Research Report

Medical Cannabis: Effects on Opioid and Benzodiazepine Requirements for Pain Control

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Abstract

Background: There is currently little evidence regarding the use of medical cannabis for the treatment of intractable pain. Literature published on the subject to date has yielded mixed results concerning the efficacy of medical cannabis and has been limited by study design and regulatory issues. **Objective:** The objective of this study was to determine if the use of medical cannabis affects the amount of opioids and benzodiazepines used by patients on a daily basis. **Methods:** This single-center, retrospective cohort study evaluated opioid and benzodiazepine doses over a 6-month time period for patients certified to use medical cannabis for intractable pain. All available daily milligram morphine equivalents (MMEs) and daily diazepam equivalents (DEs) were calculated at baseline and at 3 and 6 months. **Results:** A total of 77 patients were included in the final analysis. There was a statistically significant decrease in median MME from baseline to 3 months (−32.5 mg; $P = 0.013$) and 6 months (−39.1 mg; $P = 0.001$). Additionally, there was a non–statistically significant decrease in median DE at 3 months (−3.75 mg; $P = 0.285$) and no change in median DE from baseline to 6 months (−0 mg; $P = 0.833$). **Conclusion and Relevance:** Over the course of this 6-month retrospective study, patients using medical cannabis for intractable pain experienced a significant reduction in the number of MMEs available to use for pain control. No significant difference was noted in DE from baseline. Further prospective studies are warranted to confirm or deny the opioid-sparing effects of medical cannabis when used to treat intractable pain.

Keywords

pain management, narcotics, benzodiazepines, pharmaceutical care, FDA issues

Introduction

Medical cannabis was approved in the state of Minnesota for the indication of intractable pain in August 2016. The definition of intractable pain specifies, "pain whose cause cannot be removed and, according to generally accepted medical practice, the full range of pain management modalities appropriate for this patient has been used without adequate result or with intolerable side effects."[1] However, it is not completely clear what effect cannabis has on pain control.[2] Cannabis is classified as a schedule I substance by federal law, making it difficult to conduct randomized controlled trials. Little research has been published on the subject to date.

There are different formulations of cannabis based on individual cannabidiol (CBD) to delta-9-tetrahydrocannabinol (THC) ratios. Production is regulated by the manufacturers to ensure standardization of the products used by patients in this program. Available products are categorized into 3 groups: high THC (THC > CBD), high CBD (THC < CBD), and balanced (THC = CBD). It is thought that a higher THC concentration is more effective for pain control, whereas higher CBD concentrations are better for indications such as seizures.[3,4] CBD is used as an adjunct in all products to prolong the half-life and reduce adverse effects caused by the THC component.[3]

Some evidence exists to support the use of medical cannabis for pain, which may reduce the amount of analgesics required for pain control, such as opioids and benzodiazepines.[5,6] One open-label study found that patients cotreated

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with cannabis and opioids were able to decrease their use of opioids over a 6-month period.[7] Although benzodiazepines are not FDA approved for the indication of pain, there is some limited evidence that they may be useful for some chronic pain conditions, and they are commonly coprescribed with opioids.[8] The driving factor for the initiation of medical cannabis in the setting of chronic pain may be to reduce patients' opioid burden in some cases.

Published research for cannabis use in the treatment of pain is limited. In addition to the regulatory barriers posed by federal laws on cannabis research, there are other limitations to research that has been conducted thus far. For example, each cannabis manufacturer has proprietary standards for the products it allows to be used and distributed, making the research done on other formulations, such as synthetics and street product, not entirely generalizable to the population served by the products used in this program. Many previous studies looked at relatively short-term data and outcomes at intervals of several weeks to months of therapy. Another limitation to the study of pain in general is the subjective nature of the condition itself. Results are often based on patient reporting of pain scores, which are limited by an inability to incorporate pain catastrophizing, quality of life, and impact on activities of daily living or other medical conditions (ie, sleep, mental health) as well as interpatient variability regarding pain thresholds.

Despite these barriers, published evidence variably supports medical cannabis for pain.[9,10] In a meta-analysis evaluating cannabinoids for medical use, the average number of patients who reported at least a 30% reduction in pain was higher in the treatment groups than placebo groups; however, the result was not significant (37% vs 31%; odds ratio = 1.41, 95% CI = 0.99-2.00; 8 trials).[11] Limitations of this study included a lack of standard formulation and delivery systems and subjective patient reported pain outcomes. Other meta-analyses and reviews have reported mixed results. Kansagara et al[4] found low-quality evidence that THC alone improved pain and spasticity in patients with multiple sclerosis, whereas CBD alone and THC/CBD combined had variable effects. They also found that patients with neuropathic pain were more likely to report an improvement in pain by ≥30%, but this was not statistically significant ($P = 0.111$).[4] They found inconsistent evidence that cannabis improved pain in mixed or general populations.[4] Other analyses have concluded that there is insufficient evidence or low-quality evidence for using medical cannabis in patients with chronic pain.[11,12] These studies cite short durations, small sample sizes, heterogeneity of dosing and route, and lack of functional outcomes as limitations.[11,12]

This project aimed to address some of the gaps in current research regarding the use of medical cannabis. The purpose of this study was to examine the relationship between the use of medical cannabis and the doses of opioids and benzodiazepines available to maintain adequate pain control based on objective evidence over a 6-month period.

