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Cannabis for Chronic Pain: Challenges and Considerations

Running Head

Cannabis for chronic pain: Challenges for modern pharmacy

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Abstract

The National Academies of Sciences, Engineering, and Medicine has found substantial evidence that cannabis (plant) is effective for the treatment of chronic pain in adults, and moderate evidence that oromucosal cannabinoids (extracts, especially nabiximols) improve short-term sleep disturbances in chronic pain. The paradoxical superiority of the cannabis plant over cannabinoid molecules represents a challenge for the medical community and the established processes that define modern pharmacy. The expanding and variable legalization of cannabis in multiple states nationwide represents an additional challenge for patients and the medical community because recreational and medicinal cannabis are irresponsibly overlapped. Cannabis designed for recreational use (containing high levels of active ingredients) is increasingly available to patients with chronic pain who do not find relief with current pharmacologic entities, which exposes patients to potential harm. This article analyzes the available scientific evidence to address controversial questions that the current state of cannabis poses for health-care professionals and chronic pain patients, and sets the basis for a more open discussion about the role of cannabis in modern medicine for pain management. A critical discussion on these points, the legal status of cannabis, and considerations for healthcare providers is presented.

Introduction

Evidence for cannabis for chronic pain

The National Academies of Sciences, Engineering, and Medicine has analyzed current evidence on the health effects of cannabis (plant) and cannabinoids (extracts of the plant or synthetic molecules). The report stated that there is substantial evidence that inhaled cannabis is effective

for the treatment of chronic pain in adults, and moderate evidence that oromucosal cannabinoids (especially nabiximols) improve short-term sleep disturbances associated with chronic pain (and other conditions such as fibromyalgia, multiple sclerosis, and sleep apnea syndrome).[1] These conclusions have been supported by other systematic reviews, meta-analyses, or randomized controlled trials, as we have recently described.[2]

Cannabis mechanism of action

Cannabis exerts its action via its 2 major active components, delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). The major active ingredient in cannabis, THC, activates cannabinoid receptors type 1 and 2 (CB1 and CB2 receptors). Interestingly, CBD does not seem to act through these receptors,[3, 4] Furthermore, CBD may reduce unwanted psychotropic effects of THC and potentiate other effects (i.e. anticonvulsant, analgesic, etc.) when given concomitantly,[5] probably due to its negative allosteric effects of CB1 receptors[3] or its positive modulation of the endocannabinoid system.[5] Other studies have shown that oral CBD does not alter some psychotropic effects induced by smoked cannabis, which indicates that CBD and THC interactions might depend on pharmacokinetics and routes of administration,[6] in addition to their actions on CB1 or CB2 receptors.

CB1 receptors are most widely expressed in the central and peripheral nervous system, while CB2 receptors are mostly expressed in immune cells, and therefore in the periphery.[7, 8] As a result, the mechanism of action of cannabis seems to be through THC via neuronal actions (centrally and peripherally). These actions are not only responsible for the analgesic effects of cannabis, but also for its psychotropic (i.e. euphoric or "high") effects.

Modern pharmacy paradox of cannabis and pharmaceutical cannabinoids

Scientific advancements on the mechanisms of action of cannabis have allowed for extraction of its active components and development of synthetic THC molecules. This makes it possible to hypothesize that pure cannabis extracts or synthetic cannabis extracts (namely THC or THC plus CBD) will provide safe and effective reduction of pain. This hypothesis is based on the normal path that medicine and pharmacy has followed to develop safer and more effective drugs than plants themselves. For example, nabilone and dronabinol are pharmaceutical grade THC molecules currently available and approved by the United States (US) Food and Drug Administration (FDA). Similarly, nabiximols, an oromucosal spray preparation that contains virtually equal concentrations of cannabis extracts of THC and CBD, is an investigational drug in the US (see review article for more details[2]). Surprisingly, and as an unforeseen paradox to modern pharmacy and FDA guidelines and procedures, oral pharmaceutical grade cannabinoids show conflicting results in patients with chronic pain (ranging from not significant to significantly moderate reduction in pain scores over a short-term vs. placebo) based on moderate quality placebo-control trials.[9] They also provide only partial benefits in some aspects related to chronic pain, such as sleep and quality of life (moderate evidence).[10] In addition to their limited efficacy to treat pain, tolerability seems to be a major limitation for clinical use. The number of patients that stop treatment (long-term) with oromucosal cannabinoids due to drug-related adverse events or lack of efficacy is larger than those observed when using the cannabis plant.[2] This evidence indicates that the tolerability and efficacy profiles of oral cannabinoids are inferior when compared to those of the cannabis plant. This has been noted by chronic pain patients who prefer use of the whole plant than oral cannabinoids.[11]

