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Determining the effects of cannabis use on pain reduction in patients already using opioids for chronic pain

Abstract:

Chronic pain is experienced by nearly 1 in 5 Canadians. Pharmacological therapy is the most common, however, most are ineffective and have an abundance of side effects. The effects of Cannabis use on pain-reduction in patients currently using opioids for chronic pain was analyzed in ten studies of varying qualities of evidence. Five out of seven studies that focused on pain relief concluded an improvement in pain relief or improvement in quality of life Four out of six studies found a statistically significant decrease in opioid doses over time in patients using some form of cannabis. Two out of six studies found no temporal relationship between cannabis use and reduction of pain in patients using opioid therapy. Due to the severe limitations in each study, the ability to draw conclusions about the true pharmacological efficacy of cannabis in this literature study was limited.

Introduction:

Chronic pain is experienced by nearly 1 in 5 Canadians (Schopflocher et al., 2011). Chronic pain has high direct costs and indirect costs, with total costs estimated to be $43-60billion annually in Canada (Schopflocher et al., 2011). The impact of pain on the affected individual is also high, as up to 70% of people with chronic pain have comorbid depression and there are also above normal rates of sleep disruption and other mental health concerns (Davis et al., 2011). Current treatment is done to decrease pain intensity (with a reduction of 30% considered meaningful), improve the quality of life and increase function in social, physical and psychological domains (Dale and Stacey, 2016).

Many approaches are currently used for pain treatment, including: pharmacological, psychotherapy, physiotherapy, and combined treatments (Reinecke et al., 2015). The most common treatment for pain is pharmacological therapies (analgesics) due to cheap cost and quick initial relief from pain. However, most are ineffective on their own and come with adverse side-effects (Reinecke et al., 2015; Dale and Stacey, 2016). Due to ineffective responses from most individual treatments, patients end up trying multiple agents and more than a ⅓ of patients end up on multiple interventions (Davis et al., 2011; Dale and Stacey, 2016). Using multiple medications with different mechanisms of action is thought to lead to more effective analgesia and minimize the side-effects from each individual agent (Dale and Stacey, 2016).

One commonly used class of analgesics is the opioids, including codeine, morphine and fentanyl. Opioids bind to the central and peripheral mu, kappa and delta-opioid receptors in the body which prevent the perception of pain through two main mechanisms (Pergolizzi et al., 2017). The first is through inhibition of ascending nociceptive input, therefore decreasing the sensation of pain reaching the brain. The second mechanism is by activating descending pathways in the brain that modulate the transmission of pain to the brain. Although opioids are a common pharmacological agent for both acute and chronic pain, a meta analysis performed in

2018 on 96 randomized control trials comparing opioids with placebo on non-cancer chronic pain revealed that opioid use led to only a slight, but significant reduction in pain (Rosenquist et al., 2019). The effects of opioids combined with their addictive potential have sparked an increase in long-term opioid prescriptions (Pergolizzi et al., 2017). This has led to an opioid crisis, marked by elevated rates of opioid use disorders and opioid overdoses.

Besides the addictive and overdose potential of opioids, they also have side-effects including: gastric upset, constipation, sedation, confusion, hallucination, a decreased seizure threshold and increased suicide risk (Rosenquist et al., 2019). Opioid use is very prevalent in Pine Falls, where many patients attending medical appointments are looking for refills of long-standing prescriptions. Due to the risks associated with opioid use, there is a need to find more effective and less risky therapies.

A potential adjuvant treatment for chronic pain with growing interest from patients and health-care providers is cannabis (Campbell et al., 2018). Cannabis contains a number of active components, most notably the cannabinoids THC and CBD. The cannabinoids act on the cannabinoid receptor CB1 and CB2 that are widely distributed throughout the body (Woodhams et al., 2015). Due to the impact of cannabinoid signalling throughout the body, cannabis is used to treat a variety of medical conditions (Woodhams et al., 2015). However, medical cannabis registries indicate that most prescriptions for medical cannabis are for its analgesic properties (Barone et al., 2018; Boehnke et al., 2019). Systematic reviews and meta-analyses have shown a beneficial effect of cannabis for pain, though the clinical significance is uncertain (Aviram and Samuelly-Leichtag, 2017). Unfortunately, like opioids, cannabis also has potentially detrimental side-effects, including: memory and coordination impairment, mood changes, addictive potential, social implications and the potential for lung injury if smoked or GI side-effects if taken orally (Aviram and Samuelly-Leichtag, 2017).

