International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 945-956 www.ijprajournal.com ISSN: 2249-7781

A Review on Cannabis and Pain

Dhananjay Aniruddha Padul, Saurabh Sugan Patil
Shastry Institute of Pharmacy, Erandol 425109 Dist Jalgaon

Submitted: 12-01-2023 Accepted: 24-01-2023

ABSTRACT
Cannabis has been used for a variety of purposes, including medicine, for centuries, typically without following any kind of formal approval procedure. However, interest in cannabis as a medicine has grown over the past ten years, and some nations, like the United States and Canada, have created their own legislation regarding marijuana and cannabis-based medications. This has increased interest in research and made it imperative to provide evidence of its medical effects. We reviewed the research on the use of cannabis for pain. Cannabis had previously been found to be effective in treating both acute and chronic pain, but these findings have recently come under scrutiny. Weak evidence exists for neuropathic, rheumatic, and headache kinds of chronic pain, as well as for pain associated with multiple sclerosis and as adjuvant therapy. Cannabis is not strongly advised for patients who use opioids frequently in order to reduce their intake. Despite the fact that cannabis-based medicines seem to be generally safe, moderate side effects are frequent; somnolence, drowsiness, amnesia, euphoric mood, hyperhidrosis, paranoia, and confusion may prevent cannabis from being used in clinical settings. There hasn't been a methodical analysis of risks. Particular worry is raised about how negative effects can affect vulnerable groups like elderly patients. To assess advantages and dangers, as well as the best delivery method and dosages, more research is required.

Keywords:Acute pain;Cannabis;Neuralgia;Review;Cancer pain

I. INTRODUCTION

Cannabis has been utilised for a variety of purposes over the years, including medicine. 1 The seeds were suggested as a remedy for pain, constipation, and malaria in the Chinese encyclopaedia Shennong Ben Cao Jing, which was written around 2900 BC. 2 The plant was often used with wine to provide surgery patients a general anaesthetic effect. 3 Cannabis flowers, which have analgesic, hypnotic, antispasmodic, and anti-inflammatory properties, gained popularity in India around 1000 A.D. 4 Western medicine started investigating cannabis in the twenty-first century, but only plant extracts were used1 and the active components of both the leaves and the flowers were extracted. 5 The endocannabinoid system was better recognised throughout the 20th century, and in the 3rd edition of the US Pharmacopoeia published in 1851, cannabis was included as a cure for uterine bleedings, gout, rheumatism, tetanus, cholera, hysteria, depression, and other conditions. Although cannabis had been available in US pharmacies since 1845 and in British pharmacies for more than a century, it was removed from the US Pharmacopeia in 1941 due to growing concerns about its psychotropic effects. 7 Cannabis was designated as a Schedule I narcotic under the US Controlled Substances Act in 1976 because it had a high potential for abuse and no recognised medicinal purpose. 1 The interest in using cannabis as medicine has grown over the past ten years, and various nations, including the United States and Canada, have passed their own laws governing marijuana and products containing cannabis. 8 In 2017, cannabis was legal for medical purposes in 38 states and the District of Columbia, and it was also legal for recreational use in 8 states and the District. 9 Similar to the United States, Health Canada has authorised the use of cannabis for medical purposes since 1999, and as of 2013, more than 37,000 people had received cannabis treatments for a variety of ailments. 10 In Germany, doctors may recommend cannabinoids to patients with severe illnesses who have no other options for treatment. The costs of these prescriptions are covered by health insurances. 11

Recently, there has been an increase in interest in the use of cannabis in therapeutic settings. Numerous countries' legal systems have also undergone adjustments. Due to this, there is now a need for assessing the available information in order to keep practitioners informed. The evidence for pain management is the main focus of this evaluation.

Cannabis in Pain

About 60 cannabinoids are present in the cannabis plant. 12

There are three different types of cannabinoids: phytocannabinoids (derived from plants, such as nabiximols), endocannabinoids (endogenous substances, such as anandamide and 2-arachidonulglycerol (2-AG)), and synthetic cannabinoids (dronabinol and nabilone). Cannabinoids are endogenous or exogenous substances that have activity on the cannabinoid receptors13.

6 Delta-9-tetrahydrocannabinol (THC), cannabidiol (CBD), and cannabinol are the main cannabinoids present on the cannabis plant (CBN). 14,15 This review will concentrate on Cesamet® (nabilone), Marinol® (THC + dronabinol), and Sativex® (THC + CBD), three commercially available medications that can stimulate the cannabinoid system.

Cannabinoids have a half-life of around 30 hours on average in the terminal phase, compared to about 30 hours for the dispersion phase. 6,16 The review did not cover CBD by itself.

A cannabis-based spray called Sativex® (also known as Nabiximols® in the US) mixes CBD, a cannabinoid system modulator, with THC, which functions as a partial agonist for the CB1 receptor.

17 In various European nations as well as Canada, where it has also been authorised for neuropathic and cancer pain, it has been approved for spasticity in multiple sclerosis (MS). 18 An artificial version of THC called Marinol (Dronabinol) has been licenced by the FDA to treat chemotherapy-related nausea and vomiting. 17 A synthetic homologue of THC is called nabilone (Cesamet®) 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 pharmacology of marijuana

The endocannabinoid system is present in every organ and system of the human body. It is often connected to brain tissue, but it has also spread to the skin, bone, joints, and hematopoietic defence cells.