Objectives

The primary objective of this study was to determine if the use of medical cannabis for intractable pain affects the amount of opioids and benzodiazepines patients use on a daily basis. The secondary objective of this study was to determine if there are any observable differences in pain scores between the different medical cannabis products. In addition, this study observed changes in pain scores over time.

Methods

Approval

This study was approved by the HealthEast Institutional Review Board through expedited review on October 11, 2017. This approval included a waiver of informed consent and Health Insurance Portability and Accountability authorization. The procedures followed in this study were in accordance with the ethical standards of the institution's committee on human experimentation.

Design and Setting

This was a single-center, retrospective cohort study. All patients were certified to have intractable pain by the same medical doctor with a pain specialty. Patient charts were reviewed to determine if the doses of opioids and/or benzodiazepines available were affected with the initiation of medical cannabis during the first 6 months of use. All available daily milligram morphine equivalents (MMEs) and diazepam equivalents (DEs; including as needed and scheduled doses) were calculated at baseline, 3 months, and 6 months. These calculations were made using standardized opioid and benzodiazepine equivalence calculators and were based on medication lists found in the patient's electronic medical record at the closest possible time to each of the study intervals.[13] Benzodiazepines with an as-needed indication specifically for anxiety or sleep were not included in the dosage calculations. As-needed doses of benzodiazepines were included if they were prescribed for indications such as muscle spasms or if there was no specific indication noted in the medical record. This was done in an attempt to prevent inaccurate results based on benzodiazepine doses that were not being used for pain. Information regarding prescribed cannabis products and use over time was obtained via the Medical Cannabis Registry. A standardized data collection form was used to collect patient information from electronic medical records and the Medical Cannabis Registry.

Table 1. Patient Demographics (n = 77).

Female (%)	45 (58.4)
Patient age (years)	54.1 (average); 26-76 (range)
Daily MME at baseline (mg)	140.64 ± 184.64 (average); 5-1144 (range)
Daily DE range at baseline (mg)	18.33 ± 10.84 (average); 5-40 (range)
Patients prescribed opioids at baseline (%)	74 (96)
Patients prescribed benzodiazepines at baseline (%)	12 (15.6)
Patients coprescribed opioids and benzodiazepines at baseline (%)	9 (11.7)
Average pain score: baseline (1-10)	6.25
Type of pain[a] (%)	Abdominal pain: 3 (3.9) Avascular necrosis: 1 (1.3) Back pain: 25 (32.5) Cervical radiculopathy: 1 (1.3) Chronic pain syndrome: 25 (32.5) Complex regional pain syndrome: 4 (5.2) Cystic hygroma: 1 (1.3) Fibromyalgia/Myofascial pain: 6 (7.8) Headache: 7 (9.1) Inguinal pain: 1 (1.3) Myelopathy: 1 (1.3) Neck pain: 5 (6.5) Neuropathy: 9 (11.7) Osteoarthritis: 12 (15.6) Paraplegia: 1 (1.3) Postoperative pain: 1 (1.3) Rheumatoid arthritis: 3 (3.9) Spinal cord injury: 1 (1.3) Trauma: 1 (1.3)

Abbreviations: DE, diazepam equivalents; MME, milligram morphine equivalents.
[a]Patients may have more than one type of pain.

Population

All patients that the prespecified provider had certified for the Medical Cannabis Program as of December 1, 2017 were screened for inclusion. Patients were included if they had been certified to use medical cannabis for intractable pain and were using opioids and/or benzodiazepines for pain control at baseline. At least one transaction must have been made at an approved medical cannabis dispensary on behalf of each patient. Transactions were tracked using information from the Medical Cannabis Registry. Patients were excluded if they were less than 18 years of age.

Data Analysis

Data collection began on December 1, 2017, and concluded on March 19, 2018. The primary objective compared MME and DE at baseline with 3 and 6 months of treatment. Each patient served as their own control from no treatment (baseline) to 6 months. Data analysis was completed using IBM SPSS Statistics software, and differences were compared using Wilcoxon signed rank tests with an a priori level of significance of less than 0.05. Descriptive analysis was used to report secondary outcomes.

