Review Article

Medical Cannabis in Chronic Pain Management – Where Are We Now?

Shamim Haider, Wan Jane Liew[1]

Department of Pain Management, Colchester General Hospital, ESNEFT, Turner Road, Colchester CO4 5JL, UK, [1]Department of Anaesthesiology and Surgical Intensive Care Singapore General Hospital Singapore

Abstract

Chronic pain is a debilitating condition that afflicts a significant number of people throughout the world. The mechanisms of chronic pain remain to be fully understood, and treatment for chronic pain has remained a challenge for pain practitioners. Cannabis and cannabis-based medicine (CBM) have emerged over the last two decades as potential treatment options for an array of medical issues, of which chronic pain is one of them. Clinical trials thus far seem to suggest that medical cannabis may have some clinical effect in reducing pain severity in chronic noncancer pain as an adjunct to standard treatment, but inherent weaknesses in the available evidence mean that the verdict for medical cannabis has yet to be set in stone. The issue of medical cannabis is further complicated by the connection of cannabis with neuropsychiatric side effects and substance misuse. Much work needs to be done by both clinicians and government bodies to translate the benefits of medical cannabis in the laboratory into positive patient outcomes at the bedside in a safe manner.

Keywords: Cannabinoids, chronic pain, medical cannabis, pain management

Received: 03-01-2021 **Revised: 24-05-2021** **Accepted: 27-05-2021** **Published: 31-08-2021**

Introduction

The International Association of the Study of Pain (IASP) has updated its definition of pain in 2020, defining it as "*An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage.*"[1]

Chronic pain is defined as pain that lasts or recurs for more than 3 months. Recently, chronic pain diagnoses and its classification have been included in the latest version of the International Classification of Diseases (ICD-11). The IASP and ICD-11 definitions highlight distinctions between chronic primary pain and chronic secondary pain; of which there are six subcategories of chronic secondary pain classified by etiology and anatomy.[2]

Epidemiological studies from different regions have revealed the high prevalence of chronic pain from between 20% and 50% of the population.[3-5] A 2016 report from the Centers for Disease Control and Prevention in the US projected an economical cost of 560 billion dollars per year for chronic pain conditions – taking into account direct medical costs, lost productivity, and disability programs.[5] Similarly, a 2016 report from the UK suggests that a third to half of the population may be suffering from some sort of chronic pain.[3]

These epidemiological reports also highlight that chronic pain is a common yet complex medical issue that is underdiagnosed, undertreated, and poorly managed. To further exacerbate the issue at hand, the prevalence of chronic conditions is expected to increase as the global population ages.

The treatment of chronic pain is vastly different from the treatment of acute pain. It is recognized that management requires a multidisciplinary approach, given the interplay of biological, psychological, and social factors in chronic pain. Furthermore, usual analgesic options such as opioids are not

Address for correspondence: Dr. Shamim Haider, Department of Pain Management, Colchester General Hospital, ESNEFT, Turner Road, Colchester CO4 5JL, United Kingdom.
E-mail: shamim.haider@esneft.nhs.uk

Access this article online

Quick Response Code:

Website: www.indianjpain.org

DOI: 10.4103/ijpn.ijpn_1_21

How to cite this article: Haider S, Liew WJ. Medical cannabis in chronic pain management – Where are we now? Indian J Pain 2021;35:97-104.

as effective in relieving chronic pain.[6,7] Due to the increasing prevalence of chronic pain and the relative lack of effective pharmacological agents, there is a demand to seek out novel drug therapies to improve pain management.

Over the last two decades, both clinicians and scientists have taken an interest in studying the use of cannabis and cannabis-based medicine (CBM) for chronic pain and other conditions. The discovery of the endocannabinoid system in the nervous system has generated great interest in developing new pharmacological targets for analgesia, especially opioid-sparing strategies for analgesia. In fact, an epidemiological study from Israel found that the most common indication for cannabis treatment is pain.[8]

However, cannabis use is linked with a long controversial history of neuropsychiatric side effects and substance abuse,[9] which has stunted research in cannabis as a therapeutic alternative in the 20th century. These are significant side effects that can impact patient outcome and well-being, hence, if we are to treat cannabis as a form of medical treatment, significant caution needs to be exercised to ensure that the risks do not outweigh the benefits of treatment.

This review aims to revisit the pharmacology of cannabis, review its clinical uses, and the controversies and hurdles surrounding its utilization in pain medicine.

Pharmacology

Cannabis sativa is a flowering plant [Figure 1] cultivated since the early recorded history for a variety of reasons – including but not limited to medicinal properties, seed oil, religious and spiritual rituals, and food. The terminology around cannabis research can be confusing due to the prefixes and suffixes that we confer the root word "cannabis." Clarification of specific terms surrounding cannabis literature is described in Table 1.

The endocannabinoid system comprises two primary cannabinoid receptors, CB1 and CB2 [Figure 2]. It is widely accepted that CB1 is found mainly in the brain and nervous system, while CB2 is largely found in the peripheries and may have some role in immunomodulation. Endocannabinoids include anandamide, which is a partial agonist at CB1, and 2-arachidonoglycerol (2-AG), which is a full agonist at CB1 and CB2. These endocannabinoids interact with the endocannabinoid system in neuromodulation of a variety of neural processes spanning from pain sensation to cognitive and higher-order thinking. Tetrahydrocannabinol (THC) is the active component of cannabis which acts as an agonist at CB1 receptors. On the other hand, cannabidiol (CBD) is a weak antagonist at both CB1 and CB2 receptors, which is believed to counteract the negative side effects of THC.[10-12]

The endocannabinoid system interacts with ascending and descending pain pathways to modulate pain processes at the peripheral, spinal, and supraspinal levels.[12,13] It is suggested that tonic endocannabinoid levels control basal nociceptive thresholds.[13-15] Peripherally, there may be control in the initiation of nociception.[16] At the spinal level, sensitization and inhibition of ascending nociceptive pathways may be involved. At a supraspinal level, descending inhibitory pathways may be activated to modulate pain transmission, while emotional and cognitive processing may be altered as well.[12,13,17,18] As CB1 and CB2 are probable targets for modulating pain, it is no surprise that medical cannabis has been explored as an analgesic option.

