁸³ This study showed a decrease on VAS in patients treated with nabilone, as well as the FIQ, the rest of the endpoints did not show any significant differences.⁸³ On another study with nabilone, patients with skeletal and locomotor system chronic pain were treated with nabilone and placebo in a 14-week cross-over period (two 4-week medication phases and wash-out phases) followed by a 16-week medication switch period with a free

choice of the study drugs.⁸⁴ On this study, the pain intensity (measured by VAS), decreased while using cannabinoids, and patients favored nabilone when they were asked to decide the drug they wanted to continue with.⁸⁴

Despite these results, three systematic reviews concluded that there is insufficient evidence to recommend any cannabinoid preparation for the treatment of rheumatic pain,^{78,85,86} based on limitations of included studies, due to small sample size, short study duration, heterogeneous medical conditions, and the differences on the products studied.^{78,85,86} Even though cannabinoids are usually well tolerated, some side effects had been seen as dizziness, drowsiness, nausea and dry mouth.⁷⁸

There is no high-quality evidence of the benefits of cannabis-based drugs in patients with rheumatic diseases with chronic pain. Nevertheless, it is advised that patients concerned by the use of cannabis as a drug should be informed about the role of the endocannabinoid system on human health and that there is ongoing research on this field. Cannabinoids for rheumatic pain still constitute off-label use.⁷⁹

Cancer pain

Around 10 million people are diagnosed with cancer around the world each year.⁸⁷ Cancer causes pain through different mechanisms: the tumor itself, chemotherapy, side effects of medications, or postoperative pain.¹⁷ Patients are usually treated with the three-step analgesic ladder proposed by the World Health Organization (WHO) making NSAIDs and opioids the most common treatment for people with cancer, achieving appropriate relief in 71–86% of patients.⁸⁸ Pain may be experienced in all the stages of cancer, but advanced stages show the highest prevalence.⁸⁹ Pain is one of the greatest fears of patients with cancer, and is associated with decreased quality of life, inability to cope with the disease, sleep disruption, and emotional symptoms such as anxiety and depression.⁹⁰ As the treatment of pain in some patients with cancer is still a challenge, there is an interest in studying new treatment options, as cannabis-based medications.⁹¹

One study compared the efficacy of THC:CBD extract, THC alone or placebo in patients with intractable cancer-related pain during two weeks, and showed a significant change on the Numerical Rating Scale (NRS) favoring THC:CBD (Sativex[®]) while compared to placebo, but no change with THC alone.⁹² There was no change on the median dose of opioid medication or number of doses between the treatment groups, and there was worsening in nausea and vomiting with the THC:CBD group when compared to placebo.⁹² On an extension study, THC:CBD oralmucosal spray was used in patients who had participated in the previous three arm study, this time on a two-week randomized controlled trial.⁹³ Patients were asked to self-titrate the THC:CBD spray or THC spray, showing that the scores for pain severity and worst pain decreased in patients with THC:CBD; additionally, patients showed improvement of insomnia, pain and fatigue.⁹³

On trials with Nabiximols[®], patients with poorly-controlled chronic cancer pain received low dose (1–4 sprays per day), medium dose (6–10 sprays per day) or high dose

(11–16 sprays per day) during 5 weeks.⁹⁴ The number of patients reporting analgesia was greater for Nabiximols than placebo, especially for the low and medium dose group.⁹⁴ On another study, Nabiximols as an oromucosal spray was used as an adjunctive therapy in advanced cancer patients with chronic uncontrolled pain.⁹⁵ Patients were able to self-titrate Nabiximols or placebo, showing that Nabiximols was superior to placebo in two of the three quality of life instruments evaluated at week 3 and on all three instruments evaluated at week 5.⁹⁵

Despite all these results, the meta-analysis suggests that there is no strong argument to recommend the use of cannabinoid based medicines as a single treatment for cancer pain, this conclusion is mainly based on sample size and other limitations of the clinical trials.¹⁷ There is some evidence that cannabinoids are effective adjuvants,⁸⁹ but there is an important gap of scientific knowledge, and further research should be encourage as the cannabinoid system could play a role in the treatment of chronic pain related to cancer, but clinicians should caution against its use as analgesics.⁸⁹

Nonetheless, cannabis has been studied for other cancer-related symptoms, such as cachexia, nausea, and vomiting. For cancer-related cachexia, two studies reported no differences between appetite and/or nausea between cannabis and placebo, whereas a third study observed that THC was superior to placebo by increasing appetite.⁹⁶ Additionally, in terms of nausea and vomiting, a meta-analysis provides mixed evidence.⁹⁷ Evidence on relevant outcomes of cannabis managing cachexia, appetite and nausea is missing.

Headache

Headache is associated with a decreased quality of life, disability, and individual and societal costs.⁹⁸ Tension type headache is the most common of all types (38%), followed by migraine (10%) and chronic daily headache (3%). Treatment of headaches includes NSAIDs, triptans, antidepressants, verapamil, or ergotamine, nevertheless, less than half of patients go through remission. Cannabis has been used for the treatment of headaches since ancient times, it appears on the Ayurvedic preparations and in ancient Greece, however, it has been ignored by the scientific community for the last decades.⁹⁹

No clinical trials comparing cannabis to placebo on headache were found. Nonetheless, the effects of cannabis can be evaluated from other studies that point at some evidence about its efficacy. On one study, medical marijuana was prescribed for patients with migraine, finding that the frequency of the headache was decreased on the arm that used marijuana.¹⁰⁰ There is a clinical case report in which the use of recreational marijuana use and subsequent use of dronabinol provided pain relief.¹⁰¹ Because of this case report, a trial was made in which 139 patients with cluster headache were asked about history of cannabis use, finding that even though cannabis use is frequent, efficacy might be limited and should be not recommended until controlled trials and strong evidence is provided.¹⁰²

One trial compared nabilone to ibuprofen in patients with medication overuse headache.¹⁰³ Patients were given the medication daily during 8 weeks, finding that nabilone was

more effective than ibuprofen in reducing pain intensity and daily analgesic intake.¹⁰³ However, there is insufficient evidence to advocate in favor of the use of cannabis-based medicine for the treatment of headache and more research is needed in order to prove both its efficacy and its risks.

