Prospective Study

Medical Cannabis Used as an Alternative Treatment for Chronic Pain Demonstrates Reduction in Chronic Opioid Use – A Prospective Study

Gregory Benedict, MD, Annas Sabbagh, DO, and Till Conermann, MD

From: Allegheny Health Network/ West Penn Hospital, Institute for Pain Medicine, Pittsburgh, Pennsylvania

Address Correspondence:
Gregory Benedict, MD
1050 SE Monterey Rd, Ste 400
Stuart, FL 34994
E-mail: gmbenedict@gmail.com

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Background: Chronic opioid therapy (COT) has been used to treat many chronic pain conditions even with poor evidence for its long-term effectiveness. Medical cannabis has emerged with certain pain-relieving properties, which has led to questions as to its' potential application, especially in relation to its effect on opioid use.

Objectives: This study investigates a proposed clinical context in offering medical cannabis as a treatment for chronic pain for those already using chronic opioid therapy. It then details patients' daily morphine milligram equivalent (MME) usage.

Study Design: This single-center prospective study follows a group of patients trialing medical cannabis treatment for chronic pain that is already using COT in order to determine individual efficacy. Continued medical cannabis treatment was a decision made by the patient, after trialing medical cannabis, to either continue medical cannabis along with COT at a reduced daily MME, or to revert back to their previous COT regimen.

Setting: This study was performed at the Allegheny Health Network Institute for Pain Medicine in Pittsburgh, Pennsylvania. The state of Pennsylvania legalized medical cannabis in April of 2016, and it became available to patients in February of 2018 through medical dispensaries.

Methods: One hundred and fifteen patients met the inclusion criteria, with the majority of those excluded due to not being treated with COT. Of the 115 who chose to undergo a medical cannabis trial in addition to their COT, 75 chose to remain certified for medical cannabis as they had significant pain relief and subsequently weaned down on opioids. Additionally, of the 115 choosing to undergo a medical cannabis trial, 30 chose to be decertified due to ineffectiveness or side effects, and those were placed back on their COT regimen. The other 10 were not included for other denoted reasons. Compliance was monitored through urine drug screens (UDS).

Results: There was a 67.1% average decrease in daily MME/patient from 49.9 to 16.4 MME at the first follow-up. There was a 73.3% decrease in MME at second follow-up from 49.9 to 13.3 MME with an ANOVA analysis denoting a significant difference of $P < 0.0001$.

Limitations: The period of follow-up presented at this point includes their first 6 months of treatment with medical cannabis and COT concomitantly.

Conclusions: Presenting medical cannabis to chronic pain patients on COT should be done in the context of a patient choice between medical cannabis WITH decrement of COT or continued current dose of COT in order to maximize effectiveness in opioid reduction as well as to limit polypharmacy concerns regarding medical cannabis. Allowing for a temporary short-term period where patients may trial medical cannabis, while concomitantly gradually weaning their COT, is also essential in determining medical cannabis' individual effectiveness for that patient's specific type of chronic pain, which should serve to maximize long-term opioid reduction results and hence decrease opioid-related overdose deaths.

Key words: Medical, cannabis, marijuana, opioid, treatment, alternative, adjunct, trial, prospective, chronic, pain, clinical

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In the United States, the leading cause of accidental death is drug overdose. Opioid overdose is now common, with prescriptions for opioid-containing medications quadrupling between 1999 and 2010. During that time, there was a fourfold increase in overdose deaths due to opioids (1). Regardless of many safety concerns, opioids continue to be used for many difficult to treat chronic pain conditions in lieu of a lack of evidence to support long-term effectiveness (2). This has led to a search for alternative or opioid-sparing treatments (3-6). As evidence to support different pain-relieving properties of medical cannabis has expanded, there is substantially increasing interest as to its potential role for many different chronic pain conditions. The use of medical cannabis as an alternative to opioids, or as an adjunctive treatment, is currently being researched.

