The role of medical cannabis in the opioid crisis

Lucy Samoilov, Claire P Browne

ABSTRACT

Opioid use increased dramatically in the 1990s upon introduction of newer, more relaxed regulations. As opioid prescriptions for pain increased, a parallel increase in opioid abuse and addiction occurred; this phenomenon is widely known as the opioid crisis. Cannabis had long been considered a recreational drug until legislation in 2001 allowed highly limited access to the drug for medicinal purposes. Although small-scale clinical trials show promising results for the use of cannabis in pain management, it is not currently indicated for chronic or severe-to-moderate acute pain, for which opioids are typically considered the standard of care. The impending legalization of recreational cannabis may mark a turning point in pain medicine as the general public becomes able to self-medicate with cannabis. This increased availability may lead individuals prescribed opioids to combine or replace them with cannabis, with potential positive impacts. There is growing evidence that cannabinoid compounds present in cannabis are able to augment opioid-induced pain relief. Increased availability of cannabis is linked to decreased opioid-related mortality and hospitalizations; furthermore, cannabis might act as a tool to treat opioid addiction. Cannabis does possess adverse effects and addiction risk, and expanded research into its properties is needed. However, its relatively decreased risk profile and potential positive effects indicate that it may serve an important role in addressing the opioid crisis.

INTRODUCTION: THE OPIOID CRISIS

The opioid crisis has continued to dominate Canadian health news headlines, and the alarming epidemic shows no signs of abating. Canada is second only to the U.S. in the use and abuse of opioids, with 13% of the population relying on these drugs for pain relief. Among users, 2% reported using opioids for non-medicinal purposes, constituting opioid abuse. In the past, opioids were falsely promoted as low-risk and non-addictive; they are now recognized for their notoriously addictive properties (5.5% addiction risk). In 2016 alone, there were over 2,400 opioid-related deaths across Canada.

Originally, opioids were approved in Canada for select populations such as terminal cancer patients. This changed in 1996, when OxyContin was approved for moderate-to-severe pain in all patients. This decision heralded a turning point in pain management and precipitated the current opioid crisis. Opioid use, abuse, and overdose rates have skyrocketed since opioids were approved for use in the chronic pain patient population. A Canadian study found that among opioid-dependent patients admitted to the Centre for Addiction and Mental Health in Toronto, 37% reported receiving opioids from physician prescriptions versus 21% obtained illicitly.

Although there is certainly an iatrogenic component to the opioid crisis, it is particularly difficult to eliminate their use in pain management. No drugs have yet been able to match their powerful and effective pain-relieving properties. Opioids remain the standard of care for many cases of severe acute or chronic pain despite their side effects and potential for addiction and overdose.

CAN CANNABIS BE USED TO ADDRESS THE OPIOID CRISIS?

Another healthcare issue making recent headlines is the legalization of recreational cannabis in Canada, projected to occur on July 1, 2018. These seemingly disparate issues - the opioid crisis and cannabis legalization - could connect in interesting ways. Although cannabis is best known for its psychoactive (“high”-inducing) properties, it may have a role to play in pain medicine and in mitigating the opioid crisis.

Cannabis has been approved for medical use in Canada since 2001 under the Marihuana Medical Access Regulations (MMAR). These regulations were introduced by Health Canada after seriously ill and dying patients fought for their right to pain relief without fear of prosecution, as marijuana was then broadly criminalized. Since then, the regulations have been replaced twice to accommodate modifications; the current iteration is the Access to Cannabis for Medical Purposes Regulations (ACMPR). Under these regulations, doctors can prescribe medical cannabis for any condition they believe it will aid. While guidelines have yet to be set for recreational cannabis, accessibility is likely to increase greatly. Interestingly, the federal government recommends maintaining a separate legal framework for medical prescription of cannabis.

PHARMACOLOGY OF CANNABIS

Cannabis, also known as marijuana, is generated from the bud and flowers of the plant Cannabis sativa. A variety of preparations are available, including smoked, vaporized, edible oil, or capsule form. Cannabis consumption leads to euphoria, altered perception, and decreased anxiety by acting on the endocannabinoid system. In this pathway, endocannabinoid neurotransmitters act on cannabinoid receptors 1 and 2 (CB1 and CB2). CB1 is the most abundant G-protein-coupled receptor in the human brain, and initiates signalling pathways responsible for anxiety, eating, growth, and learning. Its activation also facilitates the dopamine reward pathway, which is heavily implicated in addiction and substance dependence. CB1 inhibition can decrease the ability of substances to activate the dopamine pathway; examples include nicotine, ethanol, cocaine, and opiates.

Cannabis contains a multitude of active compounds; here, we will highlight two of importance: Δ-9 tetrahydrocannabinol (THC) and...
and cannabidiol (CBD). THC is the most abundant compound in cannabis and the sole molecule with psychoactive effects.\textsuperscript{14,15} As a partial agonist of the CB1 receptor, THC produces effects such as euphoria, decreased pain response, and tachycardia.\textsuperscript{20,21} Synthetic THC and its analogues have been used as antiemetics, appetite stimulants, and neuropathic pain relievers.\textsuperscript{22} CBD is the second most abundant compound in cannabis.\textsuperscript{23} It acts as an inverse agonist of CB1 and can cross-react with other receptor systems.\textsuperscript{16,24} CBD possesses antipsychotic effects and can modulate nausea, inflammation, seizures, and anxiety.\textsuperscript{15,16,28}

**IMPACT OF CANNABIS LEGALIZATION**

Although medical cannabis has occasionally been utilized for pain management, its legalization will have important implications for the field. Broader recreational use will facilitate more rigorous studies to remedy the relative paucity of cannabis research.