CBMs are pharmaceutical drugs based on the active cannabinoids in cannabis. At the moment, there are a

Figure 1: Public domain photo of the Cannabis sativa plant

Table 1: Description of common terms encountered in literature about cannabis

Term	Description
Cannabinoids	A broad term describing compounds that interact with cannabinoid receptors
Phytocannabinoids	Compounds extracted from plants (mainly *C. sativa*) that bind to cannabinoid receptors
Synthetic cannabinoids	Artificially manufactured molecules similar to phytocannabinoids that bind to cannabinoid receptors
Endocannabinoids	Molecules endogenous to the body that bind to cannabinoid receptors
Endocannabinoid system	The agonist–receptor system that encompasses endocannabinoids and cannabinoid receptors
THC	A phytocannabinoid, the principle psychoactive compound extracted from *C. sativa* which is an agonist at cannabinoid receptors
CBD	A phytocannabinoid, a nonpsychotropic compound extracted from *C. sativa* which is a weak antagonist at cannabinoid receptors
CBM	Medicinal drugs that involve the use of cannabis and/or cannabinoids (whether synthetic or extracted)
Medical cannabis	Use of cannabis or cannabis-based medicine (regardless of route of administration) for medical purposes
Recreational cannabis	Use of cannabis recreationally for nonmedical purposes

C. sativa: Cannabis sativa, THC: Tetrahydrocannabinol, CBD: Cannabidiol, CBM: Cannabis-based medicines

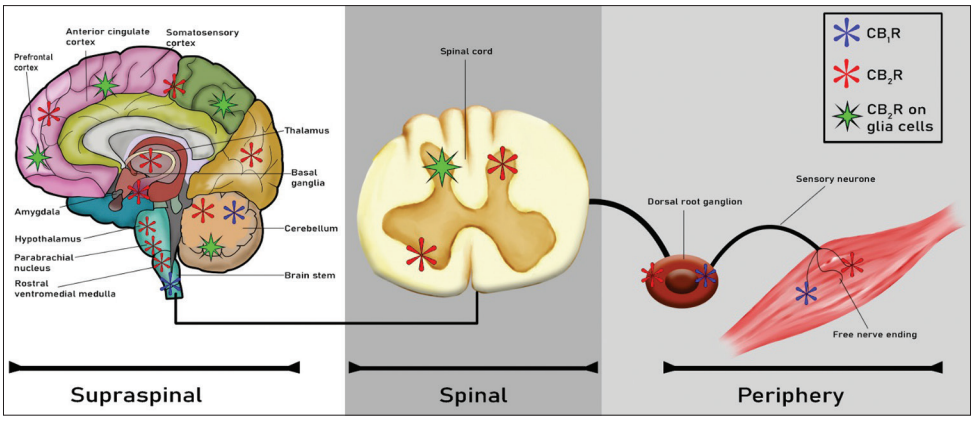

Figure 2: Cannabis receptors

few CBMs available for clinical use, namely Sativex, Epidiolex, dronabinol, and nabilone.[19] Epidiolex is a pharmaceutical-grade cannabidiol and has been approved by the Food and Drug Administration (FDA) in the USA and the National Institute for Health and Care Excellence (NICE) in the UK.[20,21] Sativex, arguably the most studied form of CBM, is still under clinical trials in the US, while it has been approved for clinical use in the UK for MS-related spasticity.[22] Sativex is an oromucosal spray of THC: CBD in a 1:1 ratio. Dronabinol and nabilone are synthetic THC compounds.

The pharmacokinetics of cannabis is a complicated topic. Pharmacokinetics of THC varies with the route of administration; and THC can be delivered via a variety of ways – oral, inhaled, rectal, and even transdermal. Maximal concentration is achieved much faster via the inhalation route compared to the oral route.[18] Both THC and CBD are hepatically metabolized; hence, drug interactions due to selective inhibition or induction of hepatic enzymes can complicate the dosing of medical cannabis. With regard to dosing, quality control of the herb and its constituent THC concentration can be difficult to achieve without standardized production methods, and even more so if patients self-medicate and obtain cannabis via nonprescription routes.

Treatment of Chronic Noncancer Pain

Clinical trials of medical cannabis in chronic pain are largely divided into management of chronic noncancer pain and chronic cancer pain. Although the ICD-11 has subcategorized chronic pain into multiple categories depending on anatomical location and body systems, studies around CBM and chronic pain do not clearly specify the different kinds of chronic pain examined in the individual studies. However, it is important to note that a large majority of the studies include participants that suffer from some form of neuropathic chronic pain.

