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Is administration of marijuana effective in reducing pain?

David Cui, PA-S

A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

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Abstract

Objective: The objective of this selective EBM review is to determine whether or not “Is administration of marijuana effective in reducing pain”

Study Design: Systematic review of 2 randomized, double-blind placebo controlled trials (RCTs) and 1 cohort study published after July 2016.

Data Sources: Both RCTs and the cohort study were found through the PubMed database

Outcome(s) measured: All 3 studies utilized the 11-point numerical rating scale to measure pain intensity.

Results: Wilsey et. al showed a notable improvement in pain intensity when participants inhaled both 2.9% delta 9-THC and 6.7% delta 9-THC concentrations when compared to visually matched placebo with no significant distinction between the lower and higher concentrations of delta 9-THC at the end of 7 hours. Although Schimrigk et. al did show pain reduction with administration of both dronabinol (PO form of THC) and placebo after 16 weeks, the results between the two were not significant when compared to each other. Lastly, the cohort study performed by Vigil et al. did reflect a significant change in pain intensity reduction after self-administrated use of marijuana after 12 months.

Conclusion: This EBM review demonstrated that marijuana is an safe, effective treatment option for chronic pain patients looking to reduce their pain intensity. Although marijuana should not replace current conventional medical therapies, it may serve as an alternative for patients willing to try other options for pain relief.

Introduction

Pain is a component of many physical and mental health conditions, which can limit daily life and work activities for certain individuals, as well as contribute to high healthcare costs. Pain can be classified as acute or chronic, with chronic pain being defined as lasting more than 12 weeks. ¹ There are many etiologies of pain, which can include but are not limited to: injuries/post-operation incision pain, being related to a condition (ex. herniated discs, arthritis, migraines, multiple sclerosis, cancer, nerve damage), or even those without an apparent cause (fibromyalgia).

Pain is one of the most common reasons for Americans to access the healthcare system presently. Among pain sufferers, 63% have visited their PCP, 40% have visited specialists, and 25% have visited a pain management physician or chiropractor. ² There are an estimated 100 million U.S. adults living with chronic pain, making this affect more people than diabetes, heart disease, and cancer combined. Unfortunately, this translates to contributing to an estimated \$560-635 billion each year in direct medical costs, lost productivity, and disability resources. ² Without proper pain relief, people may be reluctant to attend work, leading to difficulties with maintaining employment and thus insurance coverage. This can result in depression and a host of other health issues. Because chronic pain is the leading cause of long-term disability, it is therefore extremely important for healthcare practitioners to understand the different approaches in pain management for the diversity of conditions they may treat, while maintaining quality of life for each individual patient.

While extensive research on pain has been exceptionally beneficial, not all is fully understood about the multiple microbiological mechanisms that can be involved in pain. We do

understand the basic pathophysiology behind many types of pain as well as the pharmacodynamics of many drugs we use to treat pain, such as over-the-counter analgesics, opioid medications, and even medical marijuana. However, it becomes increasingly difficult because pain is largely a subjective experience and there can be psychosocial contributors that can modify pain levels such as stress, anxiety, and weather.³ While there are indeed many different tools healthcare practitioners can use to assess the cause of pain such as radiological imaging, blood tests, electromyography, etc., the results may not correlate to what a patient may actually be personally expressing.

Depending on the specific etiology, there are a number of conventional treatment options to treat pain. These can be broken down into the categories of: medications, therapy, procedures, and self-care. Medications include acetaminophen, NSAIDs, COX-2 inhibitors, opioids, antidepressants, anti-epileptics, and others. Therapy may include physical therapy, massage, cognitive behavioral therapy, acupuncture, and others. Procedures include nerve blocks and surgery. Lastly, self-care in the form of relaxation techniques, diet, and stretching techniques can also be utilized. Effective management for chronic pain may require using many different options and including the coordinated efforts of many healthcare professionals to obtain the best results.

Marijuana is being researched as an alternative for chronic pain management. With our current opioid epidemic leading to increasing overdose death rates and new CDC guidelines of maintaining less than or equal to 90 morphine milligram equivalents (MME) a day, there needs to be safer and similarly effective options for patients suffering from chronic pain. When compared to opioid prescriptions, marijuana options generally have less severe side effects. Even

despite today's marijuana products being more potent than in the past, there have been no deaths from overdoses with marijuana alone according to the DEA. ⁴ In addition, marijuana may help promote sleep, increase appetite, and relieve nausea - relieving some additional symptoms patients with chronic pain may concurrently suffer from.

Objective

The objective of this selective EBM review is to determine whether or not: "Is administration of marijuana effective in reducing pain?"