In rodent models of pain, synergistic use of opioid and cannabinoid 2 receptor agonists leads to a greater reduction in pain and reduced side-effects compared to either treatment alone (Grenald et al., 2017). In humans, some evidence suggests improved pain-reduction when cannabis and opioids are used in conjunction (Nielsen et al., 2017). There is also some evidence that cannabis may be beneficial in lowering doses of opioids and used as an opioid substitute (Sohler et al., 2018; Baron et al., 2018). However, other research has found no effect of the addition of cannabis to opioids for pain management. There are even correlations between cannabis use and lower self-efficacy and increased misuse of prescription opioids (Hefner et al., 2015; Nugent et al., 2018). This conflicting research indicates a need to better delineate the effectiveness of dual therapy of cannabis and opioids on pain, what conditions best respond to treatment and potential adverse consequences of adding cannabis to opioid treatment.

We conducted a review to determine (1) whether cannabis has an effect on pain-reduction in patients concurrently using opioids for chronic pain, and (2) what conditions, if any, were most benefited by cannabis use.

Methods

To answer the proposed research question, an electronic search of PubMed was conducted to identify keywords related to cannabis, opioids and chronic pain. The refined search was; (((((((marijuana) OR medical marijuana) OR cannabinoids) OR THC) OR CBD)) AND ((opioids) OR opiates)) AND ((chronic pain[MeSH Terms]) OR non-cancer pain[MeSH Terms]) . This

resulted in 80 available articles. To attempt to extract a high quality of existing evidence surrounding the research question, the following criteria were put in place:

1. A focus on patient's pain levels or side-effects after the addition of medical or recreational cannabis to a current prescribed opioid pain therapy program
2. One of the following; an experimental study, Systematic/Meta review or an analytical study (cohort or cross-sectional). Case reports were excluded due to small sample sizes.
3. Articles published in English
4. No publication time frame

After two reviewers independently narrowed down the articles in the database, there were 10 articles that matched the above criteria and all were reviewed in full text. Disagreements were resolved by consensus. Outcome data on post-cannabis intervention pain levels, opioid dosages and adverse effects were recorded and compiled. Pain scores were extracted based on the scale used in that publication and if numerical values were not available, other markers such as quality of life were used as a substitute.

Results

From the 10 articles that matched the criteria for the research question, six were analytical studies (two prospective cohort studies, two retrospective cohort studies and two cross-sectional studies) of low quality evidence (Jadad Score). Two articles were Randomized control trials which were double blinded, placebo controlled and of high quality evidence (Jadad Score). One Non-randomized control trial was included in the literature search. Lastly, a secondary data analysis of an RCT was included. All articles included any type of chronic pain in their study except for one RCT that focused on abdominal pain.
Compiling the ten studies led to a sample size of n=3,529. All participants were dealing with chronic pain that lasted greater than 3 months. As well, all participants had already been on an opioid therapy for their pain and cannabis was trialled as an adjunct therapy for pain in all studies. Out of the studies that were analyzed, five studies out of seven that focused on pain relief concluded an improvement in pain relief or improvement in quality of life. Four out of six studies also found a statistically significant decrease in opioid doses over time in patients using some form of cannabis. Three studies commented on the side effects associated with cannabis use in comparison to opioid use. As well, two out of six studies found no temporal relationship between cannabis use and reduction of pain in patients using opioid therapy and two out of six studies concluded that cannabis use was not associated with a lower opioid dose. Another study reported an increase in psychoactive effects with cannabis but did not directly comment on its relation to pain relief. Since the quality of evidence varies for each of these studies, an analysis of each study individually will be most effective in extracting the best evidence and conclusion.

In a non-randomized controlled trial of 21 caucasian participants prescribed opioids, pain was significantly decreased (average 27%, 95% confidence interval (CI) 9, 46) after the addition of vaporized cannabis (Abrams et al., 2011). It was therefore concluded that vaporized cannabis augments the analgesic effects of opioids without significantly altering plasma opioid levels. The biggest limitation in this study was the small sample size.