12 Pain, mood, hunger, sleep promotion, emesis, memory, immunity, cell formation, the cardiovascular system, and the "fight or flight" response are all modulated by this lipid signalling system. 19—-21 However, the knowledge of the endocannabinoid system is quite new and began with the finding of the cannabinoid receptors CB1 and CB2 throughout the 1980s and the identification of its ligands. These are intriguing targets for numerous treatment alternatives. 22

Arachidonoyl ethanolamide and 2-arachidonoyl glycerol (2-AG) are the best-studied endogenous ligands (endocannabinoids) (anandamide, AEA). These are made from arachidonic acid and are released during inflammation brought on by tissue damage or in response to a presynaptic neural trigger. 8 This ligands suppress the inflammatory and painful responses. 8 Phytocannabinoids and pharmaceutical formulations are examples of exogenous ligands that can bind to these receptors. 23,24

Pain is a subjective feeling made up of sensory, physiological, psychological, motivational, cognitive, and emotional components.

Nociceptive, neuropathic, and central pain are the three primary types of pain systems. 1 Nociceptive pain is characterised by throbbing, aching, or acute pain and is brought on by tissue destruction. The lesion and injury signals are often sent by C and A gamma peripheral nerve fibres to the dorsal root ganglia, up to the thalamus, and then to the cerebral cortex, where immune cells secrete cytokines such histamine, serotonin, prostaglandin, and bradykinin. 26 The function of nociceptive pain is to alert the person to danger. 1 Neuropathic pain is brought on by nerve injury, which sends false pain signals to the brain and thalamus. Centralized pain is the consequence of continuous central nervous system malfunction, which amplifies the pain experienced by the peripheral nervous system. 28

It is challenging to develop straightforward pharmaceutical targets for pain since it is a complicated process that is influenced by several subjective elements. Cannabis is rarely the first medication used to treat pain; instead,

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 945-956 www.ijprajournal.com ISSN: 2249-7781

nonsteroidal anti-inflammatory medications (NSAIDs), cyclooxygenase inhibitors (COX), and opioids are frequently utilised as starting points. 1 The discriminating and affective elements of pain are controlled, respectively, by the two main ascending routes in mammals that are dedicated to pain, the spinothalamic pathway and the spinoparabrachial system. 29 The lower brain stem and the spinal cord are under the descending influence of pain, which can be either inhibitory or facilitative and originates in upper cortical areas, including the amygdala and hypothalamus.

Both the ascending and descending pathways express the endocannabinoid system. The antinociceptive properties of cannabinoid receptors 1 and 2 (CB1 and CB2), either separately or in combination, have been well researched. 30 The dorsal root ganglion and the peripheral and central terminals of primary afferent neurons both include CB1 receptors; nevertheless, the therapeutic value of cannabinoids acting on the CB1 receptor may be constrained by the high incidence of unfavourable central effects and the development of tolerance. 33 The immunological cells as well as the reproductive, circulatory, gastrointestinal, and respiratory systems all include the CB2 receptor, which is the traditional peripheral cannabinoid receptor. 34 In certain inflammatory or pathologic situations, it is also found in the cerebral cortex, hippocampus, striatum, amygdala, thalamic nuclei, cerebellum, and brain stem. 35 It has been demonstrated that upregulating the activation of cannabinoid receptors or increasing endocannabinoid synthesis can both modify the consequences of inflammation. 36 Additionally, the endocannabinoid system influences axon growth and pruning during neuronal development,37 which may have an effect on brain development; this should be taken into account throughout neuronal development. 8

Animal Models

Animal models have been used to research inflammatory and neuropathic pain with cannabinoids. These results imply that even at levels that have not demonstrated analgesic benefits, CB1 and CB2 agonists can reverse allodynia brought on by inflammation. 38 Under inflammatory circumstances, it has been observed that the CB2 receptor is activated on the spinal cord in rats, which may imply that it has analgesic effects on peripheral locations as well as at central levels of the spinal cord. 35,39

Studies on the effects of cannabinoid intracerebral injection have focused on the nucleus reticularis, which is well recognised to be a significant source of descending pain regulation. 40 A CB1 antagonist is also injected intracerebrally into rats to reverse the analgesia in animal models. 41 Also seen was an increase in prefrontal cortex activity and an inhibition of pain-related neuronal activity in the central nucleus of the amygdala following intraarticular injection of cannabis in an animal model of arthritis and activation of the CB1 receptor. 42

On the other hand, cannabinoids have been demonstrated to decrease activity-dependent enhancement of nociceptive stimuli on the spinal cord as well as C-fiber evoked potentials on neurons of the dorsal horn in rats with neuropathic pain43. 29 Strangman and Walker proposed that general inhibitors of the central sensitization, by inhibition of calcium entry, were responsible for the suppression of nociceptive facilitation. 44 Additionally, following 7 days of chronic sciatic nerve damage, higher levels of AEA and 2-AG have been detected in the periacueductal grey (PAG) and the rostral ventromedial medulla (RVM) of rats. 45

However, there is conflicting evidence about the efficacy of cannabis in preclinical models of neuropathic pain. 29

While some writers claim that cannabis administered systemically reduce allodynia,46 other investigations have demonstrated that CB1 receptor overexpression and activation might be unhelpful and increase sensitivity.

47 But it is undeniable that the endocannabinoid system affects pain, and these receptors may prove to be worthwhile targets for novel treatments in the future.

Clinical studies with cannabis

Actual Pain

Cannador® has been investigated for postoperative pain at dosages of 5, 10, and 15 mg,48 revealing a dose-dependent decrease in pain overall, with the 10 mg dose providing the best pain relief without major side effects. 48 In other investigations, however, dronabinol and nabilone were unable to demonstrate advantages on postoperative pain in women undergoing

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 945-956 www.ijprajournal.com ISSN: 2249-7781

abdominal hysterectomy, with some patients seeing an increase in pain levels. 49,50

In another trial, low dosage THC was found to be superior to placebo in delivering analgesia during tooth extraction, but less effective than diazepam. THC at high doses, on the other hand, was more effective as an analgesic than placebo or diazepam. 51 However, it was more effective as an analgesic than placebo or diazepam. 51 Another research comparing the impact of levonantradol injected intramuscularly vs placebo on postoperative or trauma pain found that levonantradol provided superior analgesia than placebo, despite the lack of a dose-dependent curve. 52

