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The Use of Medical Cannabis for Treatment of Chronic Pain: An Integrative Research Review

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Abstract

Chronic pain is a common problem that affects patients in the United States (US) and Canada. The treatment of chronic pain includes the use of opioids, however, with the growing epidemic, alternative options are being sought. The use of medical cannabis (marijuana) as treatment for chronic pain is increasing in popularity as an alternative for opioids. The aim of this integrative research review (IRR) was to explore the efficacy of medical cannabis for chronic non-cancer pain treatment. PubMed and Google Scholar were used for literature search engines. Keywords used to retrieve articles were efficacy, medical cannabis, medical marijuana, non-cancer chronic pain, neuropathic pain, opioids, substitution, and treatment. Inclusion criteria were articles published in the US, Canada, and Australia, and those written in the English language. Exclusion criteria were articles prior to 2010 and subjects less than 18 years of age. Ten articles were included in the IRR: four systematic reviews of randomized controlled trials, one randomized controlled trial, two cross-sectional observational studies, one secondary data analysis, one prospective cohort study, and one historical cohort study. Pain was measured using the Visual Analog Scale (VAS), Descriptor Differential Scale (DDS), numerical rating scale, Brief Pain Inventory (BPI), and/or quality of life in these studies. Most results showed that medical cannabis was an effective treatment for the reduction of chronic pain and increased quality of life, with the exception of the Australian prospective cohort study. Adverse effects of cannabis included short-term neurocognitive decline and worsening of psychiatric illness. Cannabis was also associated with a reduction or cessation of opioid use in the US and Canadian articles, prescribing patterns and spending in Medicare enrollees in states where medical cannabis laws were implemented. Findings suggest that clinical practice should include substituting medical cannabis for opioids in the long-term management of chronic pain in countries with medical cannabis laws.

INTRODUCTION

Chronic pain is a worldwide issue that can be devastating to patients if not managed appropriately. According to the Center for Disease Control and Prevention (CDC), in 2016, an estimated 20.4% (50 million) of United States adults suffered from chronic pain [1]. Opioids have been the drug of choice for several years in the treatment of chronic pain. The overuse of opioids has led to the current opioid epidemic. As a result, many patients are using opioids to treat chronic pain, which can lead to problems such as addiction, overdose, and diversion. Meanwhile, opioids kill an average of 115 Americans a day [2]. Therefore, the use of medical cannabis needs to be examined further for management of chronic pain.

Chronic pain affects quality of life and productivity, and "may be accompanied by difficulty moving around, disturbed sleep, anxiety, depression, and other problems" [3]. Chronic pain has also become a costly burden for the United States healthcare system. According to [3], the annual economic cost of chronic pain, including both treatment and lost productivity, has been estimated at up to $635 billion. It is imperative that we find effective long-term pain management treatment to prevent further complications in the healthcare system and the economic consequences.

The purpose of this integrative review was to examine the use of medical cannabis as a treatment option for chronic non-cancer pain. The goal of this review was to determine how medical cannabis was used in the treatment of chronic pain in patients who were18 years and older in the last eight years from 2010 to2018.

BACKGROUND

Medical cannabis has been explored as a therapeutic option for pain management throughout the United States (U.S.) and Canada. In the U.S., federal regulations limit researchers to conduct rigorous studies on medical cannabis due to its schedule I status. On the other hand, in Canada, medical cannabis is legal both for medical and recreational purposes. Since cannabis is classified in the same category as heroin in the U.S. at the federal level with no currently accepted medical use and high potential for abuse, it hinders researchers' ability to explore its treatment efficacy and safety [4]. However, at the state level, cannabis is legalized for medicinal use in 31 states [5]. Therefore, studies can be conducted in certain states due to its legality. Additionally, medical cannabis use was decriminalized in Australia on October 20, 2016 [6]. Although, randomization of a sample may not be feasible since statewide cannabis programs involve patient self-enrollment into a medical cannabis program. With these barriers to research studies, medical cannabis access to patients and

physicians is limited when exploring it as a safe alternative to opioids.

The focus of this review is on the US and Canada due to the overwhelming use of opioids than anywhere else in the world [7] illustrated the following:

The United States and Canada are in the midst of an epidemic of the use, misuse and overdose of opioids, and deaths related to overdose. This is the direct result of overstatement of the benefits and understatement of the risks of using opioids by advocates and pharmaceutical companies. Massive amounts of prescription opioids entered the community and were often diverted and misused. Most other parts of the world achieve comparable pain relief using fewer opioids. (p. 856).