In an ambulatory pain clinic in Jerusalem, 176 participants in a prospective open label study were given 20 g/month of either cannabis to smoke or ingest in oil form (Haroutounian et al.,

2016). At follow-up, the pain symptom score improved from median 83.3 (95% confidence interval [CI], 79.2-87.5) to 75.0 (95% CI, 70.8-79.2) (P<0.001). The study also found that opioid consumption at 6 months follow-up decreased by 44% (P<0.001). As stated in the study, “The main limitation was the lack of a control group. In treating pain, the placebo effect can be substantial; therefore, our ability to draw conclusions about the true pharmacological efficacy of cannabis in this study is limited” (Haroutounian et al., 2016).

At a medical marijuana dispensary in Michigan, 244 participants were involved in a questionnaire regarding cannabis use in a cross-sectional, retrospective study. 45% of respondents indicated an improved quality of life with cannabis use on top of opioid therapy. Medical cannabis use was associated with a 64% decrease in opioid use (n = 118) (Boehnke et al., 2016). They also found a reduction in side-effects from medication and an improved quality of life. Bias may have been introduced in this trial due to the environment of the cannabis clinic and because the cohort studied already engaged in regular cannabis use.

A study done at the New Mexico Cannabis program found that there was a 47 percentage point reduction in daily opioid dosages relative to a mean change of positive 10.4 percentage points in the comparison group (CI -90.68 to -3.59, p = 0.034) (Vigil et al., 2017). Survey responses 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 enrollment in the Mexico Cannabis Program (ps<0.001) in comparison to the non-enrolled group. The main limitation to this study is that it was not a clinical trial.

A study done in Australia with 1514 people resulted in two different publications that had different conclusions. The participants in this prospective cohort study had been prescribed opioids and then were surveyed on their use of cannabis over 4 years. In one publication by it was found that individuals who had more severe pain were more likely to be using cannabis as an adjunct for pain therapy (Degenhardt et al., 2015). The conclusion was that users report greater pain relief from combination therapy in comparison to opioids alone. However, due to the observational nature of this study and contrasting conclusion found in another study (Campbell et al., 2018) using the same participants limits the inferential nature of this study. For example, Campbell et al. found an increase in generalized anxiety disorder symptoms, and no temporal relationship between cannabis used and pain severity. There was also no evidence of it leading to reduced prescribed opioid use or increased rates of opioid discontinuation.

A secondary data analysis of screening interviews from a randomized control trial done in New York State with HIV affected patients found that cannabis use was significantly associated with a lower odds of prescribed opioid analgesic use (adjusted odds ratio = 0.57 (95% C.I. 0.38–0.87) (Sohler et al., 2018). However, due to the specific cohort used in the study, it is possible that the generalizability of the results are decreased.

A cross-sectional study done in Israel that focused on the mental health effects of Cannabis, Opioids and combination therapy found that the prevalence of depression among patients in the Opiod, Medical Marijuana and OPMM (combination) groups was 57.1%, 22.3% and 51.4%, respectively and rates of anxiety were 48.4%, 21.5% and 38.7%, respectively (Feingold et al., 2017b). Individuals in the OPMM group were at significantly smaller odds for depression (AOR=0.4 CI=0.2–0.83) and anxiety (AOR=0.38; CI=0.19–0.78) as well as moderate (AOR=0.2; CI=0.05–0.76) depression and severe anxiety (AOR=0.26; CI=0.08–0.83) compared to individuals in the OP group alone. A main limitation of this study was that it was difficult to determine causality.

In a retrospective cohort study with 48 patients admitted to a 3-week outpatient pain rehabilitation program, cannabis use as determined by urine THC was not associated with a significantly lower morphine equivalence, pain severity, pain interference, depressive symptoms, and pain catastrophizing (Shah et al., 2017). Limitations included the sample size and interdisciplinary nature of the program, which confounds any study endpoints.

The higher quality evidence that was reviewed on this topic included 24 participants with chronic abdominal pain at Radboud University Medical Centre in The Netherlands (de Vries et al., 2016).. Although the sample size was relatively small, the study was a RCT, double-blind, placebo controlled trial and therefore its conclusions have some significance to this literature review. It was found that a single 8mg dose of Δ9-THC was not efficacious in reducing chronic pain on a delta VAS pain score in comparison to diazepam, an active placebo.