However, new research have cast doubt on this data. In 2020, vaporised cannabis had no benefit over placebo for discomfort induced with sickle cell anaemia. 53 A new meta-analysis comparing cannabis to analgesics for acute pain found no increased advantage for cannabis over standard analgesics. 54

Chronic non-cancer pain

Chronic pain is described as pain that remains beyond the typical healing time or beyond 3 to 6 months. 55 Many illnesses cause chronic pain; it is estimated that one in every five individuals will suffer it at some point in their life, and this proportion is likely to rise due to an older population and rising rates of survival from cancer and other chronic disorders. 10 Several research have looked into the usage of cannabis-derived substances to relieve chronic pain. In these research, the causes of chronic pain are diverse, including various combinations of neuropathic pain, cancer, diabetes or HIV-associated neuropathy, and fibromyalgia. 56 Each of these factors requires a separate examination of the evidence.

Neuropathic pain

Neuropathic pain is produced by somatosensory system57 damage and is the result of direct neuronal tissue destruction. 58 Diabetic neuropathy, postherpetic neuralgia, phantom limb pain, trauma, spinal cord damage, trigeminal neuralgia, and HIV infection are some of the most prevalent causes. However, the source of the discomfort is frequently unclear. 58 It is difficult to treat, and NSAIDs are ineffective, if at all, and patients must take opioids, antidepressants, or antiepileptic medications. 59,60 Abrams et al. assessed the subjective assessment of 24-hour pain (on a 1-—100 mm scale) of patients with HIV-induced neuropathy who were randomised to 3.56% THC smoked cannabis cigarettes vs placebo cannabis cigarettes, restricting the trial to patients who had previously been exposed to THC. 61

The number of side effects was minimal, but on the cannabis arm, they were much greater, including sedation, disorientation, confusion, dizziness, and anxiety. 61 Ellis et al. investigated the use of smoked cannabis to treat HIV neuropathy using the Descriptor Differential Scale as a key metric. Patients in both arms (THC-free cannabis and THC-cannabis) were permitted to titrate their dosage between 1 and 8%. 62 Participants titrated to 8% while using THC-free cannabis but stayed at 2 and 4% when using THC-cannabis ($p = 0.016$); nevertheless, analgesic usage did not diminish throughout the THC-cannabis phase. 62

Another research employed four concentrations of THC smoked cannabis (0%, 2.5%, 6%, and 9.4%) as treatment for post-traumatic or postsurgical neuropathic pain, and 63 patients reported a change in average daily discomfort, as well as enhanced perceptions of time to sleep when on the highest dosages. 63 The research, however, found no increase in mood, quality of life, or mobility. 63 Wilsey et al. compared smoked cannabis for neuropathic pain by randomising patients to THC levels of 0%, 3.5%, and 7%, with prior cannabis exposure necessary. 64 Both THC treatments (at 3.5% and 7% concentrations) reduced pain intensity when compared to placebo, however there was no difference in efficacy. 65 Furthermore, cannabinoid blood levels were not related to analgesia. 65

Despite the fact that these findings appear encouraging, studies have limitations and outcomes are uneven. As a result, there is no high-quality data supporting the use of cannabis to treat neuropathic pain. 58 Furthermore, a recent comprehensive review by Stockings et al found that cannabis had modest efficacy in chronic neuropathic pain. 66 Furthermore, some negative effects (such as somnolence, drowsiness, or disorientation) may limit the use of cannabis in therapeutic practise even further. 58 The Special Interest Group on Neuropathic Pain indicated that the evidence for cannabis usage is weak,67 but the Canadian Pain Society approved cannabis as a third line of treatment when the preceding lines of treatment were ineffective. 68

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 945-956 www.ijprajournal.com ISSN: 2249-7781

Cancer pain

Every year, around 10 million individuals worldwide are diagnosed with cancer. 87 Cancer produces pain through a variety of processes, including the tumour itself, chemotherapy, drug side effects, and surgical pain. 17 Patients are frequently threatened with the World Health Organization's (WHO) three-step analgesic ladder, which makes NSAIDs and opioids the most prevalent medication for persons with cancer, achieving enough relief in 71---86% of patients. 88 Pain can be felt at any stage of cancer, although it is most common in advanced stages. 89 Pain is one of the most common anxieties among cancer patients, and it is linked to a lower quality of life, an inability to manage with the disease, sleep disruption, and mental symptoms such as worry and sadness. 90

As the management of pain in certain cancer patients remains difficult, there is interest in researching novel therapy possibilities, such as cannabis-based drugs. 91 During two weeks, one research examined the effectiveness of THC:CBD extract, THC alone, or placebo in patients with persistent cancer-related pain, and found a substantial difference on the Numerical Rating Scale (NRS) favouring THC:CBD (Sativex ®) as compared to placebo, but no change with THC alone. 92 There was no difference in the median amount of opioid medicine or the number of doses between the treatment groups, and the THC:CBD group had greater nausea and vomiting when compared to the placebo group. 92

THC:CBD oralmucosal spray was administered in patients who had previously participated in a three-arm study on a two-week randomised controlled trial in an extension study. 93 Patients were asked to self-titrate the THC:CBD spray or THC spray, which revealed that the scores for pain severity and worst pain dropped in THC:CBD patients; also, patients improved in sleeplessness, discomfort, and exhaustion. 93

During 5 weeks of Nabiximols® studies, individuals with poorly managed chronic cancer pain were given a low dosage (1-—4 sprays per day), a medium dose (6-—10 sprays per day), or a high dose (11-—16 sprays per day).