Objectives

Can medical cannabis help reduce the amount of opioid use for patients with chronic pain conditions being treated with chronic opioids? Thus far, studies have shown mixed results. Multiple studies have demonstrated that simply legalizing medical or recreational marijuana has not led to a significant decrease in chronic opioid use for those with chronic pain (7,8). Other observational and epidemiological studies have demonstrated that medical cannabis use is associated with a decrease in opioid use, as well as a decrement in associated morbidity and mortality (4,5,9-11). These studies, as well as the pain-relieving properties of marijuana, demonstrate a potential application for medical cannabis in patients treating their chronic pain with opioids, but shed limited light on medical cannabis' effectiveness and appropriate role in clinical application.

Study Design

There are relatively few clinical studies detailing morphine milligram equivalent (MME) use in relation to medical cannabis used for chronic pain conditions (12,13). There are even fewer studies detailing the context in which medical cannabis is offered to patients as a treatment option. As far as the authors of this study are aware, there has not been a prospective study demonstrating the effectiveness of introducing medical cannabis into a treatment plan that includes a mandatory opioid weaning program if the patient decides to continue treating their pain with medical cannabis. In other words, medical cannabis was offered to patients with a qualifying pain condition with the understanding that concomitant use of medical cannabis and opioids would not be acceptable after a trial period of medical cannabis to determine individual effectiveness in treating the patients' chronic pain.

This single-center prospective study offers a specific presentation of medical cannabis treatment for patients treating chronic pain with opioids and has yielded significant decrement of MME for the majority of patients in this study. With the lower abuse potential and relative safety profile of medical cannabis, the authors of this study present a potential treatment plan which may reduce opioid use among many difficult to treat chronic pain patients.

Setting

This study was performed at the Allegheny Health Network Institute for Pain Medicine in Pittsburgh, Pennsylvania. The state of Pennsylvania legalized medical cannabis in April of 2016, and it became available to patients in February of 2018 through medical dispensaries.

Methods

Study Population

The patients included in the current study are organized by demographics (Table 1), as well as type of pain (Table 2). Notably, all patients included in this study met the state medical cannabis certification indication for "severe chronic or intractable pain."

Inclusion Criteria: 1) History of chronic non-malignant intractable pain that has failed conventional therapy; 2) Chronic opioid use for more than 6 months; 3) Patient understanding and agreement to Allegheny Health Network medical cannabis consent form and policies, including the goal to be weaned off all opioids as the policy does not allow patients to be on long-term opioids with medical cannabis for non-malignant pain; 4) At least one routine follow-up after medical cannabis certification.

Exclusion Criteria: 1) Patients on opioid maintenance therapy for opioid use disorder; 2) Patients on methadone therapy for chronic pain as there is no agreeable morphine milligram equivalent for the medication; 3) Patients currently with or a history of malignant pain; 4) Patients not willing to wean off opioids when presented medical cannabis, initially as an adjunctive treatment, and subsequently thereafter, as an alternative treatment; 5) No follow-up after certification.

Table 1. *Patient demographics.*

Gender	
Female	46
Male	29
Median Age (yrs)	59
Mean Age (yrs)	58.4
Age Breakdown	
30-39	4
40-49	14
50-59	22
60-69	24
70-79	9
80-89	2

Table 2. *Patient type of pain.*

Post laminectomy syndrome	23
Rheumatoid arthritis	7
Compression fracture	3
Myofascial pain	3
Neuropathic pain	3
Spinal stenosis	3
Chronic pelvic pain	2
Chronic postoperative abdominal pain	2
Chronic postoperative knee pain	2
Degenerative disc disease lumbar	2
Facet arthropathy lumbar	2
Osteoarthritis	2
Psoriatic arthritis	2
Sacroiliitis	2
Ankylosing spondylitis	1
Brachial Plexopathy	1
Central Pain syndrome	1
Cervical neural foraminal stenosis	1
Chronic knee pain	1
Chronic pancreatitis	1
Cranial neuralgia	1
CRPS type 1	1
Ehler-Danlos syndrome	1
Fibromyalgia	1
Lumbar spondylolisthesis	1
Mixed Cutaneous tissue disease	1
Polyarticular joint Pain	1
Sarcoidosis	1
Systemic Lupus Erythematosus	1
Thoracic intervertebral disc herniation	1
TMJ	1