When reviewing discrete clinical trials on medical cannabis and chronic pain, it seems that there is some clinical effect of medical cannabis in reducing pain scores. However, most of these results are not statistically significant, and most studies are too short and too small to draw cogent conclusions. The many systematic reviews conducted are of much better guidance on the topic. One of the earlier systematic reviews in 2009 by Martín-Sánchez *et al.* concluded that cannabis and CBM are moderately efficacious in the treatment of chronic pain, but the benefits may be outweighed by other harms such as serious adverse events involving the central nervous system.[23] A few years down the road in 2015, Whiting *et al.* have similarly found moderate-quality evidence for medical cannabis in the treatment of chronic pain. The studies reviewed by the workgroup were found to suggest improvements in pain relief, but the results did not reach statistical significance.[24] Similarly, Häuser *et al.* have concluded that studies show inconsistent results regarding the efficacy of medical cannabis for the treatment of chronic pain.[25] The latest 2018 Cochrane review by Mücke *et al.* has also come to the same conclusion that the potential benefits of medical cannabis are outweighed by its harms, especially adverse events that may have resulted in higher dropout rates in the cannabis arm of randomized controlled trials reviewed by the workgroup.[26] The Cochrane review also reports an alarming rate of 17% with psychiatric disorders in the medical cannabis arm but also concluded that there is a lack of high-quality evidence in the area of medical cannabis and chronic pain. Similarly, a prospective 2018 Lancet cohort study found that there was no evidence that cannabis use reduced pain severity in patients with chronic noncancer pain.[27]

Due to the lack of compelling evidence, medical cannabis has not been recommended for the treatment of chronic pain from the standpoint of government agencies. A report from the Canadian Agency for Drugs and Technologies in Health in 2016 evaluated the effectiveness of Sativex and commented that there may be a perceived benefit of short-term treatment, but its long-term effectiveness is unclear. Caution is advised with the use of medical cannabis.[28] Similarly, the 2019 NICE guidelines on cannabis-based medicinal products clearly advised not to offer any medical cannabis for the treatment of chronic pain.[22] The Australian government 2017 guidance for the use of medical cannabis has also acknowledged that there is limited evidence to provide recommendations for treatment.[29]

One of the promising aspects of medical cannabis is the possibility of synergistic interaction with opioid use, which can assist with reducing opioid doses. Preclinical studies of rat models seem to suggest synergistic action at the molecular level,[30] but this effect has not been clearly demonstrated in clinical studies. Some clinical studies and epidemiological studies claim to observe this synergistic effect,[31,32] but there are other studies that disagree with this observation.[33,34] So far, no clear clinical correlation exists between reduction of opioid use and cannabis use but will continue to be an area of interest, especially since opioid addiction continues to be a cause for public concern.

Treatment of Chronic Cancer Pain

There are many ways that pain can occur as a result of cancer. Pain may result from a mass effect of the tumor pressing on surrounding structures such as bone and nerves. Local inflammatory mediators released by aberrant cancer cells may also propagate signaling pathways. Idiosyncratic reactions to chemotherapy or other treatments of cancer can result in pain as well. It is likely that a variety of biological pathways culminate in the symptom of cancer pain.

Most of the studies investigated the use of Sativex as an adjunct on top of existing analgesic therapy in the alleviation of chronic cancer pain. A large proportion of these studies found that medical cannabis did not confer any significant improvement in cancer pain compared with placebo.[35-37] A recent meta-analysis by Boland *et al.* has succinctly summarized the evidence around the treatment of cancer pain – addition of medical cannabis to opioids did not reduce cancer pain compared with placebo; hence, it cannot be recommended for the management of cancer-related pain.[38] Furthermore, short-term side effects of medical cannabis may limit its use, especially in cancer patients who are already symptomatic, to begin with.

Treatment of Other Medical Conditions

The role of medical cannabis has also been explored in a variety of medical conditions. For most of these indications, medical cannabis is largely limited in its usefulness and further evaluation should be conducted to draw clearer conclusions.

Spasticity in multiple sclerosis

Medical cannabis has shown the most benefit for treating spasticity in multiple sclerosis.[39,40] This is also reflected in the NICE guidelines for use of CBM: a 4-week trial of Sativex can be offered if the patient has failed other treatments for spasticity (gabapentin, baclofen, dantrolene, and benzodiazepines).[22] This is by far the most well-established and evidence-based indication for CBM use.

Acute pain

Medical cannabis has been studied for its potential role in treating acute pain in the postoperative period since the endocannabinoid system interacts with the modulation of pain pathways. However, current available evidence is conflicting and of low quality. Some trials report improved pain scores,[41] but conversely, there are trials that report worsening postoperative pain with medical cannabis.[42] Furthermore, significant short-term adverse events have been reported. Overall, there is no evidence for routine use of medical cannabis for acute pain when other more reliable analgesic options with predictable side effect profiles are readily available.[43]

Refractory epilepsy

A Cochrane systematic review article in 2014 has concluded that there is no evidence to conclude the efficacy of CBM as a treatment option for epilepsy.[44] However, in the more recent years, research on cannabidiols has shown that it can reduce seizure frequency when added onto other standard antiepileptic regimes for patients with Lennox–Gastaut syndrome or Dravet syndrome.[45] This has since translated into the approval of Epidiolex (pharmaceutical-grade cannabidiol) for treatment-resistant epilepsy in Lennox–Gastaut syndrome, Dravet syndrome by NICE in the UK,[21,46] and additionally, for tuberous sclerosis by the FDA in the US.[47]

