Medical Cannabis for Chronic Pain: Can it make a difference in pain management?

Mari Kannan Maharajan[1]*, Yong Yu Jing[2], Hong Yang Yip [2], Woon Sze Shee[2], Yeap Kar Mon[2], Yap Khai Yeng[2] Yip Shuen Chi[2], Yap Kai Xian[2]

[1]Department of Pharmacy Practice, School of Pharmacy, International Medical University, Kuala Lumpur, 57000, Malaysia.

[2]School of Pharmacy, International Medical University,
Kuala Lumpur, 57000, Malaysia.

*corresponding Author

Mari Kannan Maharajan

Department of Pharmacy Practice,

School of Pharmacy, International Medical University, Kuala Lumpur, 57000, Malaysia.

Email: kanpharm2002@gmail.com; Marikannan@imu.edu.my

Contact: +60 1127634171

Key Words: Medical Cannabis, Chronic pain, Addiction, Dependence, Regulations

Abstract word count: 193

Manuscript Word count: 3,877

Number of figure: 1

Abstract

Globally, chronic pain is a major therapeutic challenge and affects more than 15% of the population. As the patients with painful terminal diseases may face unbearable pain, there is a need for more potent analgesics. Although opioid-based therapeutic agents received attention to manage severe pain, their adverse drug effects and mortality rate associated with opioids overdose are the major concerns.

Evidences from clinical trials showed therapeutic benefits of cannabis, especially delta-9-tetrahydrocannabinol and cannabinoids reduced neuropathic pain intensity in various conditions. Also, there are reports on using combination cannabinoid therapies for chronic pain management. The association of cannabis dependence and addiction has been discussed much and the reports mentioned that it can be comparatively lower than other substances such as nicotine and alcohol. More countries have decided to legalise the medicinal use of cannabis and marijuana. Healthcare professionals should keep themselves updated with the changing state of medical cannabis and its applications.

The pharmacokinetics and safety of medical cannabis need to be studied by conducting clinical research. The complex and variable chemically active contents of herbal cannabis and methodological limitations in the administration of cannabis to study participants, make the clinical research difficult.

Introduction

Pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage. Although pain is most often related to a disease or injury, it may also be linked to one's emotional state [1]. Pain, especially, chronic pain (i.e., a persistent pain lasting longer than 3–6 months) has been recognised as a major cause of disability globally [2]. Globally, it was estimated that 1 in 5 adults is affected by chronic pain, and 1 in 10 adults is newly diagnosed with chronic pain each year, thus indicating its significance in affecting the quality of life [3]. Also, chronic pain influences the social- economic implications negatively due to its association with loss of productivity and spending additional cost on treatment [4]. In addition to the physical and emotional burden, chronic pain has associated with a rising epidemic of prescription opioid misuse, abuse, and overdose-related deaths [5].

Pain management is important to provide a better quality of life to a patient. Generally, a reduction in pain intensity is regarded as the core outcome in any intervention involving pain treatment. The continuous assessment of pain usually involves the use of a numerical rating scale from 0 to 10 or a visual analogue scale from 0 to 100 mm, in which the lowest figure indicates no pain, whereas the highest figure indicates worst possible pain. In most studies, a clinically significant improvement in pain intensity is defined as a reduction of ≥30% in pain or 2 points on numerical rating scale or 20 mm on visual analogue scale [6, 7]. Patients with chronic diseases may face unbearable pain on a daily basis and require more potent analgesics and their more frequent administration. The chronic pain may cause fatigue, sleep disturbance and mood disorders which can seriously impact the patient's quality of life [8]. In spite of the pharmacological advances, management of pain, remains as one of the main clinical challenges confronting most healthcare providers. Mild pain is generally managed with analgesics such as

paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase-2 (COX-2) inhibitors [9].

Therapeutic options for the management of chronic pain

During chronic pain, changes in neuronal phenotypes and brain circuits can alter sensory, emotional, and motivational centres of the brain. This activation and interfere with the action of many analgesics [10]. NSAIDs, which are used for inflammation, as well as acute and chronic pain, may increase the risk of developing peptic ulcers and acute renal failure. On the other hand, paracetamol which has inferior analgesic activity compared to opioids is only used for mild to moderate pain; it may also cause dose-dependent hepatotoxicity, which requires dose monitoring [11]. Later, opioids are often the choice of analgesic in chronic pain management [9]. The recent aberrant use of opioids is a major concern due to various issues arising from their adverse effects [12]. Current clinical evidence also suggests that early trials of opioids in pain management provided misleading information relating to opioids' efficacy; there were 32,445 deaths worldwide in 2016 due to opioid overdoses [13]. Opioids are generally used for cancer related pain, acute surgical and post-traumatic pain. Long-term opioid use may result in the development of tolerance, in which progressively higher doses of opioids are required to achieve the same pharmacological outcome [14].