94 The number of patients reporting analgesia with Nabiximols was higher than for placebo, especially in the low and medium dosage groups. 94

Nabiximols as an oromucosal spray was utilised as an additional treatment in advanced cancer patients with persistent uncontrolled pain in another trial. 95 Patients were able to self-titrate Nabiximols or placebo, demonstrating that Nabiximols was better to placebo in two of the three quality of life measures assessed at week 3 and in all three assessed at week 5. 95

Despite these findings, the meta-analysis concludes that there is no compelling evidence to recommend cannabinoid-based drugs as a single treatment for cancer pain; this decision is based mostly on sample size and other clinical trial constraints.17

There is some evidence that cannabinoids are effective adjuvants,89 but there is a significant gap in scientific knowledge, and more research should be encouraged because the cannabinoid system may play a role in the treatment of cancer-related chronic pain, but clinicians should be cautious about using them as analgesics. 89 Cannabis has, however, been examined for various cancer-related symptoms such as cachexia, nausea, and vomiting.

Two trials found no changes in appetite and/or nausea between cannabis and placebo in cancer-related cachexia, while a third found that THC was superior to placebo in improving appetite.

96 A meta-analysis also found conflicting data in terms of nausea and vomiting. 97 There is a lack of evidence on the effects of cannabis on cachexia, appetite, and nausea.

Headache

Headache is linked to a worse quality of life, disability, and personal and social expenditures. 98 The most prevalent kind of headache is tension headache (38%), followed by migraine (10%) and chronic daily headache (3%). NSAIDs, triptans, antidepressants, verapamil, or ergotamine are used to treat headaches; nevertheless, less than half of patients experience remission. Cannabis has been used to cure headaches since ancient times, appearing in Ayurvedic medicines and in ancient Greece, but it has been largely neglected by the scientific community in recent decades. 99

There were no scientific trials comparing cannabis to placebo for headache. Nonetheless, the effects of cannabis may be assessed using other research that provide proof of its efficacy. In one trial, medicinal marijuana was provided to migraine sufferers, and the frequency of the headache was reduced in the marijuana-using arm. 100 A clinical case report describes how recreational marijuana use, followed by the usage of dronabinol, gave pain alleviation. Because of this case report, a trial was conducted in which 139 patients with cluster headache were asked about their cannabis use history, and it was discovered that while cannabis use is common, efficacy may be limited and should not be recommended until controlled trials and strong evidence are provided. 102

In one study, nabilone was compared to ibuprofen in individuals with drug overuse headache. 103 During an 8-week study, patients were given the medicine daily, and it was discovered that nabilone was more effective than ibuprofen in lowering pain intensity and daily analgesic intake. 103 However, there is inadequate data to support the use of cannabis-based therapy for headache treatment, and additional study is needed to verify both its efficacy and its hazards.

Cannabis use on decreasing opioid treatment

Abnormal opioid prescription usage is frequent in patients suffering from chronic pain and has become a public health concern. 1 Opioid prescriptions have quadrupled in the United States during the previous 15 years, indicating an increasing trend. 104 Opioids, contrary to popular opinion, are not an appropriate pharmacotherapy for chronic pain because they provide a progressive hyperalgesia effect over time, causing patients to increase their opioid dosage with time. 1 A synergism between cannabis and opioids has been hypothesised because morphine's antinociceptive effects are mediated by mu-opioid receptors and may be improved by THC activation of kappa and delta-opioid receptors. 105 Opioid and cannabinoids receptors link to comparable intracellular signalling processes via G proteins, resulting in a reduction in cAMP synthesis. 105,106 Furthermore, there is some evidence that cannabis can boost endogenous opioid release and vice versa. 105,106 Because of this synergy, cannabis's potential effect in reducing opiate usage has been investigated. One study looked at the pharmacokinetics and safety of the combination of these drugs by subjecting 21 patients with chronic pain to a regimen of morphine or oxycodone BID and vaporised cannabis in the evening on day one, three times a day on days two through four, and once in the morning on day five. 107

The addition of vaporised cannabis reduced pain, but there was no change in the area under the plasma concentration-time curves for morphine or oxycodone following cannabis exposure. 107 According to Bachhuber et al., medicinal cannabis legislation is connected with a decrease in opioid overdose mortality in California, Oregon, and Washington. 108 Unfortunately, there is no good data to support a recommendation about the synergic activity of cannabis and opioids, despite some study indicating that this interaction may be of clinical and pharmacological significance.

Risks of the use of cannabinoids for analgesia

Given the promise of cannabis as a medicinal therapy and the issues raised by recreational cannabis usage, data on security is a top goal for cannabis-based pharmaceutical regulation. The extrapolation of the risk of recreational cannabis use is not optimal, but it may give some information when clinical trials are insufficient. 8 The COMPASS trial looked at the safety of cannabis for medicinal reasons by comparing individuals with severe chronic pain who used THC at 12.5% to those who did not. 109 There was no difference in significant adverse events across the groups in this trial, but the cannabis group had a higher risk of non-serious side effects; the most prevalent were somnolence, forgetfulness, cough, nausea, vomiting, 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 do not affect lung function over about 20 years, but some evidence suggests that some adverse pulmonary effects may arise over a longer period of time,104 but there is insufficient evidence to link cannabis use with cardiovascular events or cancer.

It is vital to note that older persons are more vulnerable due to slower drug metabolism, comorbidities, and concurrent drugs.

111 Cannabis can decrease gait and stability, which may predispose to falls in the psychomotor domain. Cannabis can exacerbate pre-existing cognitive impairment in the cognitive domain by impairing short-term memory and emotional processing. 112 Concerns have been

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 945-956 www.ijprajournal.com ISSN: 2249-7781

raised concerning cardiovascular risk, including the increased risk of myocardial infarction, arrhythmia, and stroke, as well as mental health, specifically the chance of psychotic episodes. 111 Addiction and dependency should also be taken into account. Cannabis addiction and dependency are thought to be lower than for other narcotics. 113 According to the National Household Survey on Drug Abuse, the prevalence of dependency decreased significantly with age, and teenagers were far more prone to addiction and dependence. 114 The difficulties connected with cannabis usage, such as overuse, addiction, and dependency, are linked to societal and personal variables and should be considered while using marijuana for medical purposes.