Protocol Description

Patients that met the aforementioned inclusion/exclusion criteria were offered medical cannabis as a potential treatment option. After discussing the risks, benefits, and potential side effects of each patient's chronic opioid therapy, we presented medical cannabis as an alternative, potentially effective treatment for pain. We offered certification for medical cannabis, initially on a short-term basis, to determine individual efficacy for their type of pain. We deemed this the "trial" or "overlap" period as they were allowed to continue chronic opioid therapy. It was discussed at this initial visit, prior to certification, that after the trial period was over that a mandatory opioid weaning process would be initiated should they decide to continue medical cannabis as a treatment. It was made clear that concomitant use of medical cannabis and opioids would not be acceptable on a long-term basis.

Patients were counseled on the risks, side effects, and benefits of medical cannabis as supported by current evidence-based medicine. The limited scientific evidence base for medical cannabis treatment in certain diagnoses was discussed with the patient. Additionally, we discussed that the degree of effectiveness varies from patient to patient, and a trial of different medical cannabis formulations may be required to achieve an effect.

We discussed that trial periods could vary between 3 to 6 months. If patients met the aforementioned inclusion/exclusion criteria, an individual clinical trial was then conducted. At the initial visit and subsequent follow-ups, we encouraged patients to try various formulations, types, and strengths of cannabis to assess effectiveness. The patients were counseled on the cannabis strains of sativa, indica, and hybrid, as well as the differing ratios of tetrahydrocannabinol:cannabidiol (THC:CBD). As noted, possible side effects were discussed. One such well-documented risk includes the possibility that some strains of sativa have been linked with increased anxiety and may have various psychoactive side effects. We encouraged patients to avoid sativa, start with low doses of THC, and gradually increase the dose for effect. We also recommended that all patients avoid the inhalational route of medical cannabis to minimize other risks. At the end of their trial period, patients were clinically evaluated for their response to medical cannabis and screened for adverse side effects. At that time, if the patient was personally

satisfied with their level of response, barring adverse side effects, they subsequently underwent a mandatory opioid weaning process tailored to their specific clinical situation.

Depending on the type of opioids, dose of opioids, type of pain, and overall clinical situation, the opioid weaning period was variable. After the trial period was complete, patients were gradually weaned off opioids, starting with long-acting opioids, with the goal of discontinuation in several weeks. If patients did not find an effective medical cannabis regimen, they were subsequently de-certified for medical cannabis use, and they were again treated with an opioid regimen following minimally effective dosing principles.

The Pennsylvania Prescription Drug Monitoring Program (PDMP) was inquired on every patient at each visit. This was done initially to determine the length and dose of opioids before certification. Additionally, this information aided in structuring a personalized opioid weaning program as part of the overall clinical situation, should the patient decide to continue with medical cannabis treatment. The PDMP, along with random urine drug tests (UDT), were used to monitor compliance with the stipulations of the protocol.

The opioid doses were converted to morphine milligram equivalents using standardized conversion factors. During the study, patients were monitored with routine follow-ups every 1 to 3 months, random urine drug screens, and prescription monitoring using the Pennsylvania Prescription Drug Monitoring Program.

Results

Of the 542 patients certified for medical cannabis, 115 met the inclusion/exclusion criteria to evaluate those with chronic pain being treated with chronic opioids. The majority of those that were excluded were those certified for medical cannabis that were not using COT to treat their chronic pain. Seventy-five out of the 115 remained certified for medical cannabis as they had significant pain relief, with increased functional ability, and did not report or demonstrate any major adverse effects. Out of the 40 patients that were decertified, 27 were decertified secondary to ineffectiveness, 4 failed to follow-up, 3 for side effects, 3 for costs, one passed away independent from their medical cannabis use, one transferred care elsewhere, and one was transferred to a skilled nursing facility where medical cannabis was prohibited. For the side effects, one patient experienced agitation and asthma hyperreactivity, one experienced déjà vu, and the last patient experienced hallucinations. It is notable that the patient who experienced asthma hyperreactivity did not follow recommendations to avoid the inhalational route.

