EJP
European Journal of Pain

REVIEW ARTICLE

# Medical cannabis: A forward vision for the clinician

M.A. Fitzcharles[1,2], E. Eisenberg[3,4]

1 Alan Edwards Pain Management Unit, McGill University Health Centre, Montreal, QC, Canada
2 Division of Rheumatology, McGill University Health Centre, Montreal, QC, Canada
3 Pain Research Unit, Institute of Pain Medicine, Rambam Health Care Campus, Haifa, Israel
4 Technion-Institute of Technology, Haifa, Israel

**Correspondence**
Mary-Ann Fitzcharles
E-mail: mary-ann.fitzcharles@muhc.mcgill.ca

**Funding sources**
No funding was received for this work.

**Conflicts of interest**
MAF received consulting fees, speaking fees, and/or honoraria from ABBVIE, Abbott, amgen, Bristol-Myers Squibb Canada, Janssen, Johnson & Johnson, Lilly and Pfizer. EE received research grants from: Mundipharma, Rafa Laboratories, Taro Pharmaceutical Industries, Dexcel Pharma, Pfizer, MSD, Novartis, Syqe Medical, St. Jude Medical, Israel Pain Association, Israel Cancer Association, Israel Scientific Foundation, Focused Ultrasounds Surgery (FUS) Foundation and Teva Pharmaceutical Industries.

**Accepted for publication**
19 December 2017

doi:10.1002/ejp.1185

## Abstract

Medical cannabis has entered mainstream medicine and is here to stay. Propelled by public advocacy, the media and mostly anecdote rather than sound scientific study, patients worldwide are exploring marijuana use for a vast array of medical conditions including management of chronic pain. Contrary to the usual path of drug approval, medical cannabis has bypassed traditional evidence-based study and has been legalized as a therapeutic product by legislative bodies in various countries. While there is a wealth of basic science and preclinical studies demonstrating effects of cannabinoids in neurobiological systems, especially those pertaining to pain and inflammation, clinical study remains limited. Cannabinoids may hold promise for relief of symptoms in a vast array of conditions, but with many questions as yet unanswered. Rigorous study is needed to examine the true evidence for benefits and risks for various conditions and in various patient populations, the specific molecular effects, ideal methods of administration, and interaction with other medications and substances. In the context of prevalent use, there is an urgency to gather pertinent clinical information about the therapeutic effects as well as risks. Even with considerable uncertainties, the health care community must adhere to the guiding principle of clinical care *'primum non nocere'* and continue to provide empathetic patient care while exercising prudence and caution. The health care community must strongly advocate for sound scientific evidence regarding cannabis as a therapy.

**Significance:** Legalization of medical cannabis has bypassed usual drug regulatory procedures in jurisdictions worldwide. Pending sound evidence for effect in many conditions, physicians must continue to provide competent empathetic care with attention to harm reduction. A vision to navigate the current challenges of medical cannabis is outlined.

## 1. Introduction

Unprecedented in this era of modern medicine is the current challenge of cannabis as a treatment for a vast array of medical conditions. In the last decade, cannabis as a therapy has been catapulted into the medical arena as a result of legalization for medical use in various jurisdictions, especially the United States, Canada and Israel. Propelled largely by public advocacy, the media and political agendas, with limited sound scientific study, patients are exploring use of cannabis as a treatment strategy and are also self-medicating with this substance. Medical cannabis is a current reality and is here to stay. Contrary to usual medical practice whereby a product proceeds through a defined process before acceptance as a

therapy, cannabis has bypassed standard scientific scrutiny and has entered mainstream medicine in countries worldwide (D'Souza and Ranganathan, 2015). It is therefore the responsibility of the medical community to hasten to assemble as much information regarding benefits and risks of medical cannabis in order to counsel patients and provide competent clinical care.

In this review, we will focus on the cannabinoid effects in the management of pain and highlight areas that we believe are relevant to clinical practice. Knowledge of the state-of-the-art will allow the medical community to move forward in this age of prevalent use of medicinal cannabis. More detailed analyses of specific issues pertaining to medical cannabis are covered in other papers in this special issue of the journal. This article is based on the Ulf Lindblom Special lecture delivered at the 19th Congress of the European Pain Federation EFIC in Copenhagen in 2017.