II. CONCLUSION

Cannabis has been utilised by various cultures throughout history, generally without the typical official approval processes. This is a vital juncture, since scientific review of data about the efficacy and safety of its usage has gained importance. There is evidence, however limited, that cannabis-based medication is effective. This data, however, is insufficient to make any recommendations on cannabis in clinical practise. The best mode of administration and dose have yet to be determined. As cannabis usage grows in various nations, answers to these issues may be forthcoming.

Cannabis as a pain therapy requires extensive study to assess the advantages and hazards that patients will face. Furthermore, the best delivery route and dose have yet to be determined. As cannabis usage grows in various nations, answers to these issues may be forthcoming.

REFERENCES

[1]. Hill KP, Palastro MD, Johnson B, et al. Cannabis and pain: a clinical review. Cannabis Cannabinoid Res. 2017;2:96---104.

[2]. Touw M, Arboretum A. The religious and medicinal uses of Cannabis in China, India and Tibet. J Psychoactive Drugs. 1981;13:23---34.

[3]. Zuardi AW. History of cannabis as a medicine: a review. Rev Bras Psiquiatr. 2006;28:153---7.

[4]. Mikuriya T. Marijuana in medicine: past, present and future. Calif Med. 1969;110:34---40.

[5]. Bowen LL, McRae-Clark AL. Therapeutic benefit of smoked cannabis in randomized placebo-controlled studies. Pharma-cotherapy. 2018;38:80---5.

[6]. Jensen B, Chen J, Furnish T, et al. Medical marijuana and chronic pain: a review of basic science and clinical evidence. Curr Pain Headache Rep. 2015;19:50.

[7]. Grotenhermen F, Russo E. Cannabis and cannabinoids: pharma-cology, toxicology and therapeutic potential. Psychology Press;2002.

[8]. Fitzcharles MA, Eisenberg E. Medical cannabis: a forward vision for the clinician. Eur J Pain. 2018;22:485---91.

[9]. National Conference of State Legislatures. State medical mar-ijuana laws; 2016.

[10]. Lynch ME. Cannabinoids in the management of chronic pain: a front line clinical perspective. J Basic Clin Physiol Pharmacol. 2016;27:189---91.

[11]. Hauser W, Fitzcharles M-A, Radbruch L, et al. Cannabinoids in pain management and palliative medicine. Dtsch Arztebl Int.2017;114:627---34.

[12]. Pertwee R. Cannabinoid pharmacology: the first 66 years. Br J Pharmacol. 2006;147:S163---71.

[13]. Demuth D, Molleman A. Cannabinoid signaling. Life Sci. 2006;78:549---63.

[14]. Gaoni Y, Mechoulam R. Isolation, structure and partial syn-thesis of an active constituent of hashish. J Am Chem Soc.1964;86:1646---7.

[15]. Ljubi˘sa G. A comparative study on some chemical and biolog-ical characteristics of various samples of cannabis resin. Bull Narc. 1962;3, 37.6.

[16]. Amin MR, Ali DW. Pharmacology of medical cannabis. Adv Exp Med Biol. 2019;1162:151---65.

[17]. Pascual D, Sanchez-Robles EM, Garcia MM, et al. Chronic pain and cannabinoids. Great expectations or a christmas carol. Biochem Pharmacol. 2018;157:33---42.

[18]. Russo EB. Cannabinoids in the management of difficult to treat pain. Ther Clin Risk Manag. 2008;4:245---59.

[19]. Steiner M, Wotjak CT. Role of the endocannabinoid system in regulation of the hypothalamic-pituitary-adrenocortical axis. Prog Brain Res. 2008;170:397---432.