Another trial with 30 participants was done at Brigham and Women's Hospital and Mclean Hospital in the United States (Issa et al,., 2014) The sample size in this study was also relatively small but the design of the study was an RCT, double-blind, placebo controlled trial. It was found that, in patients using opioid therapy, single doses of 10 or 20 mg of dronabinol, or Tetrahydrocannabinol, had significantly elevated psychoactivity in comparison to placebo ($P<0.05$). Psychoactive effects may translate to a reduction in pain, however, this was not directly studied in this trial. The number of participants in each group was limited, and the dronabinol cohort consisted of a heterogeneous sample on various doses of opioids.

Discussion

The results of this present review indicate that rigorous research on the use of cannabis for pain control in people already using opioids is very limited. A number of factors would also impact the outcome, including but not limited to: prior doses and form of opioids; timing, duration, dose and route of administration of cannabis; the condition being treated; the target population; comorbidities.

The doses, timing, frequency, forms and route of administration are all important factors when considering both cannabis and opioids. For example, larger doses of cannabis are more likely to alter physiological processes, and lead to side-effects like tachycardia (Wiese and Wilson-Poe, 2018). The frequency of doses could also impact treatment outcomes. Two of the higher quality evidence (RCT) studies analyzed in this review only looked at the effects of one dose of cannabis or synthetic cannabinoid (Issa et al., 2014 and de Vries et al., 2016). How a single dose translates to real-world pain management with daily intake of medication is uncertain.

The effect of cannabis on outcomes may depend on the condition being treated. For example, a review of 20 studies on the impact of cannabis on health-related quality of life (HRQOL) found some improvement for pain, multiple sclerosis and inflammatory bowel disease, but decreased HRQOL in patients with HIV (Goldenberg et al., 2017). In this review the conditions treated varied between each trial, making the ability to draw conclusions on the effects of cannabis on each condition infeasible. Future trials could focus on specific conditions to determine which ones are most responsive to treatment with cannabis.

One of the main concerns around cannabis and opioid use is the potential for addiction. For example, people on opioids for pain already have higher rates of addictive behaviours than pain patients not taking opioids or the general population (Hojsted et al., 2013). Cannabis also has addictive potential, though one study did find less problematic use potential in patients using cannabis compared to opioids (Feingold et al., 2017a). However, this study did not take into consideration the dual interaction between cannabis and opioids on addictive behaviour. A large portion of patients on chronic opioid treatment use marijuana, with very high rates of continued use (Higgins et al., 2018).

Some of the more common side-effects of cannabis use are psychiatric, including increases in anxiety and depression (Aviram and Samuelly-Leichtag, 2017). However, one study analyzed in this review did show evidence of increased depression in patients using opioids alone relative to medical marijuana alone or medical marijuana in conjunction with opioids (Feingold et al., 2017b). The impact of cannabis on mood and anxiety is thought to be through THC that is present in the whole plant. This is important both for mental health and addictive potential, as development of cannabis-use disorder (CUD) is correlated with higher consumption of THC (Hasin et al, 2018). One way of potentially avoiding unwanted changes to mental status and CUD is to use isolated components from cannabis, such as CBD, that do not have as strong of psychoactive effects as THC. Not only does CBD have the potential for pain reduction, in people formerly using heroin who are now abstinent it has been found to decrease cues and anxiety (Hurd et al., 2019). This points to the need for further research looking at specific components of cannabis as adjunctive therapy for opioids in pain reduction.

With so little standardized research in combination cannabis and opioid therapy for pain, there is so much room for future research. Due to some evidence for beneficial (though often inconsistent) effects of cannabis for reducing opioid use () and improving pain () more research in this area is warranted. As Campbell et al. concluded in 2018, “it is important that large well designed clinical trials, which include people with complex comorbidities, are conducted to determine the efficacy of cannabis for chronic non-cancer pain."

Conclusion:

The evidence for the effect of cannabis use on pain-reduction in patients currently using opioids for chronic pain is insufficient. An increased amount of high quality clinical trials are needed to draw conclusions on the effectiveness. In many of the studies that were analyzed, there was a lack of standardization in study design, pain conditions, methods of administration of cannabis, dose of cannabis and type of chronic pain. Other limitations in many of the trials included a lack of a control group and a small sample size. From the 10 articles that matched the criteria only two were randomized control trials of high quality evidence. The ability to draw conclusions about the true pharmacological efficacy of cannabis in this literature study was limited.

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