## 2. Cannabinoids and the endocannabinoid system

The endocannabinoid system is found through the human body and comprises receptors and ligands. Although mostly associated with neuronal tissue, both peripheral and central, the system extends to other tissues including skin, bone, joints and hematopoietic defence cells (Pertwee, 2006). This system functions to restore homeostasis by promotion of sleep, appetite, stress reduction and modulation of pain and inflammation and thereby counterbalances the 'fight and fly' phenomenon (Steiner and Wotjak, 2008). Therefore, harnessing the effects of down-modulation of the stress phenomenon presents an attractive therapeutic option for numerous conditions. The understanding of the molecular underpinnings of the endocannabinoid system is fairly recent with identification of the cannabinoid receptors, CB1 and CB2 in the late 1980s, and then subsequent discovery of various endocannabinoid ligands (Howlett, 2005; Pertwee, 2015). The endogenous ligands termed endocannabinoids are derived from arachidonic acid and are produced on demand in response to tissue injury or following a pre-synaptic neuronal trigger. When ligands bind to the cannabinoid receptors, the neural pain signals and inflammatory responses are downregulated. The two best studied endocannabinoids are anandamide and 2-arachidonyl-*sn*-glycerol (2-AG). Other molecules that may similarly bind to the cannabinoid receptors and activate this system are those derived from plant extracts termed phytocannabinoids, and pharmaceutical preparations that are synthesized (Pertwee, 2006).

Phytocannabinoids are found in the annual flowering plant belonging to the Cannabaceae family, of which *Cannabis* is the genus, with various species. The species, *Cannabis sativa* has mostly been a commercial plant providing hemp fibre, whereas *Cannabis indica,* originating in the Indian subcontinent, was originally cultivated for psychotropic properties. Known for its fibrous qualities for over 10,000 years, the plant *Cannabis sativa* remains a valued modern commercial product in the manufacture of paper, textiles, plastics and biofuels (Tourangeau, 2015; Andre et al., 2016). The medicinal and psychoactive properties of cannabinoids have been recognized for thousands of years, with writings beginning in ancient China and Egypt attesting to effect in inflammation and rheumatic pain (Kalant, 2001; Russo, 2007). Cannabis has been used as an analgesic and antispasmodic amongst other uses in the Western world since the mid-1800s, and is currently identified as one of the 50 fundamental herbs of traditional Chinese medicine (Kalant, 2001; Aggarwal et al., 2009). The psychoactive properties of the plant were recorded by the historian Herodotus in 440 BCE when he described the Scythians scattering hemp seeds on hot stones in order to inhale the vapours in steam baths.

From the early 1920s, marijuana, which is the common colloquial term and derived from the dried leaves and flowers of the hemp plant, was increasingly regulated and mostly banned worldwide, especially following the revised International Opium Convention *International Convention relating to Dangerous Drugs* in 1925 which regulated Indian hemp and the preparations derived therefrom (Aggarwal et al., 2009). Cannabinoid molecules may be categorized into two broad groups, namely active molecules with or without psychoactive effect, and inactive molecules. Both *Cannabis sativa* and *Cannabis indica* are currently cultivated to provide delta-9 tetrahydrocannabinol (Δ9-THC) and cannabidiol (CBD), the two best studied molecules with potential for therapeutic effect. Concentrations of these two molecules in various bred strains may, however, vary greatly depending upon genetic manipulation.

## 3. Preclinical study informs the clinician

Preclinical study, the foundation upon which clinical management is built, has shown that cannabinoid receptor agonists block pain in various models of acute and chronic pain and that inflammation is

attenuated (Johanek et al., 2001; Lim et al., 2003; Baker and McDougall, 2004; Schuelert and McDougall, 2008; Sanchez Robles et al., 2012). Extensive study points to antinociceptive activity of both $CB_1$ and $CB_2$ receptor agonists, either singly or in combination, with $CB_2$ activity believed to affect microglial cells and thereby reduce neuroinflammatory mechanisms (Cheng and Hitchcock, 2007; Correa et al., 2009). The $CB_2$ receptor is believed to be particularly important in central neuronal pain circuits with agonist activity inducing dopamine release in midbrain areas that contribute to descending pain control as well as the placebo effect (Shang and Tang, 2017).