Results

A total of 224 patients were screened. Of these, 77 were eligible to be included in the primary analysis; 48 patients (21.4%) were eliminated for not taking opioids or benzodiazepines at baseline, and 2 patients (0.89%) were eliminated for certification of conditions other than intractable pain. A total of 80 patients (35.7%) were excluded from the study for never making a transaction at an approved medical cannabis dispensary, and 17 patients (7.5%) were eliminated because of lack of available information. Patient demographics are shown in Table 1. Approximately 58% of the patients were female, and the average age was 54 years. Average daily MME and DE at baseline were 140.64 ± 184.64 mg and 18.33 ± 10.84 mg, respectively. Median daily MME and DE at baseline were 105 mg (interquartile range [IQR] = 43.45 to 155.63) and 17.5 mg (IQR = 8.13 to 28.13), respectively.

The results of the primary outcomes are depicted in Table 2. A statistically significant decrease in median MME from baseline to 3 months (−32.5 mg; $P = 0.013$) and baseline to 6 months (−39.1 mg; $P = 0.001$) was observed. In addition, there was a non–statistically significant decrease in median DE at 3 months (−3.75 mg; $P = 0.285$) and no

Table 2. Median and Average MMEs and DEs and Sensitivity Analysis.

	Baseline	3 Months	6 Months	3 Months vs Baseline, *P* Value	6 Months vs Baseline, *P* Value
MME, median (IQR); n = 74	105 (43.75 to 155.63)	72.5 (30 to 141.38)	65.9 (28.13 to 150)	0.013	0.001
MME, average ± SD; n = 74	140.64 ± 184.64	108.47 ± 119.62	103.1 ± 115.31	0.022 (95% CI = 4.88, 59.46)	0.009 (95% CI = 9.74, 65.34)
DE, median (IQR); n = 12	17.5 (8.13 to 28.13)	13.75 (8.13 to 27.5)	17.5 (8.13 to 30)	0.285	0.833
DE, average ± SD; n = 12	18.33 ± 10.84	16.25 ± 12.32	19.79 ± 13.88	0.323 (95% CI = −2.35, 6.52)	0.734 (95% CI = −10.66, 7.74)
Sensitivity analysis: median and average MME; patients with greater than 500 MMEs removed from analysis					
MME, median (IQR); n = 71	94.29 (40 to 150)	60 (30 to 130)	60 (22.5 to 120.54)	0.035	0.004
MME, average ± SD; n = 71	107.65 ± 82.61	92.29 ± 86.38	87.48 ± 82.23	0.029 (95% CI = 1.6, 29.11)	0.003 (95% CI = 7.2, 33.15)

Abbreviations: DE, diazepam equivalents; IQR, interquartile range; MME, milligram morphine equivalents.

Table 3. Secondary Outcomes.

High THC product (n)	58
High THC alone (n)	34
High CBD product (n)	15
High CBD alone (n)	2
Balanced product (n)	35
Balanced alone (n)	12
High THC + High CBD	6
High THC + Balanced	16
High THC + High CBD + Balanced	2
High CBD + Balanced	5
Average pain score: baseline (1-10)	6.25
Average pain score: most recent (1-10)	6.57

Abbreviations: CBD, cannabidiol; THC, delta-9-tetrahydrocannabinol.

change in median DE from baseline to 6 months (−0 mg; $P = 0.833$).

In a sensitivity analysis, 3 patients with greater than 500 MMEs available at baseline were eliminated as outliers and Wilcoxon signed rank tests were repeated. A total of 71 patients were included in the sensitivity analysis. Results are shown in Table 2. When these patients were eliminated as outliers, the difference between the median MME at baseline and at 3 months (−34.29 mg; $P = 0.035$) and 6 months (−34.29 mg; $P = 0.004$) remained statistically significant.

Secondary outcomes examined trends in cannabis product use and change in pain scores over time using the patient-reported pain, enjoyment, and general activity (PEG) screening tool (Table 3). A majority of patients were taking a high THC product either alone (48%) or in combination with another product (30%), whereas very few patients were using a high CBD product (15% in combination and 2% alone). Average pain score increased from 6.24 at baseline to 6.57 at each patients' most recent cannabis dispensary visit.

Discussion

The outcomes of this study are intended to aid providers in their prescribing practices and possibly improve outcomes for patients. A large number of patients were excluded from the study for never making a transaction at an approved medical cannabis dispensary. This may be a result of cost.