Therefore, it is apparent that opioid use in the US and Canada needs to be curtailed and better options should be pursued.

According to the [2], almost 58 opioid prescriptions were written for every 100 Americans. Perhaps providers feel more comfortable prescribing opioids because of their familiarity with them, but this is a substantial amount of opioids considering that several Americans die of opioid overdose each day [2]. What is more, opioids are addicting and produce feelings of happiness, "the more people take them, the more they crave them" [3]. According to [8], opioid addiction inevitably develops after months of exposure and carries a high risk of relapse for years without proper treatment. Opioid addiction leads to increased doses, which consequently increases the risk of overdose. Unfortunately, the overprescribing of opioids for chronic pain management continues with these known consequences.

There is growing research that supports the use of medical cannabis for chronic back pain or hip or knee osteoarthritis pain [9], neuropathic pain, fibromyalgia [10], and other diagnoses [11]. Such study was by [12], which found that cannabis is a safe, well tolerated, and effective option to help patients cope with malignancy related symptoms. There has also been evidence suggesting a synergistic effect of cannabis combined with the use of opioids [13]. What is more, opioids have the fatal side effect of respiratory depression, which cannabis does not. However, cannabisdoes have psychoactive effects and neurocognitive decline, which have been linked to increased incidences of motor vehicle accidents, which can be deadly [**14]**. Meanwhile, in the US, there is mounting evidence that demonstrates that states with medical cannabis laws had a 24.8% lower mean annual opioid overdose mortality rate compared to states without medical cannabis laws [15]. Similarly, implementation of state medical cannabis laws was associated with a 5.88% reduction in Medicaid-covered prescriptions for opioids (95% confidence interval) [16].

Theoretical framework

Betty Neuman's Systems Model was used as a theoretical framework for this integrative review [17]. The Neuman's Systems Model posits the idea of holistic orientation to wellness, which include five variables of the person: physiological, psychological, sociocultural, developmental and spiritual [17]. The three variables pertinent to this review were physiological, psychological, and developmental. Chronic pain is a physiological variable which affects a patients overall wellbeing. Those suffering from untreated chronic pain cannot be in a stable state. Moreover, chronic pain may affect one's psychological wellbeing. It may negatively impact a person's emotions and ultimately lead to depression. Lastly, the developmental variable, such as one's age can influence his or her response to treatment and outcomes. Chronic pain becomes more prominent as one grows older and treatment remedies can affect one differently based on his or her age. For example, the very young and the elderly are considered vulnerable populations since they respond differently to medical cannabis than someone between the ages of twenty-one and sixty-five years.

METHODS

The databases used for the literature search were PubMed and GoogleScholar. Keywords used to retrieve articles included: efficacy, medical, cannabis, cannabinoids, marijuana, chronic pain, neuropathic pain, opioids, substitution, and treatment. Inclusion criteria included articles that were published in the US, Canada, and Australia, and those written in the English language from 2010-2018. Reviews outside of the US, Canada, and Australia, such as in Europe were excluded due to differences in the cannabis laws and lower use of opioids. Exclusion criteria included articles prior to 2010 and subjects less than eighteen years of age.

PubMed database

The PubMed database resulted in fifty-five articles related to the research question. From the fifty-five articles, forty abstracts were reviewed to determine if they were significant to answer the research question. From these abstracts, only six articles were isolated for full text review because they met the inclusion criteria for the study.

Google Scholar database

The Google Scholar database resulted in sixty-five results. Keywords including cannabis, marijuana, and chronic pain were used to search for article titles that related to the research question. Forty-five abstracts were reviewed to determine eligibility for inclusion. Only three articles were relevant to the research question.

Evaluation table

Appendix A is the evaluation table, Table 1, of all articles included in the IRR. Table 1 includes an evaluation of the data collection for the IRR. The table includes all ten studies used to answer the research questions. The variables of the studies include the following: citation, sample/setting, major study variables and definitions, measurement of major variables, data analysis, study findings, level of evidence, and appraisal of worth.