In animal models of inflammatory arthritis, mimicking human rheumatoid arthritis, inflammatory effects can be modulated by upregulation of cannabinoid receptor activity or increased production of endocannabinoids, with attenuation of joint destruction (Malfait et al., 2000; Schuelert and McDougall, 2008). Similarly, endocannabinoids and $CB_1$ and $CB_2$ receptor proteins are found in human synovial tissue from patients with both rheumatoid arthritis and osteoarthritis (Richardson et al., 2008). Ajulemic acid, a synthetic THC-11 analogue, has anti-inflammatory properties by reducing interleukin-6 and fibroblast metalloproteinase production and promoting apoptosis (Bidinger et al., 2003). Recent study demonstrating a profibrotic effect of CB1 receptor, but a probable anti-fibrotic effect of the CB2 receptor highlights the complexity of this system, that does not always function in a unidirectional manner (Marquart et al., 2010).

Beyond effects on the inflammatory pathway, the endocannabinoid system plays a vital role in neuronal development by affecting axon and dendrite growth and pruning in order to create specific and secure neuronal circuitry in the adult brain (Njoo et al., 2015). Finally, rat studies have demonstrated that cannabinoid administration alters brain maturation in the young animal with resulting neuropsychiatric consequences in the adult (Renard et al., 2016). Therefore, in summary, the cannabinoid system counterbalance inflammatory mechanisms with modulation of pain and inflammation holding promise for therapeutic effects, but with impact on brain development there is a cautionary note regarding neuronal development.

## 4. Evidence for effect in the management of chronic pain

With this background of the preclinical science, the clinician must turn to evidence for effect in disease. In striking contrast to the abundance of comment in the public domain concerning the therapeutic effects of cannabinoids in disease, there has been only limited sound clinical study due to the illegal status of cannabinoids in most countries. Fortunately basic science study pertaining to cannabinoids in health and disease has been able to progress.

In two recent systematic reviews, one examining the effects of all cannabinoids for all diseases, and the other focussing on cannabinoid use for chronic pain, the evidence for effect is generally poor in view of the poor study quality, small numbers of participants, short study duration, various cannabinoid preparations used and a frequent high rate of bias (Whiting et al., 2015; Nugent et al., 2017). With only two of the 28 studies reported by Whiting et al., (2015) assessed as having a low risk of bias, the authors stated that studies generally suggested improvements in pain measures, but often failed to reach statistical significance in individual studies. Notably, the odds ratio for the average number of patients reporting at least a 30% reduction in pain was reported as OR, 1.41(95% CI, 0.99–2.00), a value that crosses 1. In the second systematic review by Nugent et al., (2017), which focussed on the effects on chronic pain and harms, the authors report a low strength of evidence for effect on neuropathic pain in some patients, but insufficient evidence for effect on pain associated with multiple sclerosis, cancer and mixed pain conditions. It is therefore surprising that The National Academies Committee on the Health Effects of Marijuana concluded that there is substantive evidence that cannabis is effective for treatment of chronic pain, especially neuropathic pain in adults (National Academies of Sciences E, and Medicine, 2017). Therefore, the sum of the clinical evidence to date is confounded by many factors including studies with mixed patient populations, use of different cannabinoid preparations and in various formulations, and wide ranges in dosing. It is also notable that there are only limited studies evaluating the effects of medical cannabis in any form. Although studies generally report improvement in symptoms of pain, especially that of a neuropathic quality, the results often do not reach significance, but with all studies reporting a considerable rate of side effects.