Increasing access to cannabis

Illegal access of cannabis for recreational use has been historically high in the U.S.[12] In fact, cannabis is the most widely used illicit drug in this country, according to the National Institute

of Drug Abuse.[13] (www.drugabuse.gov) Access to cannabis has become more permissive in the U.S. due to advancing legalization of cannabis for medical or recreational purposes in several states. Access to medicinal cannabis has also been relaxed in other countries (www.unodc.org/wdr2016).[14] According to a recent review,[15] approximately 15% of patients suffering from pain in Canada and Australia self-medicate with cannabis to treat their conditions. In general, pain or chronic pain seems to be the major reason for patients to use medicinal cannabis. The abovementioned review revealed that 30%-87% of patients in different patient populations claiming to use cannabis for medicinal purposes report pain or chronic pain relief as the reason for medicinal cannabis use;[15] the results were based on 9 articles from the U.S., Israel, and the U.K.[16-24] Based on these 9 heterogeneous studies, plus 1 additional study using data from a dispensary in California,[25] we empirically estimate a median of 78% (95% CI: 31 – 82.6) of patients reporting pain as a reason for cannabis use among these diverse populations.

Even though enhancing access of cannabis for the treatment of pain could be beneficial for patients with no treatment options, this also entails risks. One of the major public risks derived from legalization of cannabis for medicinal purposes is that there is no compelling scientific evidence that cannabis provides any benefit for a multitude of medical conditions.

Should patients use cannabis or cannabinoids for pain management?

Pharmacy has progressed from botanical preparations to the development of pharmaceutical graded, safe and effective treatments for multiple ailments. Some success pertinent to pain relief and alleviation has been achieved with analgesics, i.e. opioids and opiates. However, the current widespread and alarming addiction rates and deaths from opioid misuse, abuse, and diversion, plus the modest or minimal efficacy of opiates for chronic pain have shown the biomedicine community that safer pharmaceutical alternatives are needed. Current procedures and standards in medicine and pharmacy have allowed progression from the cannabis plant to

cannabinoid extracts with pharmaceutical grade. Yet, chronic pain patients use the cannabis plant as medicine, a more archaic method, to find relief to their ailment. This is understandable because effective chronic pain pharmaceutical treatment options are scarce, while cannabis is becoming increasingly available due to legalization for both medical and recreational use. Also, it is possible that the lack of FDA approval of novel pharmaceutical cannabinoids (THC and CBD combinations) for chronic pain contributes to patient use of the cannabis plant.

The types of chronic pain that inhaled cannabis has been proven to be effective for include conditions with either peripheral or central components, such as human immunodeficiency virus (HIV) polyneuropathy, diabetic neuropathy, post-herpetic neuralgia, complex regional pain syndrome, spinal cord injury, traumatic neuropathic pain, multiple sclerosis, or cervical disc disease.[26-32] Even though these studies used a relatively short-term inhaled cannabis,[33] the efficacy of inhaled cannabis for a prolonged period (6 or 12 months) has been shown in patients with pain (cancer related or unspecified)[34] or chronic neuropathic pain.[35] More evidence is needed to determine whether inhaled cannabis is effective for other types of pain, such as rheumatoid arthritis, chronic abdominal pain, cancer pain, and acute postoperative pain, for which oral cannabinoids are not effective.

Why are THC and CBD extracts less effective and less tolerable than the cannabis plant?

Why are oral cannabinoids inferior to inhaled cannabis? There is no doubt that their bioavailability is significantly different. The erratic and inconsistent pharmacokinetics (PK) of cannabinoids administered orally (dronabinol, nabilone, or nabiximols)[2] is surely a major determinant for the lack of greater efficacy and reduced tolerability when compared to inhaled cannabis. Development of cannabinoids with improved PK that results in a favorable analgesic profile when given orally is an area of research that should be further supported and explored.