RESULTS

Initial electronic database search yielded 120 articles. Ten articles that fit the inclusion and exclusion criteria were included for review. Articles included in the review were four systematic reviews, one randomized controlled trial, two cross sectional observational studies, one secondary data analysis, one prospective cohort study, and one historical cohort study. The

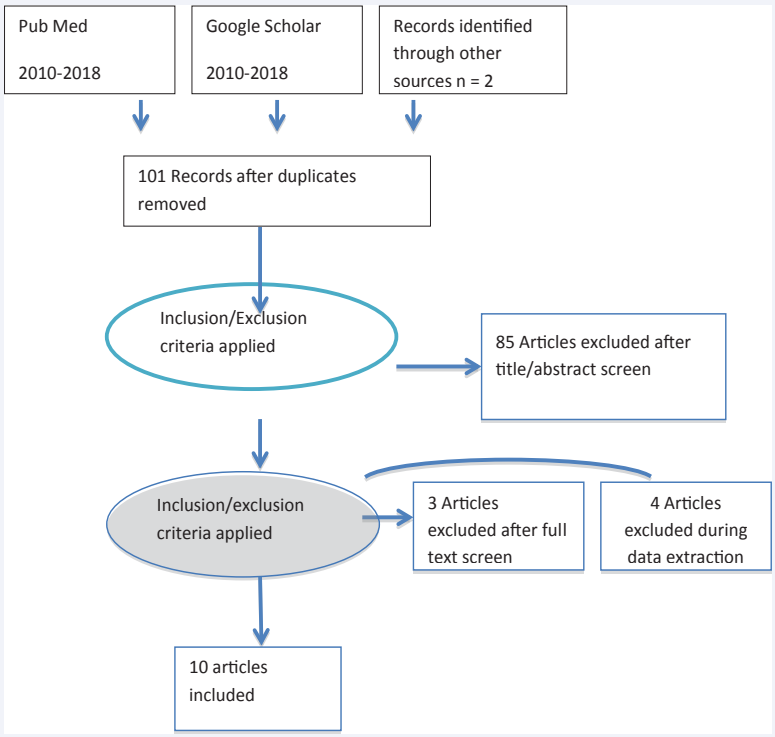

Figure 1 Database Search (PRISMA Flow Diagram).

Rating system for the Hierarchy of Evidence for Intervention and Treatment Questions by [18] was used to evaluate the level of evidence for each study. The articles consisted of four level I evidence (systematic reviews), one level II evidence (randomized controlled trial), three level III evidence (two cross sectional observational studies, and one secondary data analysis), and two level IV (cohort studies).

DISCUSSION

This IRR supports medical cannabis as a therapeutic alternative to opioids with sufficient evidence. In nine studies, medical cannabis was evaluated to test its effects on pain intensity. In the four systematic reviews of RCT's, the use of medical cannabis containing tetrahydrocannabinol (THC), the psychoactive ingredient in cannabis, demonstrated reductions in pain for all studies. However, there were about five RCT's that were used in all four systematic reviews, which clearly lead to identical results. Additionally, [19] discovered that medical cannabis had therapeutic benefits such as decreased spasticity in Multiple Sclerosis and increased appetite and caloric intake in HIV associated anorexia. Cannabis also decreased intraocular pressure in glaucoma for a short duration. Adverse effects such as neurocognitive decline were consistent in all studies, however. Similarly, decreased spasticity was also evident in [20] review. Although, [20] found adverse events including addiction and worsening of psychiatric illness. Relatedly, [6] revealed greater generalized anxiety disorder severity scores in patients who used cannabis compared to those with no cannabis use.

Furthermore, in the studies by [21-24], there was essentially a substitution of opioids with medical cannabis. In these studies, cannabis use was associated with reductions in opioid doses or cessation of opioids. Conflicting evidence by [7] established that illicit cannabis use did not have an opioid sparing effect. Though, medical cannabis patients reported improvements after three months of treatment in clinical state and health-related measures, and notable decreases in prescription medication use, particularly opioids and benzodiazepines [26].

Lastly, [9] proved that pain intensity was significantly better in non-opioids than opioids over a twelve-month period ($p = 0.03$). Therefore, treatment with opioids was not superior to other pain management alternatives in the treatment of chronic back pain or hip or knee pain related to osteoarthritis.

The implications of practice include recommending medical cannabis as an intervention for the management of chronic pain instead of opioids, in conjunction with legal use and medical supervision. If cannabis is substituted for opioids, prevention of opioid addiction and fatal overdoses will inevitably occur. Health care providers, including Nurse Practitioners, must stop overprescribing opioids because they are familiar or comfortable with that form of treatment, and choose safer alternatives such as cannabis. Thus, improvements in clinical outcomes can be achieved such as appropriately managed pain and reductions in opioid overdoses.