In the context of recent overuse of opioids for the management of chronic pain, an agent that could reduce opioid use is desirable. Although preclinical evidence points to an important opioid-sparing effect for cannabinoids, and clinical studies

showed some clinical benefits, the latter conclusions are less reliable in view of poor study quality, especially inadequate reporting of opioid dose changes and mixed findings for analgesic effects (Nielsen et al., 2017). In a recent open-label study of medicinal cannabis use for patients with chronic pain over a 6-month period, patients reported improved pain severity and interference, but more striking was that 44% of those on opioids had discontinued opioid treatments (Haroutounian et al., 2016). Indirect evidence for an opioid sparing effect of cannabinoids is the observation that there has been a reduction in prescription drugs for which cannabis could be an alternative, including opioids, in states in the United States (US) that had implemented medical marijuana legislation (Bradford and Bradford, 2016). Furthermore, any treatment focused towards relief of suffering should in addition to symptom relief be associated with benefits to health-related quality of life (HRQoL). Here again, results have been disappointing. In a systematic review of 20 studies, of which 11 were randomized controlled trials, there were small improvements in HRQoL for some patients with pain, multiple sclerosis and inflammatory bowel disease, with reduced effects in some patients with human immunodeficiency disease, leading the authors to conclude that the evidence for effect of cannabinoids and HRQoL are inconclusive (Goldenberg et al., 2017).

In contrast to the limited number of high-quality randomized clinical trials of cannabinoids in disease, observational studies report patient satisfaction with cannabinoid treatments. In a study of almost 1000 persons, two-thirds of whom had chronic pain, accessing medical cannabis from cannabis dispensaries in the north-eastern United States, cannabis was reported to be 70% effective for pain relief (Piper et al., 2017). In a review of cannabis use amongst patients receiving opioid therapy for persistent pain, Reisfeld and colleagues reported concomitant cannabis use to range from 6 to 39%, but with statistically significant associations with present and future aberrant opioid-related behaviours (Reisfield et al., 2009). Therefore in summary, there is currently limited information available from reliable randomized controlled trials examining the therapeutic effects of cannabis for chronic pain, although there is increasing report of considerable subjective effect. It is, however, evident that the current body of evidence would not be sufficiently robust to be accepted by regulatory authorities as an approved treatment for any condition.

## 5. Evidence for risk

Studies of the risks related to medical cannabis use in defined patient populations are limited. Extrapolation of risks from populations of recreational users to patients with various diseases is not ideal, but in the absence of study may provide some insight. A healthy young person using recreational marijuana is distinctly different from a person with a chronic disease seeking medical therapy. Whereas the young recreational user has made a personal choice in order to achieve a psychoactive effect, a patient is seeking relief of a symptom that is persistent, has likely not sufficiently responded to other treatments and is impacting quality of life. In a single study that was designed to evaluate side effects of smoked herbal cannabis in patients with chronic pain over a study duration of 1 year, the rate of serious adverse events did not differ between those using or not using cannabis (Ware et al., 2015). With over half of each group treated with opioids, serious adverse events were reported to be over 20 events/100 patient-years for both groups, representing a considerable high number of events (Ware et al., 2015). Harms associated with cannabis use for chronic pain have been reported in a recent systematic review (Nugent et al., 2017). Nugent and colleagues reported an increased risk of short-term adverse effects of dizziness and tiredness, as well as an increased risk of motor vehicle accidents, psychosis and short-term effects on cognition, but insufficient evidence for other harms (Nugent et al., 2017).

The National Academies Committee on Health Effects of Marijuana has highlighted the increased risks of motor vehicle accidents, increased risk of cannabis overdose injuries in children, but unclear evidence for all-cause mortality or occupational injury associated with marijuana (National Academies of Sciences E, and Medicine, 2017). This report further confirms the impaired performance in cognitive domains of learning, memory and attention related to recent cannabis use within the previous 24 h, as well as some suggestion that these impairments may persist in persons who have used cannabis previously, but stopped smoking cannabis. In addition there is mounting evidence that cannabis use during adolescence has a negative impact on educational attainment and lifetime achievement in employment, income, and social relationships and roles (Meier et al., 2012). Mental health disorders associated with cannabis use are prevalent. Aside from acute psychotic episodes related to the increased concentrations of THC in the street

product, there is evidence for decreased motivation as well as an association of psychotic-like experiences and schizophrenia related to cannabis use, especially when initiated at a younger age (Volkow et al., 2016; Bourque et al., 2017).