Antiemetic

Preclinical research suggests that manipulation of the endocannabinoid pathway can confer antiemetic properties, specifically by agonism of the CB1 receptor.[19] Several studies have been performed to investigate medical cannabis in the treatment of chemotherapy-induced nausea and vomiting. Observations thus far also suggest that medical cannabis may have an effect in reducing the incidence of nausea and vomiting, but conclusions are limited by the lack of high-quality evidence.[48] Furthermore, the development of cannabinoid hyperemesis syndrome[49] may paradoxically worsen nausea and vomiting. Despite this, both dronabinol and nabilone have been approved by the FDA in the US for the treatment of nausea and vomiting associated with chemotherapy.[50]

Appetite stimulant

Rat studies demonstrate the relation of medical cannabis use and hyperphagia. There is a paucity of studies in this area; hence, it is difficult to draw any conclusions regarding the efficacy of medical cannabis as an appetite stimulant for cachectic patients.[51]

Limitations of Current Evidence

As discussed in the sections above, there is intrinsic difficulty in conducting powerful high-quality trials for evaluating the effectiveness of medical cannabis in clinical medicine. Blinding is difficult to achieve because of the psychoactive component of medical cannabis.[52] As blinding is not perfect, it may affect the objectivity of the participants depending on their perceived beliefs regarding medical cannabis and its clinical effectiveness. Furthermore, the assessment of pain is highly dependent on the participant's subjective experience. As mentioned earlier, the biopsychosocial model of chronic pain

means that many confounders can affect the true magnitude of change in the severity of pain.

Most of the existing trials are short in duration, with relatively small sample sizes. There are significant dropout rates which are largely due to patient death (especially studies with participants with advanced cancer) or severe adverse effects. Different trials use different assessment tools for quantifying pain, which make comparing effects between studies difficult. Furthermore, different studies employ different protocols for the delivery of cannabis; for example, a sizable number of trials created standardized cigarettes with a standardized inhalation protocol. Different routes of administration/pharmaceutical products may result in different pharmacokinetic effects, making the comparison and evaluation of these studies difficult.[53] Finally, most of the trials involving medical cannabis have been conducted as adjunct therapy on top of standard treatment versus placebo. The placebo effect is an important clinical phenomenon but can also potentially confound results and undermine the clinical significance of medical cannabis. It is also difficult to quantify the efficacy of medical cannabis compared to other known agents since there is no direct comparison to a perceived "gold standard."

Controversies with Cannabis

Side effects and adverse events

Within clinical trials, there is a large variety of reported adverse events with medical cannabis, most commonly being nausea and dizziness which are minor symptoms. A systematic review in 2008 found that the incidence of nonserious adverse effects was significantly higher in subjects exposed to CBM treatment compared to controls, reporting a risk ratio of 1.86.[54] The COMPASS study in 2015 has also concluded that cannabis users were at increased risk of nonserious adverse events.[55] There are other associated negative externalities of medical cannabis, such as an observed increased risk for motor vehicle accidents[56] and also the pulmonary effects of inhaled or smoked cannabis to the patient and to others around them. This means the cost of cannabis use does not only apply to the individual using CBM but also to the wider population around them.

As mentioned earlier, most clinical trials conducted so far have been relatively short in duration, and hence, long-term effects of medical cannabis have not been assessed adequately. It is also difficult to ascertain the side effect profile of patients who are naive users of cannabis, as subpopulation analysis has not been conducted for this specific patient profile.[57] Studies report no difference in mortality rates and serious adverse events for patients who use pharmaceutical-grade cannabis versus recreational cannabis use,[54] but in reality, this information may be difficult to interpret as there may be overlapping medical and recreational use of cannabis, of which cannabis sources may be varied and questionable.

Neuropsychiatric effects

One of the severe adverse events with cannabis use is its association with neuropsychiatric disorders. The clinical concern is that the use of medical cannabis for treatment may result in the development of neuropsychiatric disorders. It is well known that cannabis use increases the risk of psychosis in a dose-dependent manner, and the greatest risk involves the use of synthetic cannabinoids and high-dose preparations.[57] Cannabis use is associated with increased risk for short-term cognitive impairment, psychotic symptoms, and neuropsychological impairments in domains such as decision-making, attention, and working memory.[56,58] On a societal level, this may translate to reduced productivity and reduced workforce numbers, once again reinforcing the concept of negative externalities surrounding medical cannabis. Whether or not these neuropsychiatric effects are permanent or transient, it is no doubt an additional cost to the patient – financially and psychologically. Changes in brain structure have been found in cannabis users; however, it is also difficult to ascertain whether these changes are reversible.[58-60]

Addiction and misuse

Recreational use of cannabis has been documented for centuries, and it is no surprise one of the main concerns of medical cannabis use is its potential for addiction and misuse. Addiction is characterized by compulsive substance use despite harmful consequences of the substance used. Long-term cannabis use is associated with tolerance, dependence, and withdrawal during abrupt cessation.[9,17,18,52,61] These are physiological effects of substance addiction; hence, the possibility of cannabis addiction and misuse should not be taken lightly. Cannabis use disorder is a medically recognized substance misuse disorder described in the DSM-V[62] and is a documented problem on the rise with increased use and potency of cannabis.[61] A study in Israel found that 15% of patients in a substance use disorder program reported using medical cannabis for pain, and there is an association between recent substance use and use of cannabis for pain.[63] Some studies have proposed that abuse liability is low with CBD or the combination of THC and CBD in medical cannabis products.[52,64] However, in reality, concurrent medical cannabis and recreational cannabis use is likely to be more prevalent than studies suggest.[65,66] This may further confound the findings in clinical trials and the perceived efficacy of medical cannabis.