Other impacting factors include: lack of standardized dosing, strength and accuracy of dose applications, variability of dose administration, and varying patient compliance factors. As mentioned, the rapid onset of effect of inhaled cannabis and the possibility for patients to titrate is a major advantage for this route of administration when compared to oral cannabinoids.[2] A disadvantage of this mode of administration is the ability, or lack thereof, to properly inhale the product. Although a poor inhalation technique could represent a disadvantage to standardized clinical studies,[36] patients with limited experience in inhalation technique could achieve sufficient analgesic effects by adding more puffs or inhalations. However, this titration strategy is rather problematic and virtually intolerable with oral preparations. A common inhalation technique is smoking the cannabis plant. Inhalation of combustion products by smoking represents a major health risk, which is a concern for regulators, pharmacists, and physicians; therefore, this particular route of administration represents another disadvantage. In poorly regulated markets, the lack of accuracy in the quality of cannabis plant (eg, active ingredient concentrations, pesticide content, microbial contamination) is also a disadvantage for cannabis inhalation.

The molecular content of oral cannabinoids vs. inhaled cannabis plant could also determine the differential efficacy for the treatment of pain. Oral cannabinoids have the advantage of being presented in a standardized concentration and in pharmaceutical graded specific cannabinoids. On the other hand, the cannabis plant has dozens of cannabinoids. Whether the combination of all cannabis-exclusive molecules, plus the possible interaction of major cannabinoids with other molecules present in the cannabis plant (called the "entourage effect"),provides an additional beneficial effect for the treatment of pain is currently unknown, but is definitely a possibility[37] that requires further research.

Challenges that the medical community faces with this scenario are multifactorial and controversial. Modern medicine paradigms do not fit perfectly in line with the cannabis plant used for medicinal purposes. Because use of cannabis will continue and most likely expand in the near future, it is imperative for healthcare professionals to understand, control, and adapt key aspects of current pharmacy and medicine procedures in relationship to cannabis. This approach will reduce the risks that entail the use of cannabis to manage pain. The key factors of modern pharmacy and medicine that will provide a safer scenario for patients include: A) safe route of administration (toxic free), B) predictable PK profile, C) pharmaceutical grade product (purity and quality of the product; toxic-free, pesticide-free), and D) known, effective, and safe concentration of active ingredients. It is important to have precise and accurate knowledge about the route of administration and PK of both oral and inhaled cannabis/cannabinoids. Scientific evidence indicates that the inhaled (vaporized) option is more predictable, effective, and potentially tolerable than oral preparations at the moment. The 2 most difficult and controversial aspects to control are the purity/quality of the product and the concentration of active ingredients within the cannabis plant.

Legalization of cannabis for medicinal purposes provides a significant advantage to control the quality of the cannabis plant by setting high quality standards to produce a "pharmaceutical grade", certified safe and clean, toxic-free and pure product with known cannabinoid concentrations. Implementation of these modern pharmacy good practices for cannabis are without a doubt controversial and challenging because it involves growers, producers, physicians, pharmacists, nurses, and dispensary personnel. Increasing accessibility of cannabis requires an urgent standardized and controlled approach or guidelines for the use of cannabis for medicinal purposes in a responsible fashion and closely following state-of-the-art pharmaceutical procedures until better cannabinoid molecules are developed. Given the current scenario and evidence, the scientific community should work in a collaborative and creative

manner to resolve the contradictive premises that cannabis/cannabinoids for pain entails when contrasted with classic FDA procedures.

What are the concerns or differences between medicinal and recreational cannabis for pain management?

Concerns related to medicinal and recreational cannabis

One of the major concerns of cannabis for the treatment of chronic pain is the evident overlap of medicinal and recreational use of cannabis. Access of cannabis is becoming more flexible in light of the increasing number of states legalizing cannabis for either purpose. Whether this could result in an increase in cannabis use and, potentially, diversion or abuse is not completely clear because there are studies with mixed results on this regard. It has been suggested that legal protection of dispensaries could result in an increase in recreational use of cannabis,[38] and that there is an association between density per a given area of dispensaries and delivery services and cannabis use.[39] The states in which medicinal cannabis is legalized have shown higher rates of cannabis use,[40] but legalization of recreational cannabis is not always associated with an increase in cannabis use.[41] Medical cannabis programs in other countries, i.e. Israel and Canada, have shown the benefits (particularly for pain patients) of having organized, segregated, and well differentiated medical programs from the recreational realm.[34, 35]