The association or development of substance use and/or abuse is a concern for patients using cannabis for medical reasons. Frequent cannabis use is associated with cannabis dependence, especially when initiated at a younger age, and is likely to increase risk of developing substance dependence for other products (van der Pol et al., 2015). In an animal model of alcohol preferring rats, stimulation of the CB1 receptor promoted alcohol intake, supporting the hypothesis that the cannabinoid system has modulatory effects on neural circuitry involved in alcohol drinking behaviour (Colombo et al., 2002). In a recent study, in the United States, a quarter of chronic pain patients using medical cannabis were identified as high-risk alcohol drinkers (Davis et al., 2018). Furthermore, the National Academies Committee has concluded that there is moderate evidence for the development of substance dependence and/or abuse disorder in the setting of cannabis use, highlighting the need for vigilance in this regard by the treating physician (National Academies of Sciences E, and Medicine, 2017).

Another area of contention that requires study and clarification is whether smoking cannabis is alone a risk factor for lung cancer. Study to date has been fraught by confounders such as concomitant cigarette smoking, self-report of cannabis use, variable smoking techniques, and unclear and small numbers for chronic or heavy cannabis use. Although the National Academies of Sciences has concluded that there is no statistical association between cannabis smoking and incidence of lung cancer, this assessment was based on information from a single systematic review and an epidemiological review, with considerable limitations identified for both reviews (Huang et al., 2015; Zhang et al., 2015; National Academies of Sciences E, and Medicine, 2017). Similar limitations of study design have been noted in the systematic review of Martinasek et al., (2016) that reported an increased risk ratio of lung cancer and cannabis use of between 2 to 4. The longest duration epidemiological study to date reported a 2.12 risk of lung cancer with heavy cannabis use, for almost 50,000 Swedish military recruits followed over 40 years (Callaghan et al., 2013). It is intuitive that lung function should be affected by inhalation of a combustible substance that is composed of many chemicals. Discordant results for effects on air-flow, both immediate and long-term as well as the development of chronic obstructive airways disease have however been reported, with limitations of studies similar to those for the cancer studies (Joshi et al., 2014).

## 6. The current reality

There is a common perception that cannabis is a harmless pleasure for recreational use and that access should not be restricted or illegal. It is also well known that once a substance has achieved legal status, there is increased widespread use as has been seen for alcohol and tobacco. There is also a common perception that medical cannabis is an excellent treatment for a variety of conditions including pain, mental health disorders especially anxiety, sleep disorders amongst others (Sznitman and Bretteville-Jensen, 2015). This perception, however, is typically supported by either weak evidence or no evidence at all. Unfortunately, the risks related to cannabis in general have been whitewashed by the media with increased focus on the purported benefits of both recreational and medicinal cannabis. It can be understood that once regulatory authorities have approved a product, the population anticipates that due diligence regarding risks has been addressed. In jurisdictions where medical cannabis is legal, there is also a notion of smudging of the fine line between recreational and medicinal use. It is also known that many persons currently using medical cannabis had previously used the product recreationally (Pacula et al., 2016).

## 7. Lessons learned

When jurisdictions are considering legalizing cannabis for medical purposes, they could do well to look to the experience of others in order to protect both patients and society. In the first instance, it is paramount that medical and recreational use remains entirely distinct (Cairns and Kelly, 2017). This has reasons that extend from reducing the risks for patients, maintaining the therapeutic relationship, providing incentive for further study, as well as addressing issues of reimbursement and education for both patients and the health care community. Treatment with medical cannabis must not be viewed as a self-administered and unregulated therapy, but should rather adhere to the basic principles of good medical care. The pitfalls that have been observed to date include the use of excessive quantities of cannabis by some persons, diversion of

medically accessed product, and indiscriminate and inappropriate use for conditions that do not justify such treatments. Finally, unethical medical practice involves the provision of prescriptions for medical cannabis by some physicians who either do not have a full knowledge of a patient, do not assume clinical responsibility for the patient, or perhaps provide prescriptions for persons who are not valid patients.

## 8. The way forward

There are currently more questions and uncertainties concerning medical cannabis than answers, and the clinician may offer a wish list to the researchers for further study. Amongst the many uncertainties are the following: are the clinical effects related to a single or combination of molecules; do molecules other than THC and CBD have potential for therapeutic benefit; do specific molecules have effect on specific symptoms or conditions; what is the effect of other drug interactions with cannabis; will adverse effects outweigh the positive effects; and will tolerance develop and require progressively higher doses to achieve clinical effects?. There is also a need to understand dosing and methods of administration (inhalation, ingestion, transmucosal or transdermal) of various cannabinoid products. Beyond administration of cannabinoid products, manipulation of the endocannabinoid system should be further explored.