Excluding reasons for medical cannabis decertification unrelated to efficacy or side effects (10 patients), the study yielded 75 patients deciding to undergo the opioid weaning process whilst continuing with medical cannabis, and 30 patients deciding to stick with COT, instead of medical cannabis, to control their chronic pain. Therefore, when presented medical cannabis within the aforementioned context, this equates to 71.4% (75/105) of patients deciding to decrease their COT as the medical cannabis trial met their personal pain-reduction standards to such a significant degree that they chose to wean their COT, as the decision was left to the patient.

The average starting MME for 115 patients was 50.5. For the patients that remained certified, their starting MME mean was 49.9 with a standard deviation of 64.5. The decertified group was 52.1 MME. There was a 67.1% decrease in the morphine equivalents from 49.9 to 16.4 after the first follow-up for the patients that remained certified for medical cannabis. For patients that had a second follow-up visit, there was a 73.3% decrease in MME from 49.9 to 13.3. An ANOVA analysis was performed and found a significant decrease in the use of opioids ($P < 0.0001$).

Limitations

An important limitation of this study is the absence of long-term data of medical cannabis in treating chronic pain currently treated with chronic opioids. To address this limitation, these patients will continue to be followed with updated results to be presented at a future time, but the initial decrement in daily MMEs has been significant. It can be argued that this decrement is the result of the prescriber's refusal to write for the patient's current dosages of opioid medication once the patient chooses medical cannabis, but contrary to that notion, the patients demonstrating this decrement have chosen this treatment route over opioids. We posit that this will help maximize long-term success rates in this group of patients.

The heterogeneity of the group of patients studied should be noted as the majority of patients had been diagnosed with post-laminectomy syndrome, but conclusions made for a specific diagnosis should be withheld and only applied to the broader category of chronic non-malignant pain.

Conclusions

Researchers are currently debating the many questions that must be answered in order to make an informed clinical recommendation regarding medical cannabis for those using chronic opioids to treat chronic pain. Notably, there is poor evidence to begin with to support any long-term reduction in pain, or functional increases, when chronic opioid therapy is used for chronic non-malignant pain. A quickly increasing number of studies looking solely at medical cannabis' effectiveness for reducing pain has demonstrated variable results. A recent article in JAMA summarized the current state of evidence noting some significant evidence for the effectiveness of cannabis when used for neuropathic pain, but stresses insufficient evidence for other types of pain, citing study-design limitations including non-clinical or population-level studies, in addition to an ill-defined proposed role in clinical application (3). The current study attempts to address some of these concerns with the understanding that many additional well-designed clinical studies are required to define the clinical role of medical cannabis better. The current study's approach has led to a significant decrement in chronic opioid use for the majority of patients with chronic pain deciding to trial medical cannabis in our clinical setting.

Multiple studies have demonstrated a lack of evidence to support that state-level policy changes regarding medical cannabis correlate with a significant decrement in opioid use in large population-level studies (7,8). Additionally, one of the longest prospective studies to date did not demonstrate a significant reduction in long-term prescribed opioid use for patients using cannabis (15). This may demonstrate a significant limitation in the efficacy of cannabis used for chronic pain when presented as an adjunctive treatment to chronic opioids. It is also plausible that the limitation in efficacy could be, in part, due to analyzing general cannabis use as opposed to medical cannabis use with physician oversight. The current study's protocol presented medical cannabis to a similar population using chronic opioid therapy as an alternative treatment, but only after an overlap period of adjunctive use to determine individual clinical efficacy. If the patient determined sufficient effectiveness of medical cannabis for their chronic pain, a mandatory opioid weaning process was subsequently initiated. With a lack of long-term safety studies for medical cannabis, there are polypharmacy and medicolegal risks associated with this treatment option, specifically for this group of patients. Offering medical cannabis with this type of protocol should minimize those risks by limiting the amount of time patients are able to use both medical cannabis and chronic opioids concomitantly. It also offers physician oversight as well as a plan to eliminate chronic opioid use for this group of patients, thereby decreasing patient risk from the well-documented risks of chronic opioid therapy. It is the authors' position that this specific clinical context in which medical cannabis was offered, as well as this specific clinical indication, that the current study yielded such impressive results from both a compliance perspective (71.4% deciding to wean their chronic opioid regimen) and from an %MME-reduction perspective (73.3% average daily MME-decrement at 2 months of follow-up).