Cannabis use on decreasing opioid treatment

The aberrant use of opioid medication is common in people who experience chronic pain, and has become a public health issue.¹ There has been a rising trend in the prescription of opioids in the US, which has quadruplicated over the last 15 years.¹⁰⁴ Despite beliefs, opioids are not an ideal pharmacotherapy for chronic pain as they present a gradual hyperalgesia effect, which is induced over time, which leads patients to increase the opioid dosage over the years.¹

A synergism has been proposed between cannabinoids and opioids as the antinociceptive effects of morphine are mediated by the mu-opioid receptors and might be enhanced by the activation of the kappa and delta-opioid receptors by THC.¹⁰⁵ Receptors for opioids and cannabinoids are binded to similar intracellular signaling mechanisms through G proteins which lead to a decrease of the cAMP production.^{105,106} Additionally, there is some evidence that cannabinoids can increase the release of endogenous opioids and vice versa.^{105,106} Because of this synergy, the role that cannabis could play in decreasing opioids consumption has been studied. One study evaluated pharmacokinetics and safety of the combination of these drugs by exposing 21 patients with chronic pain to a regime with morphine or oxycodone BID and vaporized cannabis in the evening on day 1 and then three times a day during days 2–4 and in the morning of day 5.¹⁰⁷ Pain was decreased after the addition of vaporized cannabis, however there was no change in the area under the plasma concentration-time curves for morphine or oxycodone after the exposure to cannabis.¹⁰⁷ Bachhuber et al. showed that medical cannabis regulation was associated with a reduction in opioid overdose mortality in California, Oregon, and Washington.¹⁰⁸

Unfortunately, there is no strong evidence that could support a recommendation on the synergic activity between cannabis and opioids, despite some research suggests that this interaction might be of clinical and pharmacological interests.

Risks of the use of cannabinoids for analgesia

Given the potential of cannabis as a medical treatment, and due to the concerns generated by the recreational use of cannabis, data about security is a priority for the regulation of cannabis-based medications. The extrapolation of the risk of the recreational use of cannabis is not ideal, but it might provide some insight when there are limited studies in clinical setting.⁸

The COMPASS study examined the safety of cannabis for medical purposes comparing patients with severe chronic pain using THC at 12.5% vs. patients who were not using it.¹⁰⁹ This study showed there was no difference in serious adverse events between the groups, however the cannabis group showed an increased risk of non-serious adverse effects; the most common were somnolence, amnesia, cough, nausea,

dizziness, euphoric mood, hyperhidrosis and paranoia.¹⁰⁹ This corresponds to the results of a systematic review, which showed that most adverse effects were mild, such as dizziness and light-headedness.¹¹⁰

Concerning the medical harms of cannabis use, it has been suggested that low levels of cannabis smoking does not affect lung function over about 20 years, but some evidence might suggest that for a longer period of time, some adverse pulmonary effects might arise,¹⁰⁴ however there is insufficient evidence to link the use of cannabis with cardiovascular events or cancer.

It is important to notice that elder people can be at a higher risk as they have a slower drug metabolism, comorbidities and concomitant medications.¹¹¹ On the psychomotor domain, cannabis can impair gait and stability, which might predispose to falls. On the cognitive domain, cannabis can worsen pre-existing cognitive impairment by adding impairment of short-term memory and of emotional processing.¹¹² There is concern about cardiovascular risk, especially of an increased risk of myocardial infarction, arrhythmia and stroke, and about mental health, especially on the risk of psychotic episodes.¹¹¹

In addition to this, addiction and dependence should be considered. Addiction and dependence to cannabis has been assumed to be comparatively lower than other substances.¹¹³ According to the National Household Survey on Drug Abuse, the prevalence of dependence declined strongly with increasing age and adolescents were much more vulnerable to addiction and dependence.¹¹⁴ The challenges in the use of cannabis, including misuse, addiction and dependence are associated with social and personal factors and should be taken in consideration when using it for medical purposes.

Conclusions

Cannabis has been used throughout history by different civilizations mostly bypassing formal usual approval processes. This is a critical time, as scientific evaluation of evidence concerning the effectiveness and safety of its use has gained relevance. There is evidence, though limited, that support the efficacy of cannabis-based medicine. However, this evidence is insufficient to provide any recommendations of cannabinoids in clinical practice.

Cannabis-based medications appear to be mostly safe, having common mild adverse effects such as dizziness and euphoria; however, there is an important need for research on their safety, especially on vulnerable population such as elderly patients. It is important to stress that safety has only been addressed for short term risks and evidence is insufficient concerning long-term risks.

Cannabis as a treatment for pain is a topic where much research is needed in order to evaluate benefits and risks patients will be exposed to. Additionally, ideal administration route and dosage have not been clearly established. As cannabis use increases in several countries, answers to these questions might be coming soon.

Limitations

Our review has limitations that should be mentioned. First of all, this is not a systematic review of the literature, but

a scoping review. The articles were selected by the authors based on the title and the abstract, however this is not a systematical revision of the literature and should not be interpreted as such. Further review and revision is needed to draw conclusion about the benefits and risks that patients will be exposed to.

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Conflicts of interest

The authors declare no conflicts of interest.

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