Many individuals with chronic pain are seeking alternative medications for pain management [15]. Medicines based on *Cannabis sativa L*., including herbal cannabis (marijuana) products have become increasingly available to patients in many countries. The term 'medical marijuana' refers to using the whole, unprocessed marijuana plant or its basic extracts to treat symptoms of illness and other conditions.

A study by Boehnke *et al*., (2016) reported that the patients with chronic pain used medical cannabis have reduced their opioid consumption (64% lower) and experienced fewer side effects, and improved quality of life after using cannabis [16]. Early research suggested

that there is a relationship between the medical cannabis and opioid analgesic overdose mortality. However, there are limited evidences explaining the association between the use of cannabis and opioid analgesics in chronic pain management to discriminate their effects [17, 18].

Cannabis has profound effects on motor, cognitive, nociceptive, and thermoregulatory processes [19]. Buggy et al., (2003) reported that orally administered delta-9-tetrahydrocannabinol (THC) 5 mg in postoperative pain in humans has no effect [20]. As cannabis does not offer any benefits over non-opioid analgesics in treating either acute pain or postoperative pain, this review focus on its potential use in the management of chronic pain. Overall, there is evidence that cannabinoids are safe and modestly effective in neuropathic pain. The context of the review focuses on the potential use of cannabis in chronic pain management in non-cancer patients. Also, this review will mainly be focused on cannabis and its products and as there is a limited evidence to compare the effectiveness of marijuana and cannabis and phytochemical products to treat chronic pain.

Cannabinoids and cannabinoid receptors

With the limitation of available therapeutic options to manage chronic pain, cannabis-based therapeutic agents enrich the possibilities of management of chronic pain conditions. The cannabis plant can produce at least 144 naturally occurring compounds known as cannabinoids, including THC and cannabidiol [21]. THC, a primary phytochemical constituent of cannabis, can foster dependence among some habitual cannabis users, whereas cannabidiol, is not associated with intoxicating or THC-like subjective drug effects [22]. There are secondary cannabinoids, including cannabigerol, the acid form of THC, tetrahydrocannabiverin (THC-V), cannabinol and terpenes [23]. There is a limited or no research evidence on the pharmacological effects of these less-comm3on cannabis constituents [23].

The therapeutic potentials of cannabinoids have received much attention in recent times, especially after the discovery of primary endogenous cannabinoids and cannaboid receptors 1 and 2 (CB1 and CB2) [24]. The CB1 receptor is highly expressed in the central and peripheral nervous systems in mammalians and is involved in neuromodulatory functions [25], while CB2 receptors are mostly found in cells of the immune system [26, 27]. Activation of the CB1 receptor, a subtype belongs to G-protein coupled receptor family [28], results in inhibition or activation of ion channels that, in turn, can inhibit neurotransmitter release from axon terminals. Despite the recognition of the CB1 receptor and CB2 receptor, there are several other receptors, ranging from other G protein-coupled receptors to ion channel and nuclear receptors, have been reported to interact with cannabinoids [29, 30].

High levels of cannabinoid receptors are found in brain regions implicated in the behavioural effects of cannabinoids, particularly cortex, hippocampus, amygdala, basal ganglia, cerebellum, and the emetic centres of the brainstem [31]. CB1R's extensive expression and multipurpose role received much attention as the main mediator of psychoactive effect of THC. Considering its undesired side effects, more attention has been paid to the long-ignored CB2R and other end-/Phyto-cannabinoids [31]. The lack of effective therapeutic options has driven attention towards the potential use of cannabis as a relatively new pharmacological option in the management of chronic pain [32].