[20]. Starowicz K, Malek N, Przewlocka B. Cannabinoid recep-tors and pain. Wiley Interdiscip Rev Membr Transp Signal. 2013;2:121---32.
[21]. Urits I, Borchart M, Hasegawa M, et al. An update of current cannabis-based pharmaceuticals in pain medicine. Pain Ther. 2019;8:41---51.
[22]. Howlett AC. A short guide to the nomenclature of seven- trans- membrane spanning receptors for lipid mediators. Life Sci. 2005;77AD:1522---30.
[23]. Pertwee RG. Cannabinoid pharmacology: the first 66 years. Br J Pharmacol. 2006;147:S163---71.
[24]. Pertwee RG. The pharmacology of cannabinoid receptors and their ligands: an overview. Int J Obes. 2006;30:S13---8.
[25]. Mlezack R, Wall P. Pain mechanisms: a new theory. Science (80-). 1965;150:971---9.
[26]. Koenig J, Werdehausen R, Linley JE, et al. Regulation of Nav1.7: a conserved SCN9A natural antisense transcript expressed in dorsal root ganglia. PLoS One. 2015;10:1---14.
[27]. Kremer M. Antidepressants and gabapentinoids in neuro-pathic pain: mechanistic insights. Neuroscience. 2016;338:183---206.
[28]. Arnold LM, Choy E, Clauw DJ, et al. Fibromyalgia and chronic pain syndromes: A white paper detailing current challenges in the field. Clin J Pain. 2016;32:737---46.
[29]. Starowicz K, Finn DP. Cannabinoids and pain: sites and mech-anisms of action. Adv Pharmacol. 2017;80:437---75.
[30]. Cheng Y, Hitchcock S. Targeting cannabinoid agonists for inflammatory and neuropathic pain. Expert Opin Investig Drugs. 2007;16:951---65.
[31]. Hohmann AG, Briley EM, Herkenham M. Pre- and postsynap-tic distribution of cannabinoid and mu opioid receptors in rat spinal cord. Brain Res. 1999;822:17---25.
[32]. Farquhar-Smith WP, Egertova M, Bradbury EJ, et al. Cannabi-noid CB(1) receptor expression in rat spinal cord. Mol Cell Neurosci. 2000;15:510---21.
[33]. De Vry J, Jentzsch KR, Kuhl E, et al. Behavioral effects of cannabinoids show differential sensitivity to cannabinoid receptor blockade and tolerance develop-ment. Behav Phar-macol. 2004;15:1---12.
[34]. Derbenev AV, Stuart TC, Smith BN. Cannabinoids suppress synaptic input to neurones of the rat dorsal motor nucleus of the vagus nerve. J Physiol. 2004;559:923---38.
[35]. Ashton JC, Friberg D, Darlington CL, et al. Expression of the cannabinoid CB2 receptor in the rat cerebellum: an immuno-histochemical study. Neurosci Lett. 2006;396:113---6.
[36]. Malfait A, Gallily R, Sumariwalla P, et al. The nonpsychoactive cannabis constituent cannabidiol is an oral anti-arthritic ther-apeutic in murine collagen-induced arthritis. Proc Natl Acad Sci U S A. 2000;97:9561---6.
[37]. Njoo C, Agarwal N, Lutz B, et al. The cannabinoid receptor CB1 interacts with the WAVE1 complex and plays a role in actin dynamics and structural plasticity in neurons. PLoS Biol. 2015;13:1---36.
[38]. Martin WJ, Patrick SL, Coffin PO, et al. An examination of the central sites of action of cannabinoid-induced antinociception in the rat. Life Sci. 1995;56:2103---9.
[39]. Hsieh GC, Pai M, Chandran P, et al. Central and peripheral sites of action for CB 2 receptor mediated analgesic activity in chronic inflammatory and neuropathic pain models in rats. Br J Pharmacol. 2011;162:428---40.
[40]. Monhemius R, Azami J, Green DL, et al. CB1 receptor mediated analgesia from the nucleus reticularis gigantocellularis pars alpha is activated in an animal model of neuropathic pain. Brain Res. 2001;908:67---74.
[41]. Escobar W, Ramirez K, Avila C, et al. Metamizol, a non-opioid analgesic, acts via endocannabinoids in the PAG-RVM axis dur-ing inflammation in rats. Eur J Pain. 2012;16:676---89.
[42]. Ji G, Neugebauer V. CB1 augments mGluR5 function in medial prefrontal cortical neurons to inhibit amygdala hyperactivity in an arthritis pain model. Eur J Neurosci. 2012;1:233---45.
[43]. Elmes SJR, Jhaveri MD, Smart D, et al. Cannabinoid CB2 recep-tor activation inhibits mechanically evoked responses of wide dynamic range dorsal horn neurons in naive rats and in rat

[44]. models of inflammatory and neuropathic pain. Eur J Neurosci.2004;20:2311---20.

[45]. Strangman NM, Walker JM. Cannabinoid WIN 55,212-2 inhibits the activity-dependent facilitation of spinal nociceptive responses. J Neurophysiol. 1999;82:472---7.

[46]. Petrosino S, Palazzo E, de Novellis V, et al. Changes in spinal and supraspinal endocannabinoid levels in neuropathic rats. Neuropharmacology. 2007;52:415---22.

[47]. Lim G, Sung B, Ji RR, et al. Upregulation of spinal cannabinoid-1-receptors following nerve injury enhances the effects of Win 55,212-2 on neuropathic pain behaviors in rats. Pain. 2003;105:275---83.

[48]. Beaulieu P. Cannabinoids for postoperative pain. Anesthesiol-ogy. 2007;106:397.

[49]. Holdcroft A, Maze M, Doré C, et al. A multicenter dose-escalation study of the analgesic and adverse effects of an oral cannabis extract (Cannador) for postoperative pain mana-gement. Anesthesiology. 2006;104:1040---6.

[50]. Buggy DJ, Toogood L, Maric S, et al. Lack of analgesic efficacy of oral --9-tetrahydrocannabinol in postoperative pain. Pain. 2003;106:169---72.

[51]. Beauliu P. Effects of nabilone, a synthetic cannabinoid, on postoperative pain. Can J Anesth. 2006;53:769---75.

[52]. Raft D, Gregg J, Ghia J, et al. Effects of intravenous tetrahydrocannabinol on experimental and surgical pain: psy-chological correlates of the analgesic response. Clin Pharmacol Ther. 1977;21:26---33.

[53]. [52]. Jain A, Ryan J, McMahon G, et al. Evaluation of intramuscular levonantradol and placebo in acute postoperative pain. J Clin Pharmacol. 1981;21, 320S-6.

[54]. Aziz Q, Barke A, Bennett MI, et al. A classification of chronic pain for ICD-11. Pain. 2015;156:1003---7.

[55]. Johal H, Devji T, Chang Y, et al. Cannabinoids in chronic non-cancer pain: a systematic review and meta-analysis. Clin Med Insights Arthritis Musculoskelet Disord. 2020;13,1179544120906461.

[56]. Jensen T, Baron R, Haanpää M, et al. A new definition of neu-ropathic pain. Pain. 2011;152:2205---6.

[57]. Mucke M, Phillips T, Radbruch L, et al. Cannabis-based medicines for chronic neuropathic pain in adults. Cochrane database Syst Rev. 2018;3:1---102.

[58]. Lunn M, Hughes R, Wiffen P. Duloxetine for treating painful neuropathy, chronic pain or fibromyalgia. Cochrane Database Syst Rev. 2014:CD007115.

[59]. Moore R, Straube S, Wiffen P, et al. Pregabalin for acute and chronic pain in adults. Cochrane Database Syst Rev. 2009:CD007076.

[60]. Abrams DI, Jay CA, Shade SB, et al. Cannabis in painful HIV-associated sensory neuropathy: a randomized placebo-controlled trial. Neurology. 2007;68:515---21.