Importantly, the true effect of cannabinoids in many conditions requires objective measurement. With regard to the management of chronic pain conditions, medical cannabis should not be seen as a replacement for opioid treatment, especially in countries where overuse of opioids has been prevalent over the past few years. Studies of longer duration and with defined illnesses are required, including attention to specific patient populations, such as the young, the elderly, pregnant and lactating women and those with other medical comorbidities. There is also a need to rethink and be innovative in our methods of assembling data to direct clinical care. Perhaps this is a setting in which the traditional randomized controlled trial will be less applicable, with a need to look to large-scale, longitudinal cohort observational studies to answer clinical questions. And finally, there must be a clear distinction between recreational use of cannabis and that for medical purposes, both by regulatory authorities and the health care community.

## 9. Summary

In summary, medicinal herbal cannabis use is prevalent and is a reality. Only with information obtained through valid and reliable clinical study can the therapeutic potential of cannabinoids in general and medical cannabis in particular be assessed. In the current absence of a body of reliable information, the health care community must endeavour to inform patients as best as possible, but should not accede to anecdote in this 21st century. Cannabinoids in some form may hold outstanding promise for use in a range of conditions, but we cannot be beguiled by only advocacy. Clinicians are obligated to provide the best competent clinical care by adhering to the principles of evidence-based medicine combined with clinical wisdom. At this time, the health care community must speak with a rational, empathetic and sound scientific voice in order to effectively counsel patients. For this reason, it will be important to proceed rapidly with meticulous clinical study to allow the science to inform fundamental issues that arise in the clinic, but with the time-honoured medical ethic of ‘do no harm’ to patients and society.

### References

Aggarwal, S.K., Carter, G.T., Sullivan, M.D., ZumBrunnen, C., Morrill, R., Mayer, J.D. (2009). Medicinal use of cannabis in the United States: Historical perspectives, current trends, and future directions. *J Opioid Manag* 5, 153–168.

Andre, C.M., Hausman, J.F., Guerriero, G. (2016). Cannabis sativa: The plant of the thousand and one molecules. *Front Plant Sci* 7, 19.

Baker, C.L., McDougall, J.J. (2004). The cannabinomimetic arachidonyl-2-chloroethylamide (ACEA) acts on capsaicin-sensitive TRPV1 receptors but not cannabinoid receptors in rat joints. *Br J Pharmacol* 142, 1361–1367.

Bidinger, B., Torres, R., Rossetti, R.G., Brown, L., Beltre, R. et al. (2003). Ajulemic acid, a nonpsychoactive cannabinoid acid, induces apoptosis in human T lymphocytes. *Clin Immunol* 108, 95–102.

Bourque, J., Afzali, M.H., O’Leary-Barrett, M., Conrod, P. (2017). Cannabis use and psychotic-like experiences trajectories during early adolescence: The coevolution and potential mediators. *J Child Psychol Psychiatry* 58, 1360–1369.

Bradford, A.C., Bradford, W.D. (2016). Medical Marijuana laws reduce prescription medication use in medicare part D. *Health Aff (Millwood)* 35, 1230–1236.

Cairns, E.A., Kelly, M.E.M. (2017). Why support a separate medical access framework for cannabis? *CMAJ* 189, E927–E928.

Callaghan, R.C., Allebeck, P., Sidorchuk, A. (2013). Marijuana use and risk of lung cancer: A 40-year cohort study. *Cancer Causes Control* 24, 1811–1820.

Cheng, Y., Hitchcock, S.A. (2007). Targeting cannabinoid agonists for inflammatory and neuropathic pain. *Expert Opin Investig Drugs* 16, 951–965.

Colombo, G., Serra, S., Brunetti, G., Gomez, R., Melis, S. et al. (2002). Stimulation of voluntary ethanol intake by cannabinoid receptor agonists in ethanol-preferring sP rats. *Psychopharmacology* 159, 181–187.