Current evidence relating to the use of cannabis for chronic pain

In the past decades, many studies and reviews conducted on cannabis have provided an insight into its effectiveness in pain management. However, the therapeutic effects of cannabis and cannabinoids concluded that there was conclusive or substantial evidence that cannabis or cannabinoids are effective for the treatment of pain in adults [33]. Medical cannabis effectively used to treat chronic pain and produced a significant improvement in the management of

chronic pain [34]. There were reports mentioned that cannabis has replaced opioid analgesics due to its clinical significance efficacy [36, 37, 38]. Clinical trials showed therapeutic benefits of cannabis, especially THC in various conditions including spasticity related to multiple sclerosis [39, 40], HIV-associated sensory neuropathy [41, 42], and chronic neuropathic pain [43]. A clinical trial conducted on smoking cannabis for neuropathic pain proved that cannabis cigarettes containing 4 to 32 mg THC significantly reduced pain intensity [44]. Other randomized trials suggested that THC (up to 25 mg daily) significantly reduces pain compared to placebo [45, 46]. Fifteen and 20 mg THC produced significant analgesia in cancer patients [47, 48]. A study among cannabis users mentioned that the efficacy of cannabis for pain management is higher than prescription pain medication [49]. However, it is unclear that the efficacy of cannabis is similar across different types of pain symptoms and origins.

Pergolizzi *et al*., (2018) reported that cannabis is effective in controlling neuropathic pain, allodynia, medication-rebound headache, and chronic non-cancer pain and does not offer any benefit over non-opioid analgesics in treating acute pain [50], whereas another study mentioned lack of evidence for the treatment efficacy across of cannabis across different conditions [51]. Allan *et al*., (2018) revealed that the benefits of medical cannabis are bordering on clinically meaningful, with an improvement of 0.4 to 0.8 points on the numerical rating scale and a non-statistically significant pain reduction (≥30%) s compared with placebo and the improvement was limited to neuropathic pain with a small analgesic benefit [52]. A meta-analysis suggested that inhaled cannabis may provide short-term relief of neuropathic pain in 1 out of 5 to 6 patients [53]. A study by Wilsey *et al*., (2013) found that low doses of vaporized cannabis, may be effective for treatment-resistant neuropathic pain [54]. However, there is a lack of evidence supporting the use of cannabis for refractory and chronic neuropathic pain [55, 56].

For other types of chronic pain, cannabis produced no clear benefit compared with placebo in the treatment of cancer pain, rheumatoid arthritis, fibromyalgia, visceral pain, musculoskeletal pain and chronic pancreatitis [50, 57]. From a clinical standpoint, the use of medical cannabis in chronic pain should be restricted to patients in whom the usual first- and second-line treatments produced inadequate responses or intolerable side effects [56, 58]. Intermittent use of cannabis helps the patients to decrease amount of opioids they consume when they use cannabis for pain [59] and reduce opioid withdrawal symptoms for individuals in naloxone treatment [60]. Most of the current evidence on cannabis use for pain is derived from small, short-duration studies and as adjunctive therapy, thus leaving uncertainties on the reliability of the effects [57]. The emerging evidence of using cannabis in pain management need to be supported by more clinical trials, including people with complex comorbidities to determine the therapeutic efficacy of cannabis in managing pain [61]. Larger scale trials with sufficient quality and duration will be required to provide a conclusive result on the use of cannabis for pain management. At this time, it is unlikely that cannabis can be used as a monotherapy or first-line therapy for chronic pain [62].

Current concerns of using cannabis in pain management

While it is being used increasingly in pain control, albeit in the face of limited evidence for its effectiveness, medical cannabis can be potentially harmful, thus limiting its therapeutic potential. Approximately 4800 adverse events have been reported over the past 40 years in relation to the clinical use of medicinal cannabinoids [63]. The most frequently reported adverse effects are central nervous system (CNS) -related such as psychosis and cognitive impairment, and gastrointestinal-related such as dry mouth, nausea, vomiting and the cannabinoid hyperemesis syndrome [63, 64]. These adverse effects can be further categorised into non-serious and serious adverse effects. Whiting *et al*., (2015) showed that there is a higher

incidence of non-serious adverse effects in patients receiving medical cannabis for pain management after one year [65]. In contrast, another study by Ware *et al*., (2015) reported that cannabis at average doses of 2.5 g/d is safe for the patients currently using cannabis for pain management program [66]. The clinical use of cannabinoids is most commonly associated with a higher risk of adverse cognitive effects, especially long-term deficits of higher-order cognitive functions [67]. Use of heavy doses for a longer period causes dose-related impairments in executive function, including memory and psychomotor speed [68]. There is contradictory evidence from a published review of complex cannabinoid-dopamine interactions [69].