Differences between medicinal and recreational cannabis

It is important to highlight that the use of cannabis for recreational purposes is not equivalent to cannabis use for chronic pain management. Perhaps the most obvious difference between cannabis for recreational and medicinal use is the concentration of THC. In the available randomized clinical trials of inhaled cannabis for chronic pain,[26-32] the concentration of THC for cannabis was never higher than 10%, ranging from 0-1.29% to 9.4%. In fact, in several

studies,[28, 30, 32] significantly lower THC concentrations (1%, 1.29%, or 2.9%) have shown sufficient efficacy to manage pain. Furthermore, in virtually all of these studies the highest THC concentration used consistently yielded side effects that resulted in several instances of treatment discontinuation. The contrast with the THC concentration found in cannabis for recreational purposes cannot be greater. According to a 2009 report regarding THC concentration in confiscated cannabis in different forms, the highest THC concentration for cannabis was 37% (average of 13% in 2009 vs. 3% in the 1980s).[42] Strikingly, high THC cannabis could be easily found in the vast majority of dispensaries or cannabis stores. A visit to well-known cannabis websites (eg, www.weedmap.com™, www.marijuana.com™, www.leafly.com™) confirms the broad availability of cannabis varieties, chemovars, or preparations with high concentrations of THC and CBD. Furthermore, these cannabis varieties are advertised for medical purposes, including the type of ailments that specific varieties treat, and links to medical and recreational cannabis dispensaries, which shows the overlap that exists between recreational and medicinal cannabis.

On one of these websites, the user or patient can find hundreds of cannabis chemovars divided by varieties (sativa, indica, or hybrids). Each variety of cannabis is matched with recommendations to multiple pathological indications, unsupported by scientific evidence, which is formulated in recreational use language (Table 1). For example, when cannabis is sorted by "ailment", selecting "back pain" for instance, the site provides over 100 chemovars. These varieties highlight their high content in THC, and typically low concentration of CBD and cannabinol. In most cases, there is little or no information on how or where these cannabinoid concentrations were measured, content of other cannabinoids, terpene profile, or toxicological report. On these websites, the cannabis varieties that contain the highest concentrations of THC, typically above 15% (many with 30% THC), are the best rewarded, most popular, and are paired with more medicinal potencies. Perhaps the information on these websites could orient

recreational cannabis users, but their information about cannabis medicinal properties is not rigorous or supported by scientific evidence. Thus, chronic pain patients visiting these sites to obtain information about cannabis are exposed to this information and linked articles that enthusiastically celebrate cannabis varieties with higher than 20% THC concentrations, including competitions and prizes. It seems clear that these websites are filling an informational (and business) gap that has been left open by the scientific pharmacy and medical community.

Evidence for medicinal cannabis with 10%-15% THC content

While cannabis for recreational use seems to be focused on obtaining the higher THC concentration cannabis strains, pharmacologically and medically, more THC is not necessarily better, particularly for cannabis-naïve patients. It has been shown that even experienced and regular cannabis users (who might have developed a certain degree of tolerance, therefore needing higher concentrations of THC to experience its effects) find pain relief when inhaled cannabis with 12.5% THC is used for 12 months.[35] In the COMPASS (Cannabis for the Management of Pain: Assessment of Safety Study) trial, regular users consumed significantly more cannabis than non-current users and cannabis-naïve subjects (median 2.8 g/d; range: 0.2-13.4 vs. 1.8 g/d; range: 0.1-3.7 or 2.0 g/d; range: 0.1-3.4, respectively and 2.0 g/d; range: 0.1-3.4 for naïve subjects). Patients who inhaled 12.5% THC cannabis had higher adverse events (mild to moderate) than the non-cannabis users control group.[35] Therefore, recreational cannabis that contains higher THC levels does not seem to be compatible with cannabis for medicinal purposes. It is worth noting that the adverse events observed in the COMPASS study using cannabis[35] were similar to the ones observed in a recent placebo-controlled clinical trial using dronabinol.[43] In this 48-week study, dronabinol did not show superiority to placebo for pain intensity.[43] Interestingly, dronabinol-induced side effects were higher than placebo but were reduced after 4 weeks of administration, suggesting that tolerance could be developed in a relatively short time when pure THC is given orally.

