Role of Medicinal Cannabis as Substitute for Opioids in Control of Chronic Pain:

Separating Popular Myth from Science and Medicine

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Introduction

Messages that marijuana is the solution to the opioid crisis are everywhere: billboards, mainstream press, conservative media and cannabis industry websites. They include statements that cannabis can effectively substitute for opioid medications to control chronic pain and that cannabis legalization can reverse the epidemic of opioid-related overdose deaths.

Many recovery professionals are skeptic and suspicious about these claims. Often, their response to these optimistic statements is a laconic “there is not research enough to support any of this”.

This skepticism has been reinforced by the current US administration, by equating cannabis to opiates. The President’s Commission on Combating Drug Addiction and the Opioid Crisis, headed by former New Jersey Gov. Chris Christie, released a report in November 2017 stating: "The Commission acknowledges that there is an active movement to promote the use of marijuana as an alternative medication for chronic pain and as a treatment for opioid addiction. . . . The Commission found this very disturbing. There is a lack of sophisticated outcome data on dose, potency, and abuse potential for marijuana. This mirrors the lack of data in the 1990’s and early 2000’s when opioid prescribing multiplied across health care settings and led to the current epidemic of abuse, misuse and addiction. The Commission urges that the same mistake is not made with the uninformed rush to put another drug legally on the market in the midst of an overdose epidemic." (p. 10-11) https://www.whitehouse.gov/sites/whitehouse.gov/files/images/Final_Report_Draft_11-1-2017.pdf

This brief synthesizes current scientific evidence around the claims that cannabis can substitute for opiates in the management of chronic pain, and that cannabis legalization can prevent opioid-related deaths. It focuses on research conducted in the U.S. or reviewed by North American scientists in the context of current U.S. policies. It considers both population-based studies as well as studies that look at the behavior of individuals.

Types of studies

Pre-clinical - involves the evaluation of potential therapeutic interventions in cells and animals.

Clinical research – involves human subjects and health-related outcomes. It includes longitudinal (following people over time), cross-sectional (e.g., surveys, interviews) and ecological studies (e.g. analysis of how drug policies and outcomes are associated over time)

Clinical trials – studies in which one or more human subjects are randomly assigned to one or more interventions to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.

Is Cannabis Effective for Chronic Pain?

The human body's responses to pain are regulated by multiple brain areas, including our internal opioid and cannabinoid systems. When in pain and/or stress, we release endorphins.[2] Less known but well documented is that we also release endo-cannabinoids, in an attempt to bring our bodies back to balance[4]. Pre-clinical studies have long demonstrated that external cannabinoids (such as those found in the marijuana plant) have the ability to enhance body's own response to pain by binding with our endocannabinoid receptors [5].

To date, 28 well conducted randomized clinical trials (RCTs) have documented that cannabinoid agents are effective analgesics for chronic pain [7]. An Expert Review Committee assembled by the National Academy of Sciences (NAS) in 2017[8] concluded that "there is substantial evidence that cannabis is an effective treatment for chronic pain in adults." (p.90) Still, according to NAS, the effect size of cannabis in treating pain is modest, which challenges the popular myth of a "miracle drug," while debunking the myth that people who report benefiting from cannabis use are just making an excuse to "get stoned".

A caveat to these findings is that none of these randomized trials used the marijuana products legally available for purchase in the U.S. Thirteen (out of 28) RTCs tested the efficacy of the Nabiximols[8], a cannabis botanical extract not available in our country. Commercialized under the name of Sativex in 28 countries (including Canada and UK), Nabiximols is produced by a pharmaceutical company based in England. Sativex presents equal concentrations of THC and CBD and is sold as an oral mucosal spray.

Another five trials evaluated synthetic THC (Nabilone)[8], which is available in the US but has low-acceptability among patients, since THC alone has a high propensity of induce very intoxicating and dysphoric effects [6].

The remaining studies used cannabis provided by the National Institutes on Drug Abuse (NIDA), as required by federal law, a product that bears little resemblance with the cannabis products that are available in Washington's regulated marijuana market. NIDA-controlled cannabis has a much lower concentration of THC and is only provided rolled as joints.

In conclusion, and as stated in the National Academy of Sciences report "…while the use of cannabis for the treatment of pain is supported by well-controlled clinical trials…. very little is known about the efficacy, dose, routes of administration or side effects of commonly used and commercially available cannabis products in the United States" p.4-4. [8]

This somewhat awkward state of affairs has been one of the many factors sustaining the continuing U.S. debate about the role of cannabis in the treatment of chronic pain. The evidence supports the use of cannabis for the treatment of chronic pain, but skeptics point to the

DEFINITIONS

Cannabinoid agents: include cannabis plant, cannabinoids. THC-only and Cannabis-based medicines, as defined below.
Cannabis (or marijuana) refers to the whole cannabis plant.
Cannabinoids: natural, unique components found within the cannabis plant. The most well-known cannabinoids are:
Delta-9-tetrahydrocannabinol (THC), which causes the psychoactive effects of cannabis and is usually the component sought by non-medical users. Medicinally, THC is a powerful analgesic, antispasmodic, and muscle relaxant, with 20 times the anti-inflammatory power of aspirin and twice that of hydrocortisone[1].
Cannabidiol (CBD): CBD has neuroprotective, anti-inflammatory, analgesic, and anticonvulsant properties.[3] Another important property of CBD is that it has the capacity to "tame" THC effects such as euphoria, memory loss, paranoia, and anxiety.(6)

THC- based Medicines
Dronabinol: available in the U.S. since 1985, is semi-synthetic THC in capsules, marketed under the trade name Marinol.
Nabilone: available in the US since 2006 and is synthetic THC in capsules, with the trade name Cesamet. It is indicated as an antiemetic for cancer patients and is used off-label to treat fibromyalgia pain.