The major concern in using medical cannabis is the development of neuropsychiatric effects, ranging from disorientation to psychosis. Medical cannabis may exacerbate the mania phase in patients with bipolar disorder and give rise to new onset of manic symptoms [70]. This finding may limit the clinical use of cannabinoids among the general population, especially those with pre-existing bipolar disorders or a tendency to suffer from this condition. However, due to the fact that this study identified a small number of studies of varying quality, the conclusion conclusions remain preliminary. Cannabis consumption can distort perception and psychomotor performance as evidenced supported by findings that acute intoxication with cannabis is associated with a moderate risk of motor vehicle accidents [71]. Rogeberg and Elvik (2016) demonstrated that acute cannabis intoxication significantly increased the accidents of low to medium magnitude [72]. The use of medical cannabis may confer vulnerability to cognitive impairment, which was found to be more consistently associated with the residual effects of cannabis or withdrawal symptoms, as concluded from a meta-analysis [73]. Other work demonstrated that long-term exposure to medical cannabis among adolescents leads to brain impairment during the developmental period, resulting in a reduction in intelligence quotient (IQ) [74, 75].

Long-term use, or accidental overdose of cannabis may result in the cannabinoid hyperemesis syndrome [76], in which patients experience severe episodes of cyclical vomiting associated with abdominal pain. Sorensen *et al*., (2016) reported that individuals aged between 20 to 29, and those with continuous use of cannabis daily to weekly, are more susceptible to the development of cannabinoid hyperemesis syndrome [77]. Although the mechanisms underlying this syndrome remain unclear, accumulation of THC, or dysregulation of peripheral enteric nerves may be involved [78, 79].

Addiction and dependence

The usage of cannabis has been greatly debated because of the assumption that it is associated with addiction and dependence. Addiction is defined as the chronic compulsive desire for certain substances such as drugs, and the inability to refrain from substance use in spite of the consequences [80]. Dependence, on the other hand, is defined as the consequences of long-term usage of substances such as opioids and benzodiazepines which usually produce rewarding effects [81]. Therefore, addiction and dependence can be interpreted as being closely related; addiction to a particular substance can ultimately lead to dependence after being exposed for a certain period of time. According the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), the cumulative probability that the use of cannabis was linked to a lifelong risk of dependence was 9% as compared to 67.5% of nicotine, which is the most addictive and 22.7% for alcohol [82-84]. Therefore, addiction to and dependence on cannabis can be assumed to be comparatively lower than other substances. It was also reported that among the adults, males are more prone to developing dependence compared to females [85]. However, the percentage of cannabis use among young adults can increase up to 17% if initiation of cannabis occurs in early adolescence usually around the age of 11 to 15 [83, 86]. So far, there are no standard measures of the quantity used in most countries. According to the

data from the National Household Survey on Drug Abuse (NHSDA), the prevalence of dependence declined strongly with increasing age, while ethnicity showed no significant influence on the risk of dependence [74]. As the early onset of usage of cannabis results in an increased risk of cannabis dependence, it is predicted that this will also increase the risk of using other illicit drugs [87]. This is because during adolescence, the brain, including the endocannabinoid system, is actively developing; this explains the vulnerability of adolescents to adverse effects such as addiction and dependence [88]. Furthermore, peer pressure, antisocial behaviour and poor academic performance are greatly associated with the risk of early and regular use of cannabis, especially in developed and developing countries [89]. The above-mentioned predisposing factors are considered to contribute to the incidence of cannabis addiction and dependence in adolescents.

As expected, another significant factor that leads to cannabis addiction and dependence is the acute, rewarding effects of cannabis [83]. Nonetheless, long-term sensory adaptation, induced by cannabis abuse also one of the factor leads to addiction [89, 90]. Data from France's Susceptibility Addiction Gene Environment (SAGE) study showed that those reported to have experienced positive effects after being exposed to cannabis for the first time are more likely to develop dependence at the ages of 18 to 21 [91]. Other factors that contribute to cannabis dependence include frequent usage, prior exposure to illicit drugs, emotional disorders like depression or anxiety, stressful and negative life events include physical abuse, low parental support, early parental death or financial problems [81, 83, 85, 86, 88, 92]. In short, addiction to and dependence on cannabis are associated with cannabis effects, as well as personal, social and environmental factors, which eventually evoke concerns on health issues regarding the usage of cannabis for medical purposes.