The exposure of chronic pain patients to cannabis with high THC concentrations puts them at risk of experiencing side effects or adverse events without further beneficial effects, and of developing tolerance or potential abuse. It seems that patients with history of long-term cannabis use could get pain management benefits with 10%-15% THC. Figure 1 shows the major aspects of cannabis for recreational or medicinal use in relation to its THC concentration and potential outcomes.

What considerations should pharmacy practice, physicians, and healthcare professionals evaluate for patients using cannabis for pain management?

Potential misuse and/or abuse

Regardless of the position (pro or con) on the use of cannabis for the treatment of chronic pain, physicians, nurses, pharmacists, dispensary personnel, and healthcare providers in general should be informed about the different aspects of the use of cannabis, and provide guidance and professional support to ensure safety and pain relief to patients. With cannabis being a substance with potential for abuse, this possibility should be kept in mind when a patient is using cannabis (either medically or recreationally).

Around 13.5% of people 12 years of age or older in the US reported using marijuana in 2013 (The CBHSQ Report, https://www.ncbi.nlm.nih.gov/books/NBK343537/). [44] A subgroup of these patients will report problems of cannabis abuse. According to the report of the National Academy of Sciences on Medicinal Cannabis, there is substantial evidence that suggests that consumption of cannabis at early ages represents a risk of developing problems with cannabis use. The report also indicates that the frequency of cannabis use is associated with progression to cannabis abuse.[1] In fact, approximately 18.8% of people who use marijuana daily develop cannabis use disorder.[45]

Vulnerable populations

Physicians should take into consideration the characteristics of each patient and evaluate the risks before recommending marijuana or its discontinuation. For instance, there is substantial and moderate evidence that the following groups of patients are at risk of developing problems of cannabis use: males who smoke cigarettes, adolescents who consume cannabis regularly or exhibit oppositional behaviors, adolescents with poor school performance or antisocial behaviors, and patients who started to consume alcohol or nicotine at a young age or experienced childhood sexual abuse.[1] Although alcohol or nicotine dependence alone does not represent a risk factor for the progression to cannabis abuse, the evidence indicates that a combined use of abused substances presents a risk factor for the development of problem cannabis use.[1]

There is also moderate evidence suggesting that patients with major depressive disorders are vulnerable to developing cannabis addiction or use disorder.[1] However, in a recent cross-sectional study, patients with chronic pain using medicinal cannabis displayed lower prevalence levels of depression and anxiety than chronic pain patients using prescription opioids.[46] Because depression often accompanies chronic pain, physicians should pay special attention to patients suffering chronic pain and depressive disorders who use cannabis.

Patients with posttraumatic stress disorder (PTSD) and patients with a history of psychiatric treatment should also be monitored for possible cannabis abuse. There is moderate evidence suggesting that cannabis abuse is associated with psychiatric treatment and an increase in severity of PTSD symptoms.[1] However, cannabis has been anecdotally associated with PTSD symptom relief, and several clinical trials are ongoing.

The use of cannabis enhances the risk of developing psychotic outcomes. This risk has a THC concentration- and use frequency-dependence.[47] Patients with cannabis-induced psychosis, have a high risk (approximately 50% rate) of conversion to schizophrenia or bipolar disorder, especially in young adults (16-25 years).[48] Therefore, it is advisable to avoid the use of cannabis in these populations. This body of evidence argues against the use of high THC cannabis (>10%-15%) for long periods of time, which is of particular relevance in the management of chronic pain.

Interactions with opioids

Another obvious consideration in the treatment of chronic pain and the use of cannabis is its potential interaction with opioids. More than 35% of individuals using cannabis for medicinal purposes use cannabis as a substitute for opioids or narcotics for the treatment of pain, and at a lesser extent for anxiolytics and antidepressants.[49] Furthermore, inhaled (vaporized) cannabis seems to provide a better analgesic feeling when combined with opioids in patients with chronic pain.[50] Similarly, patients using prescribed pain medicine who use cannabis to treat pain, report that cannabis is more efficacious than their prescribed pain medicine.[51] In fact, in a recent open-label study, cannabis (6%-14% THC, 0.2%-3.8% CBD) taken daily for 6 months resulted in a significant reduction of pain symptom score, pain intensity score, and pain interference score.[52] In addition, as a secondary outcome, a significant proportion of patients (44%) using opioids discontinued opioid consumption with cannabis intervention.[52] In retrospective studies, a similar association between cannabis use and a reduction in opiate use for chronic pain has been observed.[53, 54] The use of cannabis as an alternative to pharmaceutical drugs for pain treatment has also been reported.[55] The notion that the use of cannabis could result in a reduction of opioid use is supported by the fact that the opioid overdose mortality rates are reduced in states where medical cannabis has been legalized.[56] Similarly, medicinal cannabis has been found to be associated with a significant reduction in opioid dependence or abuse and overdose hospitalizations,[57, 58] and with a reduction in the