Cannabis has long been thought of as a "gateway drug," a mild psychoactive agent as an introduction to misuse of other substances. The actual association of cannabis use leading to use of other psychoactive substances is unclear, but it is not difficult to appreciate that complex biological, psychological, and social factors contribute to substance misuse.[67] Some may argue that cannabis may play a role in substance substitution, that is, to substitute more harmful substances with cannabis.[68] Regardless, problematic use of other pain prescriptions such as opioids with cannabis use will continue to be a concern. Some studies have argued that opioid use has decreased with medical cannabis use,[31] but other studies differ otherwise in their findings, reporting an association with problematic opioid use.[33,34,69] The issue is unlikely to be a simple correlation

but a complex interplay of other biopsychosocial factors as mentioned earlier. To further complicate matters, another concern is the possibility of patients self-declaring medical conditions to obtain the legal right for cannabis use but for their own recreational purposes.[70] Development of sensitive assessment tools to pick up problematic use of either opioids or medical cannabis should be undertaken to monitor patients closely.[33,66,71]

To sum up the ethical controversies of cannabis use, medical professionals should appreciate that there is potential for cannabis addiction and misuse due to its psychoactive properties, and the ethical argument is whether or not we should subject patients to the risk of harmful use. Complex biopsychosocial issues are at play for both chronic pain management and substance misuse. Hence, this compels medical professionals dealing with chronic pain and medical cannabis to seek a multidisciplinary approach to continued management, by involving psychologists, psychiatrists, and counselors.[53]

What's Next for Medical Cannabis?

Due to the strong ties of cannabis to substance abuse, lawmakers and drug regulation bodies will no doubt play a very important role in the future of medical cannabis. Without approval from governing bodies, further clinical trials and research of medical cannabis will continue to be hindered by statutory limitations and approval processes.[72] However, the recognition of medical benefits of cannabis has continued to spread across the globe, one of the newer players being Thailand, who has legalized medical cannabis in December 2018.[73] Legalization paves the way for greater collaboration and research into studying medical cannabis. Relaxation of medical cannabis laws such as the reclassification of Epidiolex in the US from a schedule I to a Schedule V substance[74] suggest that governing bodies are more receptive to the therapeutic potential of medical cannabis.

However, the relaxation of medical cannabis laws is probably the beginning of a long journey. High-quality randomized controlled trials need to be conducted to contribute to the evidence base surrounding medical cannabis.[75,76] Further preclinical studies may further improve medical cannabis products such as finding new pharmacological targets that reduce psychoactive side effect profiles. Clinical studies should also investigate ways to monitor therapeutic effects and come up with clear indications and contraindications for medical cannabis. Clear patient selection criteria should also be developed to ensure minimal risk of side effects to the patient, for example, adopting a sensitive screening tool to identify populations of patients at risk of psychoactive side effects exacerbating their mental health. It will be a colossal task to come up with guidelines advising on initiation and cessation of therapy, but this will probably be some time away.

From a regulatory standpoint, there are many details to iron out wider medical cannabis use. A few examples come to mind, such as organizing a regulatory body to oversee quality control of pharmaceutical-grade medical cannabis. Stricter regulations should delineate the circumstance of cannabis prescription and the level of clinical supervision by trained medical staff. Clear guidance should be disseminated to clinicians regarding specific evidence-based indications and contraindications of medical cannabis. These details should be planned concurrently with the anticipation of wider medical cannabis use with the relaxation of medical cannabis laws.

Currently, chronic pain societies in different regions of the globe are beginning to recognize the therapeutic possibilities of cannabis, but recommendations remain polarized. The 2019 NICE guidelines on cannabis-based medicinal products specifically state that CBM should not be offered to patients for treatment of chronic pain.[22] Similarly, the 2015 NeuPSIG consensus on pharmacotherapy for neuropathic pain highlights a weak recommendation against the use of cannabinoids for neuropathic pain.[7] Conversely, the 2014 Canadian Pain Society consensus statement for pharmacological management of chronic neuropathic pain has suggested the use of cannabis as a 3rd line agent.[6] Regardless, the development of cannabis as a therapeutic option for chronic pain continues to be a topic of interest.

Conclusions

There is growing acceptance of cannabis and CBM in medicine, with some observed efficacy in the treatment of chronic noncancer pain. However, there is still a long way to go before it is regarded as one of the recommended therapeutic options. Well designed, large and robust clinical trials in near future would be the key to unlocking the full potential of medical cannabis. With the legalization of cannabis laws across regions, clinicians should keep themselves updated regarding the current evidence for medical cannabis to address possible questions from well-informed patients. Cannabis use is not free of its long controversial history with neuropsychiatric effects and substance abuse; hence, detailed studies on long-term adverse effects of medical cannabis use can also aid policymakers with the regulation of cannabis for medical use.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Raja SN, Carr DB, Cohen M, Finnerup NB, Flor H, Gibson S, *et al.* The revised International Association for the Study of Pain definition of pain: Concepts, challenges, and compromises. Pain 2020;161:1976-82.
2. Treede RD, Rief W, Barke A, Aziz Q, Bennett MI, Benoliel R, *et al.* A classification of chronic pain for ICD-11. Pain 2015;156:1003-7.
3. Fayaz A, Croft P, Langford RM, Donaldson LJ, Jones GT. Prevalence of chronic pain in the UK: A systematic review and meta-analysis of population studies. BMJ Open 2016;6:e010364.
4. Breivik H, Collett B, Ventafridda V, Cohen R, Gallacher D. Survey of chronic pain in Europe: Prevalence, impact on daily life, and treatment. Eur J Pain 2006;10:287-333.