LIMITATIONS

Most of the studies mentioned a lack of randomized controlled trials due to cannabis' schedule I status, which creates a barrier to randomly assign patients in RCT's. Therefore, medical cannabis patients self-enrolled into a program to be included in the U.S. study samples. Most studies were limited by small sample sizes, and in almost all of the systematic reviews there was variability of THC doses and short study durations [11] described the lack

Table 1: A summary of reviewed studies.

Citation: Author(s), date of publication and Title	Design method	Sample/ setting	Major variables studied and their definition	Measurement of major variables	Data analysis	Study Findings	Appraisal of worth to practice: Level of evidence, study strength and weakness*
Andreae, M. H., Carter, G. M., Shaparin, N., Suslov, K., Ellis, R. J., Ware, M. A., Abrams, D. I., Prasad, H., Wilsey, B., Indyk, D., Johnson, M., & Sacks, H. S. (2015). Inhaled Cannabis for Chronic Neuropathic Pain: A Meta-Analysis of Individual Patient Data.	Systematic review of RCT's and Meta-analysis	5 RCT's n= 178 w/ chronic neuropathic pain	Control: cigarettes w/ THC removed. Intervention: cannabis cigarettes with THC. Dependent variable – pain Independent variable - cannabis	Change in pain intensity using Visual Analog Scale (VAS) or Descriptor Differential Scale (DDS)	Results were pooled using Bayesian pooled effect w/ 95% CI. The Bayes factor is 332 w/ a posterior probability effect of 99.7%	Inhaled cannabis for chronic neuropathic pain resulted in short-term reductions in pain for about 1 of5 patients.	Level 1 evidence. Strength: RCT with control and experimental group. Consistency of results across different populations created generalizability of results. Weakness: Small sample size, small number of studies, short study duration, and inability to blind patients due to psychoactive effects of cannabis.
Deshpande, A., Mailis-Gagnon, A., Zoheiry, N., &Lakha, S. F. (2015). Efficacy and Adverse effects of medical marijuana for chronic non-cancer pain: Systematic review of randomized controlled trials.	Systematic Review of RCT's	6 RCT's n=226 adults (ages 45-50 years) w/ chronic neuropathic pain were randomized, w/ 189 adults specifically having chronic neuropathic pain	Control: cigarettes containing 0% delta-9-THC that were identical to cannabis cigarettes. Intervention: cigarettes containing delta-9-THC w/ varying potencies ranging from 1-9.4%	Pain intensity measured by Visual Analog Scale (VAS) or numeric rating scale	Data could not be pooled due to heterogeneity in delta-9-THC potency	The use of medical cannabis for chronic neuropathic pain was associated with a reduction in pain and a short-term neurocognitive adverse effects	Level 1 evidence. Strength: RCT with control and experimental group Weakness: small sample size, short study duration, and variability in delta-9-THC potencies
Bowen, L. L., & McRae-Clark A. L. (2017). Therapeutic Benefit of Smoked Cannabis in Randomized Placebo-Controlled Studies.	Systematic Review of RCT's	7 RCT's n=208 patients of which 170 were experienced cannabis smokers	Control: placebo cigarettes with 0% THC. Intervention: Cigarettes with THC ranging from 1-9.4%.	Pain intensity rating measured via VAS or Descriptor Differential Scale (DDS). Caloric intake, change in spasticity and intraocular pressure were also measured.	Data could not be pooled due to heterogeneity in delta-9-THC potency	Smoked cannabis showed subjective improvements in pain. It also had therapeutic benefits such as decreased pain and spasticity in multiple sclerosis, and increased appetite and calories in HIV associated anorexia. Additionally, smoked cannabis decreased intraocular pressure in patients with glaucoma for a short duration.	Level 1 evidence. Strength: RCT with control and experimental group Weakness:Small sample size, short study duration, and inability to blind patients due to psychoactive effects of cannabis. Also, patients with Depression were excluded, which limits generalizability
Hill, K. P. (2015). Medical Marijuana for Treatment of Chronic Pain and Other Medical and Psychiatric Problems: A Clinical Review.	Systematic Review of RCT's	28 RCT's of cannabinoids for indications other than FDA-approved cannabinoids (dronabinol and nabilone), 6 trials n= 325 patients with chronic pain, 6 trials n= 396 with neuropathic pain, and 12 trials n=1600 related to Multiple Sclerosis	Control: cannabis placebo containing 0% THC. Intervention: Cannabis w/ THC	VAS, subjective pain intensity change, mean pain severity, change in the following: spasticity, muscle stiffness, incontinence episodes, sleep disturbance, tremors, cognition, dyskinesia, and activity index	Data could not be pooled due to heterogeneity in delta-9-THC potency	Medical cannabis can treat chronic pain, neuropathic pain, and spasticity associated with Multiple Sclerosis. There are adverse effects of Cannabis such as addiction and worsening of psychiatric illness	Level 1 evidence. Strength: RCT with control and experimental group Weakness: Small sample sizes in the studies, variability in THC doses