use of prescription medication for pain and other conditions (in Medicare part D).[59, 60] This

body of evidence suggests that the concomitant use of cannabis with opioids could result in

a reduction of cannabis and opiate concentrations for pain relief.[50] According to a recent

meta-analysis, cannabinoids produce an opioid-sparing effect in pre-clinical studies;

however, more high quality clinical studies are needed to confirm these results.[61]

Interestingly, a recent randomized, double blind, placebo-controlled study has shown that

low doses of oxycodone (2.5 mg orally, but not 5 mg orally) plus low THC concentration

cannabis (5.6% smoked) increased tolerance to experimental cold pain in healthy

individuals, compared to a lack of effect with either drug alone, which suggests synergistic

analgesic effects.[62] This study also found that oxycodone does not induce subjective

changes that are indicative of cannabis abuse liability with the doses tested.[62] However, this

study found that cannabis induced a slight but significant change in some subjective aspects

of 2.5 mg oxycodone abuse liability.[62]

Even though prescribed pain medication does not result in higher consumption of illicit drugs

or alcohol in medicinal cannabis users,[51] the abuse potential of cannabis and opioids

warrants stringent caution for patients using both drugs.[63] It is worth pointing out that the

abuse potential or risk of abuse of cannabis vs. opioids is much more favorable to cannabis.

Nevertheless, this cautiousness should not be solely driven by the use of cannabis in chronic

pain patients, but also by the fact of chronic pain itself. A cross-sectional study of 589

subjects demonstrated that approximately 87% of patients with illicit drug use or prescription

drug misuse and 51% of patients using illicit drugs (cannabis, 42%; cocaine, 43%; or heroin,

71%) reported chronic pain or pain, respectively, as the reason for using 1 or more of these

drugs.[64] Therefore, close monitoring of patients with chronic pain, in general, and, in

particular chronic pain patients using opioids and/or cannabis, is recommended for potential

drug interactions between cannabis and opioids, as well as with other illicit drugs. One

approach to better monitor these patients is repeated quantitative urine toxicology analysis,

which could improve compliance and pain management in patients using opioids. This

monitoring process could be used to determine whether concomitant use of cannabis with opioids (or other prescription drugs) results in a reduction of opioid or opioid and cannabis use for pain management, rather than as a means to discontinue opioid treatment.

Supportive and multimodal approaches

The clinical presentation of patients with chronic pain is multifactorial and, therefore, healthcare providers should keep in mind that patients using cannabis for pain management would present with other clinical conditions that should be taken into consideration for their therapeutic approach. For example, veterans who use cannabis for the treatment of pain present clear signs and symptoms of PTSD and sleep-related problems.[17] It is possible that these patients may obtain some benefits for their sleep problems with cannabis; however, as stated previously, there is no sufficient scientific evidence that supports beneficial effects of cannabis for conditions such as PTSD. It should not be assumed that cannabis would be beneficial for all the clinical conditions that a patient with chronic pain presents with. In other words, the efficacy of cannabis for the treatment of chronic pain in some patients should not prevent enrollment of these patients in a multimodal therapeutic approach that helps them achieve functional restoration and reduction or discontinuation of pain medicine or cannabis for the treatment of pain. A non-randomized, non-blinded, small sample size exploratory study with 24 subjects per group showed that a program that includes self-management strategies, group-based cognitive behavioral therapy, biofeedback and relaxation, psychoeducation, physical therapy, occupational therapy, and management of mood and stress, are equally effective in chronic pain patients who use cannabis and those who do not use cannabis for their treatment of pain. Both groups reported significant (and similar) improvements in pain severity, pain interference, depressive mood, and pain catastrophizing.[65]

It is also likely that patients with chronic pain are taking other medications different from opioids; therefore, drug interactions and treatment compliance are other factors to take into consideration. Very little is known about how cannabis could interact with other drugs or how cannabis will affect other drug treatment compliance, i.e. nonsteroidal anti-inflammatory drugs or glucocorticoids, that are used in pain patients.