5. Dahlhamer J, Lucas J, Zelaya C, Nahin R, Mackey S, DeBar L, *et al*. Prevalence of chronic pain and high-impact chronic pain among adults – United States, 2016. MMWR Morb Mortal Wkly Rep 2018;67:1001-6.
6. Moulin D, Boulanger A, Clark AJ, Clarke H, Dao T, Finley GA, *et al.* Pharmacological management of chronic neuropathic pain: Revised consensus statement from the Canadian Pain Society. Pain Res Manag 2014;19:328-35.
7. Finnerup NB, Attal N, Haroutounian S, McNicol E, Baron R, Dworkin RH, *et al*. Pharmacotherapy for neuropathic pain in adults: Systematic review, meta-analysis and updated NeuPSIG recommendations. Lancet Neurol 2015;14:162-73.
8. Abuhasira R, Schleider LB, Mechoulam R, Novack V. Epidemiological characteristics, safety and efficacy of medical cannabis in the elderly. Eur J Intern Med 2018;49:44-50.
9. Ashton CH. Pharmacology and effects of cannabis: A brief review. Br J Psychiatry 2001;178:101-6.
10. Pertwee RG. The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: D9-tetrahydrocannabinol, cannabidiol and D9-tetrahydrocannabivarin. Br J Pharmacol 2008;153:199-215.
11. Walker JM, Huang SM, Strangman NM, Tsou K, Sañudo-Peña MC. Pain modulation by release of the endogenous cannabinoid anandamide. Proc Natl Acad Sci 1999;96:12198-203.
12. Weizman L, Dayan L, Brill S, Nahman-Averbuch H, Hendler T, Jacob G, *et al.* Cannabis analgesia in chronic neuropathic pain is associated with altered brain connectivity. Neurology 2018;91:e1285-94.
13. Calignano A, La Rana G, Giuffrida A, Piomelli D. Control of pain initiation by endogenous cannabinoids. Nature 1998;394:277-81.
14. Hosking RD, Zajicek JP. Therapeutic potential of cannabis in pain medicine. Br J Anaesth 2008;101:59-68.
15. Meng ID, Manning BH, Martin WJ, Fields HL. An analgesia circuit activated by cannabinoids. Nature 1998;395:381-3.
16. Fox A, Kesingland A, Gentry C, McNair K, Patel S, Urban L, *et al.* The role of central and peripheral Cannabinoid1 receptors in the antihyperalgesic activity of cannabinoids in a model of neuropathic pain. Pain 2001;92:91-100.
17. Kumar RN, Chambers WA, Pertwee RG. Pharmacological actions and therapeutic uses of cannabis and cannabinoids. Anaesthesia 2001;56:1059-68.
18. Grotenhermen F. Pharmacokinetics and pharmacodynamics of cannabinoids. Clin Pharmacokinet 2003;42:327-60.
19. Urits I, Borchart M, Hasegawa M, Kochanski J, Orhurhu V, Viswanath O. An update of current cannabis-based pharmaceuticals in pain medicine. Pain Ther 2019;8:41-51.
20. Food and Drug Administration, United States of America. Epidiolex Prescribing Information; 2018 Jun. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210365lbl.pdf. [Last accessed on 2020 Dec 20].
21. National Institute for Health and Care Excellence, United Kingdom. Cannabidiol with Clobazam for Treating Seizures Associated with Lennox-Gastaut Syndrome; 2019 Dec. Available from: https://www.nice.org.uk/guidance/ta615/chapter/1-Recommendations. [Last accessed on 2020 Dec 20].
22. National Institute for Health and Care Excellence, United Kingdom. Cannabis-Based Medicinal Products; 2019 Nov. Available from: https://www.nice.org.uk/guidance/ng144/chapter/Recommendations. [Last accessed on 2020 Dec 20].
23. Martín-Sánchez E, Furukawa TA, Taylor J, Martin JLR. Systematic review and meta-analysis of cannabis treatment for chronic pain. Pain Med 2009;10:1353-68.
24. Whiting PF, Wolff RF, Deshpande S, Di Nisio M, Duffy S, Hernandez AV, *et al.* Cannabinoids for medical use: A systematic review and meta-analysis. JAMA 2015;313:2456-73.
25. Häuser W, Petzke F, Fitzcharles MA. Efficacy, tolerability and safety of cannabis-based medicines for chronic pain management – An overview of systematic reviews. Eur J Pain 2018;22:455-70.
26. Mücke M, Phillips T, Radbruch L, Petzke F, Häuser W. Cannabis-based medicines for chronic neuropathic pain in adults. Cochrane Database Syst Rev 2018;3:CD012182.
27. Campbell G, Hall WD, Peacock A, Lintzeris N, Bruno R, Larance B, *et al.* Effect of cannabis use in people with chronic non-cancer pain prescribed opioids: Findings from a 4-year prospective cohort study. Lancet Public Health 2018;3:e341-50.