Krebs, E.E., Gravely, A., Nugent, S., Jensen, A.C., DeRonne, B., Goldsmith, E.S., et al. (2018). Effect of Opioid vs Nonopioid Medications on Pain-Related Function in Patients With Chronic Back Pain or Hip or Knee Osteoarthritis Pain: The SPACE Randomized Clinical Trial.	Randomized Controlled Trial	12 month randomized trial N = 240 patients recruited from Veterans Affairs who had moderate to severe chronic back or hip or knee osteoarthritis	Dependent variable – pain Independent variable – opioids or non-opioids pain relievers	Primary outcome = pain related function over 12 months (Brief pain inventory interference [BPI] scale) Secondary outcome = pain intensity (BPI severity scale) BPI scale = 0-10; higher score = worse pain or function	Two-sided *t* tests and *x^2* test were used Statistical significance threshold was P less than 0.05	Pain intensity was significantly better in non-opioids than opioids over a 12 month period (p=.03)	Level 2 evidence Strength: randomized sample over a long time period (12 months) Weakness: subject to patient bias and subjects were primarily male
Sohler, N. L., Starrels, J., Khalid, L., Bacchuber, M., Arnsten, J., Nahvi, S., Jost, J., & Cunningham, C. (2018). Cannabis use is associated with lower odds of prescription opioid analgesic use among HIV-infected individuals with chronic pain.	Secondary Data Analysis	N= 459 HIV-infected patients with chronic pain, a convenience population from Bronx HIV clinics and drug treatment programs.	Cannabis use, alcohol, and illicit drug use patients prescribed opioids Dependent variable – opioid use Independent variable - cannabis	31 questions via interview or telephone	Multivariate analysis was used to find the associated of medical cannabis w/ lower odds of opioids use (0.57; 95% confidence interval: 0.38-0.87)	Cannabis use was the only substance associated with decreased use of opioid analgesics in multi-variate analyses.	Level 3 evidence. Strength: Used many variables including cannabis, alcohol, cigarettes, heroin and cocaine to measure the outcome Weakness: Homogeneity of population selected which reflects local drugs use, and limited cause/effect conclusions.
Boehnke, K. F., Litinas, E. &Clauw, D. J. (2016). Medical Cannabis Use is Associated with Decreased Opiate Medication Use in a Retrospective Cross-Sectional Survey of Patients With Chronic Pain.	Cross-sectional observational study	N = 185, medical cannabis patients at a dispensary in Michigan	Effects of cannabis on opioid use: measured the change in opioid use when using cannabis for chronic pain. Effects of cannabis on number of medication classes used: measured the change in medications when using cannabis for chronic pain. Effect of cannabis on side effects: measured the change in side effects after initiation of cannabis	Variables measured via 46 question survey	Descriptive statistics was used to limit analysis to completed questionnaires. Student t-tests were used to examine cannabis use and medication classes. Paired *t*-tests were used to study changes before and after cannabis use	Medical cannabis use is associated with a decrease in opioids by 64%. Patients were essentially substituting opioids for other medication classes. Subjects found less side effects with medical cannabis	Level 3 evidence. Strength:Many variables tested such as NSAIDs, DMARDs, Antidepressants, SSRIs, and other to measure the outcome. Weakness: Small sample size and potentially unreliable recall data
Reiman, A., Welty, M., &Solomon, P. (2017). Cannabis as a substitute for opioid-based pain medication: patient self-report	Cross-sectional observational study	N= 2897 medical cannabis patients in the state of California	Cannabis, opioid, and non-opioid based medications	Measured via email survey by indicating the following: "strongly agree", "agree", "disagree", or "strongly disagree"	N/A	97% of patients who use cannabis "strongly agreed/agreed" that they are able to decrease opioids when using cannabis.	Level 3 evidence. Strength:Large sample size Weakness: data is subjective since it's self-reported from population, there is no comparison group to patients with only access to opioids or OTC pain medications, and sample is only from California and does not generalize for the U.S.