Observations on the legal aspects of cannabis

The scientific evidence presented demonstrates that cannabis does not only have potential for clinical use, but it also demonstrates that it is clinically useful for the treatment of chronic pain, and seems to be safe and tolerable for long-term use under medical supervision. However, clear monitoring parameters and extreme caution are required to standardize its extended use. Currently, the Drug Enforcement Agency (DEA) maintains cannabis and cannabinoids as schedule I substances (no accepted medical use, no accepted safety for use under medical supervision, and high potential of abuse). In 2016, the DEA issued a report following recommendations from the Department of Health and Human Services that performed a scientific and medical evaluation.[66] This report confirmed the schedule I stastus for cannabis indicating that there were no available scientific data to address the effectiveness, efficacy, pharmacology, toxicology, or safety of cannabis. The current DEA cannabis status has prevented development of more efficient and scientifically rigorous research, and resulted in the current cannabis social and legal developments in multiple states within the U.S., in which the medicinal value of cannabis is being negligently and irresponsibly utilized to enhance access to recreational cannabis. As a consequence, cannabis legalization follows a wide variety of legal provisions among states, in some cases mixing medicinal cannabis with recreational cannabis. Legalization of medicinal cannabis led by the states should be conducted in a more responsible fashion, avoiding overlap with recreational use.

Multiple areas require improvement to separate medical orientation of dispensaries from the recreational realm. More educational strategies should be in place for patients, but also for physicians and dispensary managers and staff. Similarly, it is the responsibility of scientists and researchers to establish the differences between medicinal and recreational cannabis and to develop guidelines for medical purposes and warnings for recreational uses. Likewise, the medical community and healthcare providers (including managers and staff members of cannabis dispensaries) should be accountable to follow scientific evidence and guidelines to protect patients who find benefits in medicinal cannabis, for example, in the treatment of chronic pain. Additional measures that could be taken include physical and business separation of dispensaries for medical cannabis and recreational cannabis programs, limitation of THC concentrations for medicinal purposes to lower than 10%-15%, requirement of the presence of a pharmacist in medical cannabis program dispensaries, avoidance of cannabis names that are used in the recreational domain, strict requirements for quality control (eg, active ingredient concentration, meticulous terpene profile, pesticide/microbial test certification), and a mandatory educational and certification program for dispensary staff in medical programs (similar to pharmacy technicians). Scientists and healthcare professionals should be involved in this process and lead these efforts. The lack of action of federal authorities regarding cannabis medicinal potential, cannabis use regulation, and cannabis research certainly does not provide any help in improving the current situation of cannabis legalization at a state level. The current cannabis legalization process has resulted in an alarming disproportion of participants in medical and non-medical programs. Thus, legal non-medical cannabis programs enroll more than 99% of all participants in the U.S., and their rates of enrollment are 20 times greater than legal medical cannabis programs, perhaps due to the fact that non-medical programs are older and less regulated than more recent medical programs.[67]

It would be naïve and irresponsible from both the healthcare community and policy and law makers to keep the *status quo* for medicinal cannabis, especially in light of the lack of effective treatment for syndromes like chronic pain, the enormous social and financial burden that chronic pain represents, and the use of opioids for chronic pain, which possess higher risk of misuse, dependence, diversion and addiction than cannabis.