[61]. Ellis RJ, Toperoff W, Vaida F, et al. Smoked medicinal cannabis for neuropathic pain in HIV: a randomized, crossover clinical trial. Neuropharmacology. 2011;34:672---80.

[62]. Ware MA, Wang T, Shapiro S, et al. Smoked cannabis for chronic neuropathic pain: a randomized controlled trial. CMAJ. 2010;182:E694---701.

[63]. Wilsey B, Marcotte T, Tsodikov A, et al. A randomized, placebo-controlled, crossover trial of cannabis cigarettes in neuropathic pain. J Pain. 2016;15:477---91.

[64]. Wilsey B, Marcotte T, Tsodikov A, et al. A randomized, placebo-controlled, crossover trial of cannabis cigarettes in neuropathic pain. J Pain. 2008;9:506---21.

[65]. Finnerup NB, Sindrup SH, Jensen TS. The evidence for pharmacological treatment of neuropathic pain. Pain.

[66]. 2010;150:573---81.

[67]. Finnerup NB, Attal N, Haroutounian S, et al. Pharmacotherapy for neuropathic pain in adults: systematic review, meta-analysis and updated NeuPSIG recommendations. Lancet Neurol. 2016;14:162---73.

[68]. Rice J, Cameron M. Cannabinoids for treatment of MS symp-toms: state of the evidence. Curr Neurol Neurosci Rep.2018;18:50.

[69]. Akgün K, Essner U, Seydel C, et al. Daily practice managing resistant multiple sclerosis spasticity with delta-9-tetrahydrocannabinol: Cannabidiol oromucosal spray: a systematic review of observational studies. J Cent Nerv Syst Dis. 2019;11, 1179573519831997.

[70]. Colfield S, Salter A, Tyry T, et al. Perspectives on marijuana use and effectiveness. Neurol Clin Pract. 2017;7:333---43.
[71]. Foley PL, Vesterinen HM, Laird BJ, et al. Prevalence and natu-ral history of pain in adults with multiple sclerosis: systematic review and meta-analysis. Pain. 2013;154:632---42.
[72]. Zajicek JP, Sanders HP, Wright DE, et al. Cannabinoids in multiple sclerosis (CAMS) study: safety and efficacy data for 12 months follow up. J Neurol Neurosurg Psychiatry. 2005;76:1664---9.
[73]. Zajicek JP, Hobart JC, Slade A, et al. Multiple sclerosis and extract of cannabis: results of the MUSEC trial. J Neurol Neu-rosurg Psychiatry. 2012;83:1125---32.
[74]. Turcotte D, Doupe M, Torabi M, et al. Nabilone as an adjunc-tive to gabapentin for multiple sclerosis-induced neuropathic pain: a randomized controlled trial. Pain Med (United States). 2015;16:149---59.
[75]. Lynch ME, Ware MA. Cannabinoids for the Treatment of chronic non-cancer pain: an updated systematic review of randomized controlled trials. J Neuroimmune Pharmacol. 2015;10:293---301.
[76]. Iskedjian M, Bereza B, Gordon A, et al. Meta-analysis of cannabis based treatments for neuropathic and multiple sclerosis-related pain. Curr Med Res Opin. 2007;23:17---24.
[77]. Fitzcharles M-A, Baerwald C, Ablin J, et al. Efficacy, tolera-bility 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;30:47---61.
[78]. Fitzcharles M-A, Hauser W. Cannabinoids in the management of musculoskeletal or rheumatic diseases. Curr Rheumatol Rep. 2016;18:76.
[79]. Gonen T, Amital H. Cannabis and cannabinoids in the treat-ment of rheumatic diseases. Rambam Maimonides Med J. 2020;11:e0007.
[80]. Richardson D, Pearson RG, Kurian N, et al. Characterisation of the cannabinoid receptor system in synovial tissue and fluid in patients with osteoarthritis and rheumatoid arthritis. Arthritis Res Ther. 2008;10:1---14.
[81]. Blake DR, Robson P, Ho M, et al. Preliminary assessment of the efficacy, tolerability and safety of a cannabis-based medicine (Sativex) in the treatment of pain caused by rheumatoid arthri-tis. Rheumatology. 2006;45:50---2.
[82]. Skrabek RQ, Galimova L, Ethans K, et al. Nabilone for the treatment of pain in fibromyalgia. J Pain. 2008;9:164---73.
[83]. Pinsger M, Schimetta W, Volc D, et al. Nutzen einer Add- On-Therapie mit dem synthetischen Cannabinomimetikum Nabilone bei Patienten mit chronischen Schmerzzuständen -Eine randomisierte kontrollierte Studie. Wien Klin Wochenschr.2006;118:327---35.
[84]. Fitzcharles M-A, Ste-Marie PA, Hauser W, et al. Efficacy, Toler-ability, and safety of cannabinoid treatments in the rheumatic diseases: a systematic review of randomized controlled trials. Arthritis Care Res (Hoboken). 2016;68:681---8.
[85]. Walitt B, Klose P, Fitzcharles M-A, et al. Cannabinoids for fibromyalgia. Cochrane database Syst Rev. 2016;7:CD011694.
[86]. Van Den Beuken-Van Everdingen MHJ, Hochstenbach LMJ, Joosten EAJ, et al. Update on prevalence of pain in patients with cancer: systematic review and meta-analysis. J Pain Symptom Manage. 2016;51, 1070-1090.e9.
[87]. Meuser T, Pietruck C, Radbruch L, et al. Symptoms during can-cer pain treatment following WHO-guidelines: a longitudinal follow-up study of symptom prevalence, severity and etiology. Pain. 2001;93:247---57.
[88]. Tateo S. State of the evidence: cannabinoids and cancer pain-A systematic review. J Am Assoc Nurse Pract. 2017;29:94---103.
[89]. Liang SY, Wu SF, Chao TC, et al. The impact of pain on the qual-ity of life of Taiwanese oncology patients. Pain Manag Nurs. 2015;16:128---36.
[90]. Wong SSC, Chan WS, Cheung CW. Analgesic effects of cannabi-noids for chronic non-cancer pain: a systematic review and meta-analysis with meta-regression. J Neuroimmune Pharma-col. 2020;15:801---29.