Initial investigations of cannabis for pain management are promising. Cannabis has mild-to-moderate analgesic properties and can manage chronic pain in some patients.\textsuperscript{15} Cannabis also decreases patient-reported pain when used in conjunction with opiates.\textsuperscript{21} A study of individuals with chronic pain showed a 64% decrease in opiate use when taken alongside medical cannabis.\textsuperscript{24} Other studies describe patient substitution of medical cannabis for opioids or discontinuation of opioid use.\textsuperscript{25,26} This reported augmentation of opioid analgesia is likely due to the effect of cannabis on opioid pathways. As noted above, there is a crossover between the endocannabinoid and dopamine systems; CBD, and to a lesser extent THC, can also interfere directly with opioids by increasing dissociation rates from opioid receptors.\textsuperscript{27} Further investigation into the mechanism of such effects are ongoing.

The ability of CBD to dampen the rewarding effects of opioids, combined with its inability to activate the reward pathway, makes it a promising treatment for addiction and substance abuse.\textsuperscript{28} Preliminary studies show that CBD can help prevent opioid relapse, modulate drug-seeking behaviours, and improve abstinence.\textsuperscript{28,29} However, these investigations use purified CBD or nabiximol, an oral spray containing cannabis extract. It is not yet known whether cannabis consumption will produce similar effects.

Cannabis legalization could help mitigate the opioid epidemic in broader, systemic ways. American states where medical cannabis is legalized have lower rates of opioid-related hospitalization and overdose-related mortality.\textsuperscript{29,30} This may be due to patient substitution of cannabis for opioids, augmentation of pain relief translating to decreased opioid doses, or decreased polypharmacy rates. Legalization of recreational marijuana may also lead to a decrease in opioid-related deaths, as reported in a Colorado study.\textsuperscript{31} It is worth noting that cannabis overdose is very rare, and no cannabis-related overdose deaths have yet been recorded.\textsuperscript{22} These findings suggest that opioid-related healthcare expenses may decrease upon cannabis legalization.

**CHALLENGES AND RISKS OF CANNABIS**

Medical cannabis is not specifically indicated for any condition, including chronic pain. This has likely lead to underutilization - only 7% of Canadian doctors have written a recommendation for medical cannabis prescription.\textsuperscript{32} As the standard of care for pain management is often opioids, a doctor may not consider cannabis as a first line treatment. Health Canada has also discouraged the use of medical cannabis; it states that “[d]ried marijuana is not an approved drug or medicine in Canada” and “[t]he Government of Canada does not endorse the use of marijuana.”\textsuperscript{33} This position, combined with its public perception and complicated legal status, has likely served to deter prescription of cannabis.

Research regarding the use of cannabis in pain management is limited. Although randomized-controlled trials are being conducted, methodologies vary widely and many are currently in pilot stages.\textsuperscript{35} This has led to conflicting results and speaks strongly to the need for larger, more tightly controlled trials. In addition, much is unknown regarding the therapeutic use of cannabis in combination with opioids, including vital information on dosage and safety.\textsuperscript{19,26} This is further complicated by variability in levels of THC, CBD, and other compounds across cannabis strains.\textsuperscript{37}

Physicians should also be alert to the signs of cannabis use disorder, lest one epidemic be replaced with another. Approximately one in ten adults who have used cannabis can be classified as cannabis-dependent; it is more likely in men and younger users.\textsuperscript{38} Cannabis use disorder is characterized by cravings, changed behaviours, problematic usage habits, and altered mental status.\textsuperscript{22,35} THC has also been linked to negative mental health outcomes such as psychotic disorders. The association is strongest in adolescent consumers, and may be related to family history and overall consumption.\textsuperscript{39} Additionally, some studies have reported an association between cannabis use in opioid users and future opioid misuse or dependence.\textsuperscript{40} Given the expected expansion in cannabis use upon legalization, these reports are concerning. It will be important to monitor patients for symptoms or behaviours related to dependence.

**POTENTIAL OF CANNABIS RESEARCH**

Research was previously complicated by accessibility and possession laws, and was limited in applications; legalization will make necessary studies easier to conduct. For example, direct comparisons of opioids and cannabis could indicate whether it could replace opioids for certain conditions, or provide another option where opioids are ineffective or contraindicated. It will also be important to further investigate the use of cannabis as a complement to opioids. Combination therapy may have increased efficacy due to additive effects, facilitating lower doses of each drug; this could decrease side effect rates and mitigate tolerance. Furthermore, medical cannabis may be a therapeutic tool for opioid-dependent patients. Studying the ability of CBD-high cannabis strains to alleviate opiate withdrawal symptoms and prevent relapses could prove enlightening.
CONCLUSION

Currently, opioids remain the drug of choice for pain relief, despite their risk of serious adverse events and addiction. Evidence is accruing regarding the efficacy of cannabis for pain relief, both as monotherapy and in combination with opioids; its ability to interfere in addiction biochemistry is intriguing. Although cannabis carries its own risks, they are less severe than those of opioids. If prescription or self-medication with cannabis leads to a decrease in opioid use, the reduction in risk and harm would be significant. In the long term, cannabis has the potential to decrease burden on the healthcare system and relieve opioid-related morbidity and mortality.

REFERENCES


We want to hear from you!

Please take a moment to fill out our reader survey:

goo.gl/hYN7UT