Cannabis-based Medicines
Nabiximols: Cannabis plant extract, commercialized in 30 countries, including 20 countries in Europe and in Canada, as an oral mucosal spray under the trade name Sativex. Sativex contains the whole plant extract with manipulation of THC and CBD to very similar levels.
https://www.gwpharm.com/products-pipeline/sativex-delta-9-tetrahydrocannabinol-and-cannabidiol

fact that the products available in the U.S. have not been properly investigated to date. While some progress is being made that may allow the US-based scientific community to resolve this impasse, the information available at this time can be used to support convincing arguments in many directions.

In the meanwhile, the U.S. health system have been addressing the epidemic of chronic by prescribing opioid-based medications, despite the many risks involved in this practice and the lack of good quality clinical randomized trials support for the efficacy of opioid medications for pain lasting more than 90 days [9].

Can Medicinal Cannabis Substitute for Opioids in the Treatment of Chronic Pain?

No RCTs have been conducted to date comparing the effectiveness of opiate vs. cannabis-based products on chronic pain. The absence of these studies are related to the federal barriers to conducting research using marijuana and the difficulty of getting them ethically approved. A true random clinical trial would involve randomizing chronic pain patients to take either a FDA approved product or a Schedule 1 drug (the federal classification meaning that a substance has no medical benefits and high abuse potential). Fortunately, policies permitting research are slowly changing at a state level: Colorado Public Health Department has funded a RCT using state marijuana taxes on this very topic. The study, which will be completed in 2020, will assess for the first time how cannabis compares to Oxydone and placebo in reducing chronic back and neck pain. https://clinicaltrials.gov/ct2/show/NCT02892591

Meanwhile, many people suffering from chronic pain have access to cannabis in the US: relief from pain is by far the most frequent condition reported by medical cannabis (MC) patients [8, 10, 11] and many MC patients indicate that they have been substituting all or some of their prescribed opiate-based medications with cannabis. Bruce et al [12] conducted semi-structured interviews and identified three main patterns of MC use: alternative, complimentary, or as a tapering-off mechanism to prescribed medications. Specific reasons to use MC as alternative to opioids included acting more quickly, reducing potential harm, better management of symptoms, and fewer side effects. Corroon et al [13] utilized an online questionnaire to survey 1248 cannabis users. About half of them (46%) reported using cannabis as a substitute for prescription drugs; the most frequent substitution was narcotics/opioids (35.8%). Reiman et al [14] examined the use of cannabis as a substitute for opioid-based medication in an online survey of 2897 cannabis patients. Thirty percent of the sample (n=841) reported using an opioid-based pain medication currently or in the past 6 months; of these, 61% were also using cannabis. The vast majority of these patients (97%) reported using less opioids when using cannabis, and experienced more tolerable side effects with cannabis than with opioid medications alone (92%). They also reported preferring cannabis to opioids for the treatment of their condition and would consider choosing only cannabis if it was more readily available (93%). A study among MC patients in Michigan [15] found that MC use was associated with decreased opiate medication use, reported improvement in quality of life and better side effect profile. In Canada, two surveys among MC adults [16, 17] found that substituting cannabis for prescription drugs was common and that the most frequent form of substitution was for opioid medications.

These studies are important in shedding light on an under-researched public health issue, but they have limitations. The studies vary in sample size and measures, and rely mostly on self-report of a select group of people - those who are open to try cannabis, benefit from its use, and are willing to participate in surveys. Also, inherent to their cross-sectional study design, they do not follow people over time, relying instead on research participants to determine the order of reported events.

Two recent studies of individuals utilized research procedures that are more robust [18, 19]. Both studies compared chronic pain long-term opioid patients who report MC use with those who not use MC; the findings were not based solely on self-report. One of these studies used a cohort design, meaning they were able to follow up research participants for a period of time [19].

The first study [18] was conducted in Oregon State, in two health care systems (VA Portland and Kaiser Permanente NW). It used a cross-sectional design to compared characteristics of patients that were prescribed long-term opioid therapy (LTOT) who endorsed MC for pain to patients who did not report cannabis use. The authors leveraged validated measures of pain and quality of life collected in their clinical practices and administrative database and medical records for the study, instead of self-report. They did not find significant differences between the 18% LTOT patients who reported MC use and those who did not (82%) in terms of pain-related variables, depression, and anxiety. Differences in use of tobacco and hazardous alcohol use was not significant, after using multivariate analysis to control for confounders. The only statistically significant difference detected between the two groups was a higher risk of prescription opioid misuse among the LTOT plus MC group. This finding, while clinically important, is hard to interpret in a cross-sectional study: it could be that patients more likely to misuse prescription opioid are proactively preventing opioid use escalation by seeking MC; it could also mean that the use of MC among those with higher risk for opioid misuse is an indicator that these patients are at high risk for substance misuse in general.