Campbell, G., Hall, W.D., Peacock, A., Lintzeris, N., Bruno, R., Larance, B.,... Degenhardt, L. (2018). Effect of cannabis use in people with chronic non-cancer pain prescribed opioids: findings from a 4-year prospective cohort study.	Prospective Cohort Study	N = 1514 Participants recruited from pharmacies across Australia w/ chronic non-cancer pain older than 18 years old, currently taking prescribed opioids for greater than 6 weeks	Dependent variable – pain Independent variable – cannabis	Self-reported questionnaires and interviews over a 4 year period using the following scales: pain severity and interference (how pain affects sleep, daily living, working ability, and social interaction) subscales of the Brief Pain Inventory (BPI),20 with higher scores indicating greater pain severity or interference (score range 0–10).	Multinomial logistic regression models used to compare less frequent versus more frequent cannabis use, mixed-effects models used to for associations between cannabis use and outcomes	At 4-year follow-up, compared with people with no cannabis use, participants who used cannabis had a greater pain severity score. There was no evidence found that cannabis use decreased pain severity score or reduced opioid use.	Level 4 evidence. Strength: study conducted over a long period of time (4 years), and a large sample size (n = 1514) Weakness: subjective data since it's self-reported, the patients were using illicit cannabis and were not monitored by a medical provider over the duration of the study, and cannabis doses across the population were not consistent
Vigil, J. M., Stith, S. S., Adams, I. M., Reeve, A. P. (2017). Associations between medical Cannabis and prescription opioid use in chronic pain patients: a preliminary cohort study.	Historical Cohort Study	Sample of 37 chronic pain patients (mean age 54 years old, 54% male, 86% back pain) who use opioids and are enrolled New Mexico's Medical Cannabis Program (MCP)	*Ceased opioid prescriptions*: no evidence from prescription monitoring program that an opioid was filled in the last three months of observation. *Reduction in Prescribed Daily Opioid Dosage:* average prescribed daily dose of IV morphine lower in the last three months of observation vs. the first three months. *Percentage Point Change on Prescribed Daily Opioid Dosage:* measures the difference between the average daily dose in the first and last three months of observation divided by the average daily dose in the first three months.	Survey questions measured pain levels prior to and after MCP, side effects, effects on quality of life, activity levels, and concentration	Logistic regression model was used to analyze the first 3 months and the last three months of observation	Greater than 80% of MCP participants reduced their daily opioid doses. 40% of MCP enrollees ceased filling opioid prescription after 1.5 years into the MCP. MCP patients also reported increased quality of life and decreased pain levels.	Level 4 evidence. Strength: study conducted over a long period of time (21 months) Weakness: Convenience sample from a medical cannabis program in New Mexico
*Level of evidence graded according to Melnyk, B.M. & Fineout-Overholt, E. (2015). "Box 1.3: Rating system for the hierarchy of evidence for intervention/treatment questions.							

of long-term clinical trials and the safety of cannabis among young and vulnerable populations [6] was a longitudinal study performed in Australia, but it included the use of illicitly produced cannabis and failed to incorporate the guidance or supervision of a medical provider. Additionally, cannabis doses were inconsistent across the study population.

There was also an inability to blind patients related to psychoactive effects of cannabis, which caused a few patients to drop out of studies. One review excluded patient diagnoses such as depression [15,19] stated limitations related to the inability to adjust for race/ethnicity, socioeconomic status, and medical/psychiatric diagnoses [22] lacked a comparison group, inability to determine the effective cannabis dose, low response rate, and lack of knowledge on the specific opioids being used [23] was limited to homogeneity of the group selected.

The restrictions of these studies are the support for the need for further research that can operate around legal barriers. Ultimately, most of the authors were unable to generalize the use of medical cannabis in relation to chronic non-cancer pain due to lack of supporting evidence. With such limitations, further comprehensive evidence is needed on the relationship between medical cannabis and its therapeutic outcome.

CONCLUSION

This IRR was supported by adequate evidence that medical cannabis is an effective treatment for chronic pain management and can be substituted for opioids. Although there are some negative adverse effects, they do not measure up to the harsh consequences of opioids and the amount of overdose deaths. Most of the studies reviewed indicated the positive effects and efficacy of medical cannabis as an option or alternative to opioids in the management and treatment of chronic pain associated with neurological, musculoskeletal, non-cancer as well as cancer conditions. These studies, however, recommended further rigorous research to determine the effective cannabis dose and long-term feasibility. Medical cannabis also has the potential to prevent overprescribing of opioids amidst the opioid epidemic in the US and Canada. If thorough research is performed, it may be able to reduce harmful opioid effects and prevent cannabis misuse.

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