Correa, F., Docagne, F., Mestre, L., Clemente, D., Hernangomez, M., Loria, F., Guaza, C. (2009). A role for CB2 receptors in anandamide signalling pathways involved in the regulation of IL-12 and IL-23 in microglial cells. *Biochem Pharmacol* 77, 86–100.

Davis, A.K., Walton, M.A., Bohnert, K.M., Bourque, C., Ilgen, M.A. (2018). Factors associated with alcohol consumption among medical cannabis patients with chronic pain. *Addict Behav* 77, 166–171.

D'Souza, D.C., Ranganathan, M. (2015). Medical Marijuana: Is the cart before the horse? *JAMA* 313, 2431–2432.

Goldenberg, M., Reid, M.W., IsHak, W.W., Danovitch, I. (2017). The impact of cannabis and cannabinoids for medical conditions on health-related quality of life: A systematic review and meta-analysis. *Drug Alcohol Depend* 174, 80–90.

Haroutounian, S., Ratz, Y., Ginosar, Y., Furmanov, K., Saifi, F., Meidan, R., Davidson, E. (2016). The effect of medicinal cannabis on pain and quality-of-life outcomes in chronic pain: A prospective open-label study. *Clin J Pain* 32, 1036–1043.

Howlett, A.C. (2005). A short guide to the nomenclature of seven-transmembrane spanning receptors for lipid mediators. *Life Sci* 77, 1522–1530.

Huang, Y.H., Zhang, Z.F., Tashkin, D.P., Feng, B., Straif, K., Hashibe, M. (2015). An epidemiologic review of marijuana and cancer: An update. *Cancer Epidemiol Biomarkers Prev* 24, 15–31.

Johanek, L.M., Heitmiller, D.R., Turner, M., Nader, N., Hodges, J., Simone, D.A. (2001). Cannabinoids attenuate capsaicin-evoked hyperalgesia through spinal and peripheral mechanisms. *Pain* 93, 303–315.

Joshi, M., Joshi, A., Bartter, T. (2014). Marijuana and lung diseases. *Curr Opin Pulm Med* 20, 173–179.

Kalant, H. (2001). Medicinal use of cannabis: History and current status. *Pain Res Manage* 6, 80–91.

Lim, G., Sung, B., Ji, R.R., Mao, J. (2003). Upregulation of spinal cannabinoid-1-receptors following nerve injury enhances the effects of Win 55,212-2 on neuropathic pain behaviors in rats. *Pain* 105, 275–283.

Malfait, A.M., Gallily, R., Sumariwalla, P.F., Malik, A.S., Andreakos, E., Mechoulam, R., Feldmann, M. (2000). The nonpsychoactive cannabis constituent cannabidiol is an oral anti-arthritic therapeutic in murine collagen-induced arthritis. *Proc Natl Acad Sci USA* 97, 9561–9566.

Marquart, S., Zerr, P., Akhmetshina, A., Palumbo, K., Reich, N. et al. (2010). Inactivation of the cannabinoid receptor CB1 prevents leukocyte infiltration and experimental fibrosis. *Arthritis Rheum* 62, 3467–3476.

Martinasek, M.P., McGrogan, J.B., Maysonet, A. (2016). a systematic review of the respiratory effects of inhalational Marijuana. *Respir Care* 61, 1543–1551.

Meier, M.H., Caspi, A., Ambler, A., Harrington, H., Houts, R. et al. (2012). Persistent cannabis users show neuropsychological decline from childhood to midlife. *Proc Natl Acad Sci USA* 109, E2657–E2664.

National Academies of Sciences E, and Medicine. (2017). *The Health Effects f Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research* (Washington, D.C.: The National Academies Press).

Nielsen, S., Sabioni, P., Trigo, J.M., Ware, M.A., Betz-Stablein, B.D. et al. (2017). Opioid-sparing effect of cannabinoids: A systematic review and meta-analysis. *Neuropsychopharmacology* 42, 1752–1765.

Njoo, C., Agarwal, N., Lutz, B., Kuner, R. (2015). The cannabinoid receptor CB1 interacts with the WAVE1 complex and plays a role in actin dynamics and structural plasticity in neurons. *PLoS Biol* 13, e1002286.