28. Canadian Agency for Drugs and Technologies in Health. Cannabinoid Buccal Spray for Chronic Non-Cancer or Neuropathic Pain: A Review of Clinical Effectiveness, Safety, and Guidelines; 2016 Sep. Available from: https://www.cadth.ca/cannabinoid-buccal-spray-chronic-non-cancer-or-neuropathic-pain-review-clinical-effectiveness-safety. [Last accessed on 2020 Dec 20].
29. Therapeutic Goods Administration, Australia. Guidance for the Use of Medicinal Cannabis in Australia: Overview; 2017 Dec. Available from: https://www.tga.gov.au/publication/guidance-use-medicinal-cannabis-australia-overview. [Last accessed on 2020 Dec 20].
30. Kazantzis NP, Casey SL, Seow PW, Mitchell VA, Vaughan CW. Opioid and cannabinoid synergy in a mouse neuropathic pain model. Br J Pharmacol 2016;173:2521-31.
31. Boehnke KF, Litinas E, Clauw DJ. Medical cannabis use is associated with decreased opiate medication use in a retrospective cross-sectional survey of patients with chronic pain. J Pain 2016;17:739-44.
32. Abrams DI, Couey P, Shade SB, Kelly ME, Benowitz NL. Cannabinoid-opioid interaction in chronic pain. Clin Pharmacol Ther 2011;90:844-51.
33. Feingold D, Goor-Aryeh I, Bril S, Delayahu Y, Lev-Ran S. Problematic use of prescription opioids and medicinal cannabis among patients suffering from chronic pain. Pain Med 2017;18:294-306.
34. DiBenedetto DJ, Weed VF, Wawrzyniak KM, Finkelman M, Paolini J, Schatman ME, *et al.* The association between cannabis use and aberrant behaviors during chronic opioid therapy for chronic pain. Pain Med 2018;19:1997-2008.
35. Häuser W, Welsch P, Klose P, Radbruch L, Fitzcharles MA. Efficacy, tolerability and safety of cannabis-based medicines for cancer pain: A systematic review with meta-analysis of randomised controlled trials. Schmerz 2019;33:424-36.
36. Lichtman AH, Lux EA, McQuade R, Rossetti S, Sanchez R, Sun W, *et al.* Results of a double-blind, randomized, placebo-controlled study of nabiximols oromucosal spray as an adjunctive therapy in advanced cancer patients with chronic uncontrolled pain. J Pain Symptom Manage 2018;55:179-88.e1.
37. Fallon MT, Albert Lux E, McQuade R, Rossetti S, Sanchez R, Sun W, *et al.* Sativex oromucosal spray as adjunctive therapy in advanced cancer patients with chronic pain unalleviated by optimized opioid therapy: Two double-blind, randomized, placebo-controlled phase 3 studies. Br J Pain 2017;11:119-33.
38. Boland EG, Bennett MI, Allgar V, Boland JW. Cannabinoids for adult cancer-related pain: Systematic review and meta-analysis. BMJ Support Palliat Care 2020;10:14-24.
39. Zajicek J, Fox P, Sanders H, Wright D, Vickery J, Nunn A, *et al.* Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): Multicentre randomised placebo-controlled trial. Lancet 2003;362:1517-26.
40. Zajicek JP, Hobart JC, Slade A, Barnes D, Mattison PG; MUSEC Research Group. Multiple sclerosis and extract of cannabis: Results of the MUSEC trial. J Neurol Neurosurg Psychiatry 2012;83:1125-32.
41. Holdcroft A, Maze M, Doré C, Tebbs S, Thompson S. A multicenter dose-escalation study of the analgesic and adverse effects of an oral cannabis extract (Cannador) for postoperative pain management. Anesthesiology 2006;104:1040-6.
42. Kraft B, Frickey NA, Kaufmann RM, Reif M, Frey R, Gustorff B, *et al.* Lack of analgesia by oral standardized cannabis extract on acute inflammatory pain and hyperalgesia in volunteers. Anesthesiology 2008;109:101-10.
43. Abdallah FW, Hussain N, Weaver T, Brull R. Analgesic efficacy of cannabinoids for acute pain management after surgery: A systematic review and meta-analysis. Reg Anesth Pain Med 2020;45:509-19.
44. Gloss D, Vickrey B. Cannabinoids for epilepsy. Cochrane Database Syst Rev 2014;2014:CD009270.
45. Lattanzi S, Brigo F, Trinka E, Zaccara G, Cagnetti C, Del Giovane C, *et al.* Efficacy and safety of cannabidiol in epilepsy: A systematic review and meta-analysis. Drugs 2018;78:1791-804.
46. National Institute for Health and Care Excellence, United Kingdom. Cannabidiol with Clobazam for Treating Seizures Associated with