The results show a statistically significant decrease in MME from baseline to both 3 and 6 months. The large SDs and significant differences between average and median MMEs indicate a high likelihood of outliers in the data. Therefore, a sensitivity analysis was done by eliminating patients (n = 3) with more than 500 daily MMEs available (approximately 413% higher than the average). The results remained statistically significant with the removal of these 3 patients.

The results show a non–statistically significant change in DEs from baseline to 3 and 6 months. It is possible that this may reflect an increase in anxiety associated with altering opioid medication regimens in patients with long-standing chronic pain. Additionally, anxiety is associated with the use of cannabis, possibly leading to increased doses of benzodiazepines for symptom control.[14] Another explanation may be that there were not enough patients using benzodiazepines in the study (n = 12) to provide an adequate sample to detect a difference.

Initially, the authors had planned to conduct statistical analysis on the secondary outcomes to compare changes in opioid and benzodiazepine requirements between the 3 different formulation groups of medical cannabis. However, the sample size of patients using high CBD products alone was insufficient for statistical analysis, and descriptive statistics were utilized instead. Pain scores were not available at each of the 3 time points. Thus, first and last pain scores associated with transactions at the cannabis dispensary were analyzed.

Secondary outcomes showed that a majority of patients utilize a high THC product over balanced and high CBD products. This is consistent with the current evidence suggesting that THC is superior for pain control. Somewhat unexpectedly, however, a small increase in average pain score was seen from baseline to most recent medical cannabis transaction. An explanation for this may be related to the hyperalgesia phenomenon seen in patients taking opioids for treatment of chronic pain for a long period of time. These patients have been known to experience increased pain with initiation of opioid taper.[15]

It should be noted that the Centers for Disease Control and Prevention recommends avoiding greater than 90 MME per day in patients taking opioids for chronic pain, though it was not uncommon for patients in this study to be taking 2 to 3 times this goal on a daily basis.[16] They also caution against the coprescribing of opioids and benzodiazepines because of increased risk of overdose when these medications are taken concurrently.[16]

It is important to consider the limitations of a retrospective study such as this one. The MME calculations included all opioids available to the patient, including all as-needed doses (pro re nata [PRN]), all pain pump basal doses and boluses, as well as scheduled opioids. Dosage calculations relied on the accuracy of the medication lists within the electronic medical record. The electronic medical record may not provide a precise medication list at exactly 3 and 6 months into therapy; therefore, the accuracy of the available opioid and benzodiazepine utilization cannot be definitively certain. Some patients may have been taking fewer PRN doses than prescribed. The prescription drug monitoring program could not be accessed for verification of medication use for the purposes of this study.

Additional limitations include ambiguity in dose equivalence tables. For example, although morphine equivalence for opioid dosing is fairly well established, there are some medications, such as methadone, that have unclear equivalence. Likewise, benzodiazepine equivalence is somewhat ambiguous and based on open-label observational studies to determine approximate DEs based on subjective patient response. These equivalents were utilized in this study; however, resources differ on the exact dosing, and in many cases, dose ranges are utilized.[8,17,18] To control for this, all doses were determined using a single opioid and benzodiazepine equivalence calculator.[13] This eliminated the risk for variability between patients, but should a different calculator be used to replicate these findings, MME and DE may not be universally consistent.

The results of this study may be difficult to generalize to a patient population outside of Minnesota as well as populations of patients using cannabis recreationally because the formulations used in this study are not available to individuals outside of the Minnesota Medical Cannabis program. However, the results provide evidence for an opioid sparing effect of cannabis when used in a structured and standardized way, through a program such as this. Further prospective research is needed to confirm this finding.

This study did not control for other interventions that may have had an impact on pain control that occurred during the study period. For example, there was no adjustment made if a patient had surgery requiring a change in their medication regimen. It is also feasible that patients were able to reduce their doses of opioids and benzodiazepines independent of the effects of medical cannabis. Moreover, safety outcomes and cost implications were not assessed in this study.

Conclusion and Relevance

Over the course of this 6-month retrospective study, patients using medical cannabis for intractable pain may have experienced a significant reduction in the average MME available for pain control. A non–statistically significant difference in average benzodiazepine dose was observed. The results of this study add to the currently mixed body of evidence suggesting that medical cannabis may be effective for treating pain, though they cannot be used to confirm this because of the retrospective nature. Further prospective studies are warranted to confirm or deny the opioid-sparing effects and explain the effect of medical cannabis on benzodiazepines when used to treat intractable pain.

There is much to learn about medical cannabis, and as such, it will likely be some time before the health care community is fully knowledgeable about its role in chronic pain management. There is currently little data guiding the practice of medical cannabis use and, given the high percentage of patients using the product for intractable pain, the importance of further research cannot be overstated.

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Declaration of Conflicting Interests

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