[91]. Johnson JR, Burnell-Nugent M, Lossignol D, et al. Multicenter, double-blind, randomized, placebo-controlled, parallel-group study of the efficacy, safety, and tolerability of THC:CBD extract and THC extract in patients with intractable cancer-related pain. J Pain Symptom Manage. 2010;39:167---79.

[92]. Johnson JR, Lossignol D, Burnell-Nugent M, et al. An open-label extension study to investigate the long-term safety and tol-erability of THC/CBD oromucosal spray and oromucosal THC spray in patients with terminal cancer-related pain refrac-tory to strong opioid analgesics. J Pain Symptom Manage. 2013;46:207---18.

[93]. Portenoy RK, Ganae-Motan ED, Allende S, et al. Nabiximols for opioid-treated cancer patients with poorly-controlled chronic pain: a randomized, placebo-controlled, graded-dose trial. J Pain. 2012;13:438---49.

[94]. Lichtman AH, Lux EA, McQuade R, et al. Results of a double- blind, randomized, placebo-controlled study of nabiximols oromucosal spray as an adjunctive therapy in advanced can-cer patients with chronic uncontrolled pain. J Pain Symptom Manage. 2018;55, 179-188.e1.

[95]. Brisbois TD, de Kock IH, Watanabe SM, et al. Delta-9-tetrahydrocannabinol may palliate altered chemosensory perception in cancer patients: results of a randomized, double-blind, placebo-controlled pilot trial. Ann Oncol. 2011;22:2086---93.

[96]. Levy C, Galenbeck E, Magid K. Cannabis for symptom manage- ment in older adults. Med Clin North Am. 2020;104:471---89.

[97]. Hu XH. Burden of migraine in the United States. Arch Intern Med [Internet]. 1999;159:813.

[98]. Lochte BC, Beletsky A, Samuel NK, et al. The Use of cannabis for headache disorders. Cannabis Cannabinoid Res. 2017;2:61---71.

[99]. Rhyne DN, Anderson SL, Gedde M, et al. Effects of medical mar-ijuana on migraine headache frequency in an adult population. Pharmacotherapy. 2016;36:505---10.

[100]. Robbins MS, Tarshish S, Solomon S, et al. Cluster attacks responsive to recreational cannabis and dronabinol. Headache. 2009;49:914---6.

[101]. Leroux E, Taifas I, Valade D, et al. Use of cannabis among 139 cluster headache sufferers. Cephalalgia. 2013;33:208---13.

[102]. Pini LA, Guerzoni S, Cainazzo MM, et al. Nabilone for the treat- ment of medication overuse headache: Results of a preliminary double-blind, active-controlled, randomized trial. J Headache Pain. 2012;13:677---84.

[103]. Calcaterra S, Glanz J, Binswanger IA. National trends in phar-maceutical opioid related overdose deaths compared to other substance related overdose deaths: 1999-2009. Drug Alcohol Depend. 2013;131:263---70.

[104]. Abrams DI, Guzman M. Cannabis in cancer care. Clin Pharmacol Ther. 2015;97:575---86.

[105]. Khan SP, Pickens TA, Berlau DJ. Perspectives on cannabis as a substitute for opioid analgesics. Pain Manag. 2019;9:191---203.

[106]. Abrams DI, Couey P, Shade SB, et al. Cannabinoid-opioid inter-action in chronic pain. Clin Pharmacol Ther. 2011;90:844---51.

[107]. Bachhuber MA, Saloner B, Cunningham CO, et al. Medi-cal cannabis laws and opioid analgesic overdose mortal-ity in the United States, 1999-2010. JAMA Intern Med.2014;174:1668---73.

[108]. Ware MA, Wang T, Shapiro S, et al. Cannabis for the manage-ment of pain: Assessment of Safety Study (COMPASS). J Pain.2015;16:1233---42.

[109]. Nugent SM, Morasco BJ, O'Neil ME, et al. The effects of cannabis among adults with chronic pain and an overview of general harms: a systematic review. Ann Intern Med.2017;167:319---31.

[110]. Minerbi A, Hauser W, Fitzcharles M-A. Medical cannabis for older patients. Drugs Aging. 2019;36:39---51.

[111]. Choi NG, Marti CN, DiNitto DM, et al. Older adults' marijuana use, injuries, and emergency department visits. Am J Drug Alcohol Abuse. 2018;44:215---23.

[112]. Maharajan MK, Yong YJ, Yip HY, et al. Medical cannabis for chronic pain: can it make a difference in pain management? J Anesth. 2020;34:95---103.

[113]. Zalesky A, Solowij N, Yücel M, et al. Effect of long- term cannabis use on axonal fibre connectivity. Brain.

[114]. 2012;135:2245---55.
[115]. Choi NG, Marti CN, DiNitto DM, Choi BY. Older adults' mari-juana use, injuries, and emergency department visits. Am J Drug Alcohol Abuse [Internet]. 2018;44(2):215---23. Available from: https://doi.org/10.1080/00952990.2017.1318891
[116]. Maharajan MK, Yong YJ, Yip HY, Woon SS, Yeap KM, Yap KY, et al. Medical cannabis for chronic pain: can it make a difference in pain management? J Anesth [Internet]. 2020;34(1):95---103.
[117]. Available from: https://doi.org/10.1007/s00540-019-02680-y
[118]. Zalesky A, Solowij N, Yücel M, Lubman DI, Takagi M, Hard- ing IH, et al. Effect of long-term cannabis use on axonal fibre connectivity. Brain. 2012;135(7):2245---55.