Medical cannabis/ Medical marijuana and its regulations

Cannabis use for medical or recreational purposes has been prohibited for decades. Currently, policies on medical cannabis and marijuana are changing in worldwide [93] and this change in policy might be related to a change in the perception of cannabis and attitudes towards cannabis [94]. In recent times, based on its potential benefits in managing certain conditions more countries have decided to legalise the use of cannabis products including marijuana [95]. From a global perspective, Canada and certain states of the United States of America have legalised medical marijuana, whereas some countries only permit cannabis-derived drugs [96]. North America appears to be the first region to legalise the medical use of cannabis [97]; decisions to do this were based on citizen-initiated referenda in 30 states and in the District of Columbia [98], with legalisation of marijuana being considered in more states for both medical and recreational use. The public health concerns associated with marijuana usage, such as dependence or addiction, in addition to the relationship between marijuana and opioid use also need to be considered [99]. Furthermore, some people can use cannabis without harm, whereas others experience adverse effects; this certainly has significant implications for clinical practice [100].

Recently, Thailand has emerged as the first country in Southeast Asia to legalize medical marijuana [101]. Meanwhile, in Malaysia, there is controversy on whether marijuana should be legalised. The medicinal value of cannabis is under consideration, so that, in the future, the country may allow medical cannabis-related products to be marketed when there is strong evidence for their efficacy and safety [102, 103]. Under Malaysian law, in accordance with the Dangerous Drugs Act (1952), cannabis plants can be cultivated for research, educational, experimental or medicinal purposes with authorisation from the government [104]. A transition from the general public restriction of marijuana to its legalisation requires law amendment, and its social and economic implications should be considered. Medical marijuana legalisation may in turn stimulate pharmaceutical companies to search for an effective cannabis

product, thus benefiting those patients who require medical marijuana urgently where other therapeutic options for pain management have failed. This may also spark the interest of other countries to consider the therapeutic benefits of cannabis, and move towards the legalisation of medical marijuana.

A world map (Figure 1) makes a clear distinction on the legal status of marijuana across the world, where red means 'illegal', yellow means 'decriminalized' and green means 'legal' [100]. Although marijuana remains mostly illegal worldwide, the trend is evolving to a growing acceptance of medical marijuana as a legal substance. Therefore, healthcare professionals should keep themselves updated with the changing state of medical marijuana and its applications, so that they can know the most feasible time to allow their patients to initiate treatment appropriately.

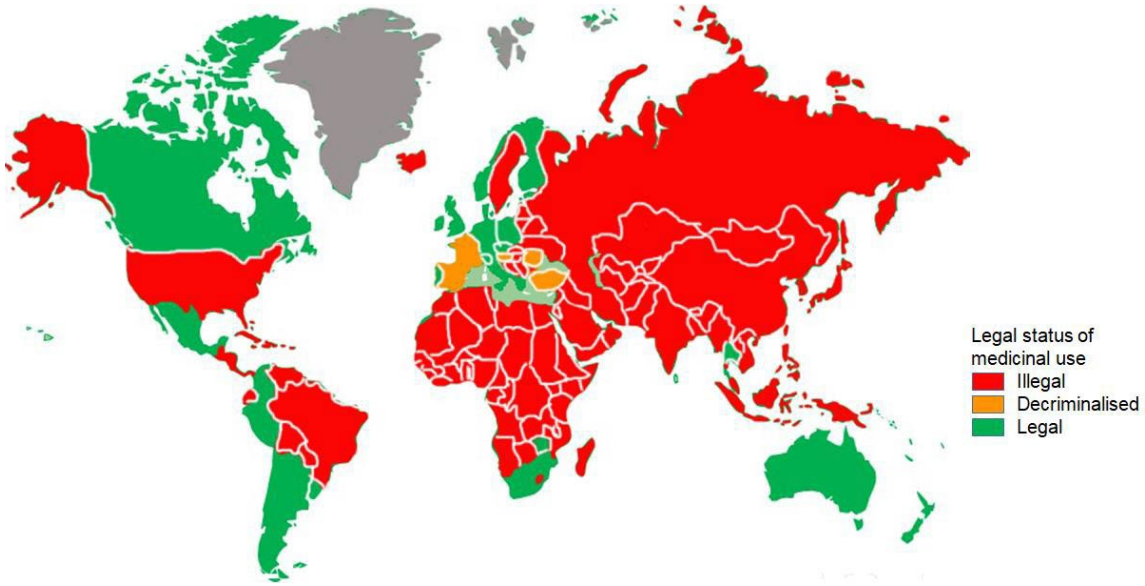

Figure 1: World map showing legal status of medical marijuana.