The authors of this study posit 2 plausible conclusions to further support the successful clinical context assertion for this study's increased effectiveness in decreasing prescription opioid use. First, allowing the patient their own individual medical cannabis trial allows them to determine the extent of effectiveness for their type of chronic pain. It allowed our patients to prepare for the opioid weaning process, knowing that they have another treatment with a degree of effectiveness that meets each patient's individual standard. This gives them the decision to undergo the opioid weaning process only if they find medical cannabis to treat their pain sufficiently. A second possible conclusion for this study's superior outcome results from inclusion criteria that differentiate those patients with a willingness to undergo opioid weaning. Our patients trial medical cannabis with the understanding that concomitant use of opioid pain medication and medical cannabis will not be tolerated on a long-term basis. This effectually narrows in on the population with a willingness to decrease opioid use. This is similar to a widely accepted approach for physicians combating tobacco use wherein the patient must first affirm a willingness to quit in order to maximize successful long-term results. Therefore, applying this same concept to patients using chronic opioid therapy, the authors of this study expect to see optimized long-term results through this unique presentation of medical cannabis as a treatment option. Therefore, we present medical cannabis as an alternative, potentially effective, class of treatment.

As previously alluded to, the safety of medical cannabis must be taken into account when considering it as a possible treatment option for this patient population. The safety profile of medical cannabis requires extensive additional research, but many have drawn initial

conclusions that apply to this patient population. Cannabis has been shown to be associated with increased risk of motor vehicle accidents, cognitive impairment, and long-term structural brain changes (3,14). These same risks have been demonstrated for those taking chronic opioids, with the exception of an increased risk of fatal overdose (3,14). Therefore, some have inferred a superior safety profile relative to chronic opioid use. Regardless, it is widely accepted that more studies are needed concerning long-term medical cannabis use in regards to safety in order to address the extent of risk a patient accepts when choosing this treatment option. Additionally, chronic use of cannabis has demonstrated relatively negligible physiological dependence in comparison to chronic opioid use, but psychological addiction should not be overlooked, especially in this grouping of patients, as euphoric effects, addiction, and even placebo-effect may play some role in patients choosing either chronic opioid therapy or medical cannabis. Regardless, a patient's long-term adherence to a treatment plan resulting in a persistent decrement in chronic opioid use, in addition to medical cannabis, argues against a significant placebo effect; therefore longer-term monitoring of the current study's population should prove useful.

With increasing awareness and education aimed at decreasing high-dose opioid prescribing patterns, the authors of this study expect to see a decline in opioid-related overdose deaths over time when viewed simply from an availability standpoint. This previous assumption does not take into account those patients that turn to illegal opioid/opiate use, as many patients are forcibly weaned from high-dose opioids without suitable alternative treatment options. During this paradigm shift regarding accepted opioid prescribing practices, many patients are at increased risk of morbidity and mortality, which places increased importance on developing improved treatment paradigms, which may include medical cannabis.

Initially, it was argued that legalizing medicinal cannabis may adversely affect opioid misuse and abuse rates. Data to date has not supported this claim. Current evidence indicates that chronic opioid therapy with concurrent medical cannabis use either does not decrease MME requirements or does so to a modest degree. Additionally, considering societal and patient-level harms of chronic opioid prescribing practices, as well as continued opioid abuse in states where medical cannabis has been legalized, we feel strongly, based on our study, that medical cannabis should only be available for treatment under a physician's oversight and as part of a treatment strategy which includes compliance monitoring to minimize harms and improve efficacy rates. After discussing the risks, benefits, and potential side effects of chronic opioid therapy with the patient, the authors of this study present medical cannabis, used with the current study's paradigm, as a potentially effective class of treatment for chronic pain.

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