Dravet Syndrome; 2019 Dec. Available from: https://www.nice.org.uk/guidance/ta614/chapter/1-Recommendations. [Last accessed on 2020 Dec 20].
47. Food and Drug Administration, United States of America. FDA Approves New Indication for Drug Containing an Active Ingredient Derived from Cannabis to Treat Seizures in Rare Genetic Disease; 2020 Jul. Available from: https://www.fda.gov/news-events/press-announcements/fda-approves-new-indication-drug-containing-active-ingredient-derived-cannabis-treat-seizures-rare. [Last accessed on 2020 Dec 20].
48. Smith LA, Azariah F, Lavender VT, Stoner NS, Bettiol S. Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy. Cochrane Database Syst Rev 2015;11:CD009464.
49. Chocron Y, Zuber JP, Vaucher J. Cannabinoid hyperemesis syndrome. BMJ 2019;366:14336.
50. Food and Drug Administration, United States of America. FDA and Cannabis: Research and Drug Approval Process; 2020 Jan. Available from: https://www.fda.gov/news-events/public-health-focus/fda-and-cannabis-research-and-drug-approval-process. [Last accessed on 2020 Dec 20].
51. Farrimond JA, Hill AJ, Whalley BJ, Williams CM. Cannabis constituents modulate Δ 9-tetrahydrocannabinol-induced hyperphagia in rats. Psychopharmacology 2010;210:97-106.
52. Russo EB. Cannabinoids in the management of difficult to treat pain. Ther Clin Risk Manag 2008;4:245-59.
53. Stockings E, Campbell G, Hall WD, Nielsen S, Zagic D, Rahman R, *et al.* Cannabis and cannabinoids for the treatment of people with chronic noncancer pain conditions: A systematic review and meta-analysis of controlled and observational studies. Pain 2018;159:1932-54.
54. Wang T, Collet JP, Shapiro S, Ware MA. Adverse effects of medical cannabinoids: A systematic review. CMAJ 2008;178:1669-78.
55. Ware MA, Wang T, Shapiro S, Collet JP; COMPASS Study Team. Cannabis for the management of pain: Assessment of safety study (COMPASS). J Pain 2015;16:1233-42.
56. Nugent SM, Morasco BJ, O'Neil ME, Freeman M, Low A, Kondo K, *et al*. The effects of cannabis among adults with chronic pain and an overview of general harms: A systematic review. Ann Intern Med 2017;167:319-31.
57. Colizzi M, Murray R. Cannabis and psychosis: What do we know and what should we do? Br J Psychiatry 2018;212:195-6.
58. Batalla A, Bhattacharyya S, Yücel M, Fusar-Poli P, Crippa JA, Nogué S, *et al.* Structural and functional imaging studies in chronic cannabis users: A systematic review of adolescent and adult findings. PLoS One 2013;8:e55821.
59. Gilman JM, Kuster JK, Lee S, Lee MJ, Kim BW, Makris N, *et al.* Cannabis use is quantitatively associated with nucleus accumbens and amygdala abnormalities in young adult recreational users. J Neurosci 2014;34:5529-38.
60. Pope HG Jr., Gruber AJ, Hudson JI, Huestis MA, Yurgelun-Todd D. Neuropsychological performance in long-term cannabis users. Arch Gen Psychiatry 2001;58:909-15.
61. Hasin DS. US epidemiology of cannabis use and associated problems. Neuropsychopharmacology 2018;43:195-212.
62. Hasin DS, O'Brien CP, Auriacombe M, Borges G, Bucholz K, Budney A, *et al.* DSM-5 criteria for substance use disorders: Recommendations and rationale. Am J Psychiatry 2013;170:834-51.
63. Ashrafioun L, Bohnert KM, Jannausch M, Ilgen MA. Characteristics of substance use disorder treatment patients using medical cannabis for pain. Addict Behav 2015;42:185-8.
64. Babalonis S, Haney M, Malcolm RJ, Lofwall MR, Votaw VR, Sparenborg S, *et al.* Oral cannabidiol does not produce a signal for abuse liability in frequent marijuana smokers. Drug Alcohol Depend 2017;172:9-13.
65. Morean ME, Lederman IR. Prevalence and correlates of medical cannabis patients' use of cannabis for recreational purposes. Addict Behav 2019;93:233-9.
66. Wall MM, Liu J, Hasin DS, Blanco C, Olfson M. Use of marijuana exclusively for medical purposes. Drug Alcohol Depend 2019;195:13-5.
67. Lucas P. Cannabis as an adjunct to or substitute for opiates in the treatment of chronic pain. J Psychoactive Drugs 2012;44:125-33.
68. Baron EP, Lucas P, Eades J, Hogue O. Patterns of medicinal cannabis use, strain analysis, and substitution effect among patients with migraine, headache, arthritis, and chronic pain in a medicinal cannabis cohort. J Headache Pain 2018;19:37.
69. Shover CL, Davis CS, Gordon SC, Humphreys K. Association between medical cannabis laws and opioid overdose mortality has reversed over time. Proc Natl Acad Sci U S A 2019;116:12624-6.
70. Savage SR, Romero-Sandoval A, Schatman M, Wallace M, Fanciullo G, McCarberg B, *et al.* Cannabis in pain treatment: Clinical and research considerations. J Pain 2016;17:654-68.
71. Häuser W, Finn DP, Kalso E, Krcevski-Skvarc N, Kress HG, Morlion B, *et al*. European Pain Federation (EFIC) position paper on appropriate use of cannabis-based medicines and medical cannabis for chronic pain management. Eur J Pain 2018;22:1547-64.
72. Freeman TP, Hindocha C, Green SF, Bloomfield MAP. Medicinal use of cannabis based products and cannabinoids. BMJ 2019;365:l1141.
73. Britsh Broadcasting Corporation, United Kingdom. Thailand Approves Medicinal Cannabis; 2018 Dec. Available from: https://www.bbc.com/news/world-asia-46679098. [Last accessed on 2020 Dec 20].
74. Drug Enforcement Administration, United States of America. FDA-approved drug Epidiolex Placed in Schedule V of Controlled Substance Act; 2018 Sep. Available from: https://www.dea.gov/press-releases/2018/09/27/fda-approved-drug-epidiolex-placed-schedule-v-controlled-substance-act. [Last accessed on 2020 Dec 20].
75. Gilron I, Blyth FM, Degenhardt L, Di Forti M, Eccleston C, Haroutounian S, *et al.* Risks of harm with cannabinoids, cannabis, and cannabis-based medicine for pain management relevant to patients receiving pain treatment: Protocol for an overview of systematic reviews. Pain Rep 2019;4:e742.
76. Fisher E, Eccleston C, Degenhardt L, Finn DP, Finnerup NB, Gilron I, *et al.* Cannabinoids, cannabis, and cannabis-based medicine for pain management: A protocol for an overview of systematic reviews and a systematic review of randomised controlled trials. Pain Rep 2019;4:e741.