Furthermore, Häuser *et al*., (2017) conducted a study based on randomized controlled trials and prospective long-term observational studies on the use of cannabinoids in pain management and palliative medicine, and reported that the data from existing studies are not leading prescribers to rational use of medical cannabis for chronic pain management [5]. However, since patients opting for cannabis are often suffering from debilitating chronic pain impacting their quality of life, it is essential that physicians can advise patients on both potential risks and benefits based on their conditions, despite the limited evidence available [105]. From an ethical perspective, it remains controversial on how much autonomy a patient should have in opting for cannabis, which some physicians believe could produce harm. This presents a challenge on what is in the best interest of the patient. Moreover, there is a need to review regulations on the amount of cannabis that can be possessed for medical purposes, and whether a prescription is needed to obtain medical cannabis.

Meanwhile, the complex and variable chemically active contents of herbal cannabis, which makes dosing and predictability of clinical effects uncertain, poses a challenge in the formulation of cannabis into a medication. The diverse cannabis strains, with their varying concentrations of THC and cannabidiol, also impede advancement in clinical trial and research, as researchers often face difficulties in obtaining the correct quantity, quality and type of cannabis product necessary to address specific research questions on the clinical effects of cannabis use [106]. Moreover, another key barrier in clinical research is the methodological limitations, specifically in the administration of cannabis and blinding of the study participants [107,108]. This is because cannabis smoking may not be an acceptable method for some study participants, and the research sites may lack facilities to ensure standardized dosing, where study participants can smoke under controlled conditions [106]. Although devices for a metered dose inhalation of cannabis exist, these have not been approved by the Food and Drug Administration (FDA) [109]. More research is required on the pharmacokinetics and safety of

medical cannabis, especially with various doses using different routes of administration. Research on cannabis remains challenging, due to restrictive policies related to its status as a controlled substance under federal law [110]. Furthermore, some of the clinical trials are subjected to bias due to difficulty in effective blinding, as the psychoactive effects of cannabis are promptly recognized by study participants, who will then speculate that they are receiving cannabis or cannabinoids instead of placebo. Therefore, continuous effort to address these methodological barriers is of significant interest in order to achieve reliable and comprehensive research outcomes. As barriers to cannabis usage continue to relax due to its legalization, the research in this area, including different formulations for cannabis and its phytochemical products will continue to grow [111].

Summary

The use of cannabis in chronic pain management is only limited to neuropathic pain in which there is some evidence of a small analgesic benefit. There is a lack of evidence to support the use of medical cannabis in treating refractory and chronic neuropathic pain. Also, there are no clear benefits of the use of cannabis in other types of chronic pains. Therefore, cannabis is unlikely to be used as a monotherapy or as a first-line therapy. Generally, cannabis is associated with CNS-related adverse effects such as psychosis and cognitive impairment, and GI-related adverse effects such as dry mouth, nausea and cannabinoid hyperemesis syndrome, which can significantly impact the quality of life of a patient. Cannabis dependence and addiction are associated with a long duration of cannabis administration and its rewarding effects. The challenges in the use of cannabis include the potential adverse effects of cannabis, the risk of misuse, and the lack of adequate knowledge and awareness on cannabis, as well as the various limitations on research and formulation. Medical cannabis is currently legalized in certain states of US, Canada and Thailand. There are challenges, including lack of guidelines to

undertake clinical trials to examine the validity of medical use of cannabis. Therefore, rigorous, randomized observational studies using standardized, validated measures are required to establish dosing targets for the effective use of cannabis as a medicine for chronic pain management. The research community has the responsibility to continue to pursue rigorous studies of cannabis-based medicines to provide more evidence that may help the healthcare professionals to make an appropriate clinical decision on chronic pain management.

Funding

This study did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Acknowledgement

All the authors acknowledge Professor Brian Furman, University of Strathclyde, for his help in improving the use of English in the manuscript.

Conflict of interest

All authors declare that there is no potential conflict of interest

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