The second study [19] was conducted in New Mexico utilized the Prescription Monitoring Program to assess opioid prescriptions filled. This preliminary cohort study design followed 37 habitual opioid using, chronic pain patients for 21 months, as they enroll in a MC program (MCP). These individuals were compared to 29 patients equally using opioid and presenting chronic pain, who were offered to enroll in MCP but declined. By the end of the observation period, 40.5% of MCP and 3.4% of non-MCP patients ceased opioid prescriptions. Reduction in opioid dosages was also observed: MC enrollees presented a 47% reduction in daily dosages, while non-MC enrollees increased their doses by 10.4%. Results were significant after controlling for other variables, using regression analysis. MCP participants also indicated improvements in pain reduction, quality of life, social life, activity levels and concentration and few side effects from using cannabis one year after enrolling in the MCP.

The studies reported in this section are consistent not only with the knowledge that cannabis is effective for pain [8] but also with preclinical research that has documented that cannabis and opiates can work synergistically in the treatment of chronic pain. Studies in rodents have demonstrated that THC stimulates beta-endorphin production, interacts with endogenous opioids, and can prevent the development of tolerance to and withdrawal from opiates [20] and even rekindles opiate analgesia after a prior dosage has become ineffective [1, 21].

In conclusion, the evidence so far suggests that – among people who are open to using cannabis – substitution of cannabis for opiates, while not risk-free, can be beneficial in preventing opioid dose escalation and in controlling chronic pain. Considering the high overdose risk of opioid-based medications these findings are reason for optimism and underscore the urgency to conduct research on medicinal cannabis soon.

Can Cannabis Legalization Help to Prevent Opioid-related Deaths?

An association between medical marijuana laws and decreased opioid-related mortality has been documented in a well conducted study published in the prestigious journal JAMA Internal Medicine, in 2014 [22]. The authors compared opioid analgesic overdose mortality in the 50 U.S. states from 1999 to 2010 in states with and without legal access to MC. They found that rate of overdose mortality increased overtime nationwide, but that states with MC laws had a 24.8% lower overdose mortality; this decrease was accentuated the longer the policy was in effect.

This promising study used an ecological design, a “real world” analysis of two historical trends. While not detecting causation, the plausibility that MC laws decrease opioid mortality is strong, considering the narratives of medicinal patients who attribute their reduction or cessation of opiates to the use of cannabis. These findings are also consistent with a recent study [23] that identified a drop in Medicare prescriptions for drugs that treat pain in MC states; the annual number of annual doses prescribed per physician fell by 1826 doses.

More studies are needed, using stronger research designs and fleshing out the role of other plausible factors before concluding that MC laws are the main factor causing less mortality in states with MC policies. For instance, Phillips and Gazmararian [24] analyzed the role of Prescription Drug Monitoring Programs (PDMP) in conjunction with medical marijuana legislations from 2011 to 2014 and found that the combination of PDMP and availability of MC combined were likely more effective in reducing opioid mortality than PDMP alone.

Final Comments

The use of cannabis to complement or substitute for opiates in the treatment of chronic pain has been described in numerous studies, despite the absence of randomized trials comparing opiate-based and cannabis-based medications in terms of effectiveness, functionality and quality of life.

The need for more funding and fewer barriers to conduct studies on the benefits and risks of cannabis use cannot be overstated. Evidence so far suggests that cannabis may have an important role both in addressing the chronic pain epidemic and the opioid crisis in the U.S. Knowing more is a matter of public health safety.

Cannabis use is not without risk and the boundaries between its use for medicinal and mind-altering purposes are murky [25]. Research available to date has not been conducted with the products current consumers actually use, because current policies do not allow scientist to access these products. Medications available in other countries have not been approved to date by the FDA.

Despite all these barriers, we believe that there is reason for optimism. The National Institutes of Health (NIH) recently awarded a grant to researchers at Albert Einstein College of Medicine and Montefiore Health System for a prospective cohort study that will follow up 250 patients with recent MC certification, severe chronic pain, and opioid use for 18 months. The study starts in 2018 and is expected to be completed in 2022; its overall goal is to understand how medical cannabis use affects opioid analgesic use over time, with particular attention to THC/CBD content, HIV outcomes, and adverse events. (https://clinicaltrials.gov/ct2/show/NCT03268551?recrs=ab&cond=Cannabis&age=1&draw=2&rank=56) Additionally, state-funded research sponsored by cannabis taxes is expected to continue, as public opinion exerts pressure for science-based answers to cannabis legalization. We believe the landscape regarding research on medicinal cannabis is changing, leading to policy and clinical practice that is informed by improved research evidence.

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