Conclusions

Based on current evidence, it is concluded that cannabis has demonstrated to be effective in chronic pain, and has the potential to reduce opioid consumption. Currently, there are very few options for the treatment of chronic pain. Any of the currently approved drugs have a very modest effect (approximately 30% pain reduction) in only a subpopulation of chronic pain patients (approximately 50%) with or without improvements in function.[68] In addition, pain drugs produce multiple side effects that limit clinical use. Chronic pain affects approximately 100 million adults, and costs $560-$635 billion in the U.S.[69] Opioids are recommended as an option for the treatment of chronic pain, despite their lack of superiority to non-opioid options and high potential for dependence: 1 day of therapy has a 6% probability of resulting in long-term opioid use (1 year, indicative of dependence), 8 or more days of therapy has a 13.5% probability, and 31 or more days of therapy has a 29.9% probability of long-term opioid use.[70] In comparison, the probability of dependence on cannabis after 10 years of use is 5.9% (ever users), and the lifetime probability is 8.9% (ever users).[71] Even though in past-year daily or weekly users the risk of dependence is approximately twice as high, 17%-18.8%,[45] this risk is considerably lower than that of opioids,[71] nicotine (46%-50%),[45] or cocaine (50%).[45]

Modern pharmacy and the biomedical research communities should implement creative new parameters to overcome the challenges cannabis represents in order to ensure effective and safe patient pain management. Further rigorous scientific research is urgently needed to understand the mechanisms of action of cannabis and develop more efficacious drug

therapy alternatives with reduced side effects. These necessary advancements would be achieved in a more efficient way if current restrictions for cannabis access were reduced.

All healthcare providers and personnel involved in the treatment of patients with chronic pain and cannabis use should exercise extreme caution in monitoring patients, and base their treatment decisions on scientific evidence in order to provide a more safe pain management plan in this vulnerable population. There are health science continuing educational programs that provide in depth training for healthcare professionals (i.e., The Skaggs School of Pharmacy and Pharmaceutical Sciences in Denver, Colorado;

http://www.ucdenver.edu/academics/colleges/pharmacy/AcademicPrograms/ContinuingEduc ation/onlineCE/CannabisRMHighlights/Pages/default.aspx). Many more of these types of programs should be offered nationally. Efforts should be made to separate and differentiate the use of cannabis for medicinal and recreational purposes.

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Figure Legend

Figure 1. Representation of cannabis delta-9-tetrahydrocannabinol (THC) concentration (%, Y axis) in inhaled cannabis and the different THC concentration ranges: In blue, THC range supported by scientific evidence for medicinal purposes (lower than 10%); in orange, THC range supported by scientific evidence for medicinal purposes for regular cannabis users, and with higher risks for cannabis-naïve or ex-cannabis users (close or slightly above 10%); in red, concentrations used for recreational purposes (higher than 15%). Note that the THC concentration range for therapeutic purposes does not overlap with the concentrations used for recreational use.

Table 1. Example of the overlap of recreational and medicinal cannabis openly available in the Internet in one of the most popular websites specialized in cannabis[72]. Different types of randomly selected cannabis with high delta-9-tetrahydrocannabinol (THC) concentration matching with medical indications for which there is no scientific evidence

Strain Name	Type	Concentrations	Effects	Indication
Sage	Hybrid	THC: 20% CBD 0% CBN: 0%	Anxious Attentive Creative Energetic Euphoric Happy Relaxed	Anxiety Fibromyalgia HIV Migraines
Pineapple Skunk	Hybrid	THC: 17% CBD: 0% CBN: 0%	Alert Aroused Creative Energetic Sociable	ADHD Back Pain Depression Fibromyalgia Glaucoma Muscle Spasms Multiple Sclerosis Neck Pain PTSD
9 lb. Hammer	Indica	THC: 25.45% CBD: 0.29% CBN: 0.83%	Happy Relaxed Sleepy	Back Pain Insomnia Neck Pain PTSD
Caveman Kush	Indica	THC: 19% CBD: 1% CBN: 1%	Euphoric Hungry Relaxed Sleepy	Back Pain Headaches Insomnia Nausea Neck Pain
Ft. Collins Cough	Sativa	THC: 20% CBD: 0%	Anxious Attentive	ADHS Asthma

			CBN: 0%	Giggly	Back Pain
				Motivated	Crohn's Disease
					Epilepsy
					Fibromyalgia
					Glaucoma
					HIV
					PTSD
AK47	Sativa	THC: 20%		Creative	Arthritis
		CBD: 0%		Energetic	Back pain
		CBN: 0%		Euphoric	Depression
				Hungry	Headaches
				Sociable	Insomnia
					Nausea
					Neck Pain

ADHD, attention deficit hyperactivity disorder; CBD, cannabidiol; CBN, cannabinol; HIV, human immunodeficiency virus; PTSD, post-traumatic stress disorder; THC, delta-9-tetrahydrocannabinol