Nugent, S.M., Morasco, B.J., O'Neil, M.E., Freeman, M., Low, A. et al. (2017). The effects of cannabis among adults with chronic pain and an overview of general harms: A systematic review. *Ann Intern Med* 167, 319–331.

Pacula, R.L., Jacobson, M., Maksabedian, E.J. (2016). In the weeds: A baseline view of cannabis use among legalizing states and their neighbours. *Addiction* 111, 973–980.

Pertwee, R.G. (2006). Cannabinoid pharmacology: The first 66 years. *Br J Pharmacol* 147(Suppl 1), S163–S171.

Pertwee, R.G. (2015). Endocannabinoids and their pharmacological actions. *Handb Exp Pharmacol* 231, 1–37.

Piper, B.J., Beals, M.L., Abess, A.T., Nichols, S.D., Martin, M.W., Cobb, C.M., DeKeuster, R.M. (2017). Chronic pain patients' perspectives of medical cannabis. *Pain* 158, 1373–1379.

van der Pol, P., Liebregts, N., de Graaf, R., Korf, D.J., van den Brink, W., van Laar, M. (2015). Three-year course of cannabis dependence and prediction of persistence. *Eur Addict Res* 21, 279–290.

Reisfield, G.M., Wasan, A.D., Jamison, R.N. (2009). The prevalence and significance of cannabis use in patients prescribed chronic opioid therapy: A review of the extant literature. *Pain Med* 10, 1434–1441.

Renard, J., Rushlow, W.J., Laviolette, S.R. (2016). What can rats tell us about adolescent cannabis exposure? Insights from preclinical research. *Can J Psychiatry* 61, 328–334.

Richardson, D., Pearson, R.G., Kurian, N., Latif, M.L., Garle, M.J. et al. (2008). Characterisation of the cannabinoid receptor system in synovial tissue and fluid in patients with osteoarthritis and rheumatoid arthritis. *Arthritis Res Ther* 10, R43.

Russo, E.B. (2007). History of cannabis and its preparations in saga, science, and sobriquet. *Chem Biodivers* 4, 1614–1648.

Sanchez Robles, E.M., Bagues Arias, A., Martin Fontelles, M.I. (2012). Cannabinoids and muscular pain. Effectiveness of the local administration in rat. *Eur J Pain* 16, 1116–1127.

Schuelert, N., McDougall, J.J. (2008). Cannabinoid-mediated antinociception is enhanced in rat osteoarthritic knees. *Arthritis Rheum* 58, 145–153.

Shang, Y., Tang, Y. (2017). The central cannabinoid receptor type-2 (CB2) and chronic pain. *Int J Neurosci* 127, 812–823.

Steiner, M.A., Wotjak, C.T. (2008). Role of the endocannabinoid system in regulation of the hypothalamic-pituitary-adrenocortical axis. *Prog Brain Res* 170, 397–432.

Sznitman, S.R., Bretteville-Jensen, A.L. (2015). Public opinion and medical cannabis policies: Examining the role of underlying beliefs and national medical cannabis policies. *Harm Reduct J* 12, 46.

Tourangeau, W. (2015). Re-defining environmental harms: Green criminology and the state of Canada's hemp industry. *Can J Criminol Crim Justice* 57, 528–554.

Volkow, N.D., Swanson, J.M., Evins, A.E., DeLisi, L.E., Meier, M.H. et al. (2016). Effects of cannabis use on human behavior, including cognition, motivation, and psychosis: A review. *JAMA Psychiatry* 73, 292–297.

Ware, M.A., Wang, T., Shapiro, S., Collet, J.P. (2015). Cannabis for the management of pain: Assessment of safety study (COMPASS). *J Pain* 16, 1233–1242.

Whiting, P.F., Wolff, R.F., Deshpande, S., Di Nisio, M., Duffy, S. et al. (2015). Cannabinoids for medical use: A systematic review and meta-analysis. *JAMA* 313, 2456–2473.

Zhang, L.R., Morgenstern, H., Greenland, S., Chang, S.C., Lazarus, P. et al. (2015). Cannabis smoking and lung cancer risk: Pooled analysis in the international lung cancer consortium. *Int J Cancer* 136, 894–903.