Methods

Among the 3 studies used in this EBM review, 2 were randomized double-blind, placebo controlled trials and 1 was a cohort study. All three studies included chronic pain patients who were adults over the age of 18. The interventions for the two RCTs included marijuana administration compared to visually matched placebo, and they looked at pain severity changes before and after. Wilsey et al. used 2.9% and 6.7% delta 9-THC vaporized marijuana, ⁵ while Schimrigk used a patient tolerable dose of dronabinol (PO form of THC) following a 4 week titration period. ⁶ The RCT performed by Wilsey et al. included a crossover design, so all patients were exposed to both dosages of vaporized marijuana as well as placebo on separate days 3 days apart to permit the metabolic breakdown of delta 9-THC metabolites. ⁵ The cohort study by Vigil et al. looked at chronic pain patients, who had filled at least 2 opioid prescriptions during the 3 months prior to enrollment into the New Mexico Medical Cannabis Program (MCP) or not enrolling. The researchers then gathered prescription records during a 21 month period (which includes the 3 months) regarding differences between opioid prescription refills between MCP enrolled patients and those who did not enroll. They also sent surveys to MCP enrolled patients

after 12 months to see if self-managed administration of marijuana improved pain severity.⁷ Outcomes for all three studies measured were changes in pain level after administration of marijuana.

Data sources were searched using the key words: “marijuana” and “chronic pain” in PubMed-NCBI. The studies were chosen if they addressed the research question and whether the outcomes addressed Patient-Oriented Evidence that Matters (POEMs). All articles were published in English in peer-reviewed journals and dated after July 2016 with adult chronic pain patients over the age of 18. Patients with significant mental health histories, substance abuse, and co-morbidities that could lead to a deleterious effect on well-being (ie. severe cardiac disease) were excluded. The mean change from baseline, p-value, CI, and NNT were statistics used to determine significance.

Table 1 - Demographics & Characteristics of included studies

Study	Type	# Pts	Age (yrs)	Inclusion criteria	Exclusion criteria	W /D	Interventions
Wilsey (2016) ³	Randomized, double-blind, placebo controlled, crossover design study	42	age >18 and < or = to 70 years	<ul style="list-style-type: none"> - age >18 and < or = to 70 years - pain intensity > or = to 4 on a 11-point pain intensity numerical rating scale - > or = to 12 on Leeds Assessment of Neuropathic Symptoms and Signs to substantiate neuropathic pain 	<ul style="list-style-type: none"> - those with significant mental health Hx - co-morbidities leading to a deleterious effect on well-being (x. severe heart dz) - substance abuse 	0	Inhalation of vaporized 2.9% and 6.7% delta 9-THC
Schimri gk (2017) ⁴	Randomized, double- blind, placebo-controlled design study	240	age >18 and < or = to 70 years	<ul style="list-style-type: none"> - age >18 and < or = to 70 years MS pts - pain intensity > or = to 4 on a 11-point pain intensity numerical rating scale 	<ul style="list-style-type: none"> - any peripheral pain syndromes - preexisting psychotic disorders - severe cardiac dz - substance abuse 	31	Administration of dronabinol (THC) patient specific tolerable dose following a 4 week titration period
Vigil (2017) ⁵	Cohort study	37	Did not specifically mention; experimental group mean age = 54 y/o control group mean age = 60 y/o	<ul style="list-style-type: none"> - pts diagnosed with “severe chronic pain” by 2 independent physicians - pts must have filled at least 2 opioid Rx during the 3 mo prior (with max daily dosages of less than 200mg IV morphine equivalence) 	<ul style="list-style-type: none"> - pts who did not fill at least 2 opioid prescriptions during the 3 mo prior - inflammatory diseases 	3	Self-managed administration of cannabis products

Outcomes Measured

Wilsey et al. used the 11-point numerical rating scale (0= no pain to 10 = strongest pain imaginable) to measure pain intensity before and after administration of marijuana. Marijuana or placebo were administered at hours 1 and 4. Each patient was assessed at baseline (hour 0) before intervention and at 1 hour intervals up to hour 7. ⁵ The scores were compared between the groups receiving 2.9% delta-9 THC, 6.7% delta-9 THC, and placebo to see if there was a difference in improvement in pain intensity.

Schimrigk et al. also used the 11-point numerical rating scale to measure pain intensity before and after administration of dronabinol. Dronabinol or placebo were administered at week 0, and mean change of pain intensity from baseline to mean weekly pain scores were measured up to week 16. ⁶ The 2 groups were compared to see if there was a significant change in pain intensity during these 16 weeks.

Vigil et al. looked at prescription records for opioid prescribed patients enrolled in the New Mexico Medical Cannabis Program (MCP) and compared them to those not in the program to see if there was a reduction in opioid medication refills. In addition, they assessed if self-managed administration of marijuana improved pain severity for patients after 1 year of being enrolled into the MCP with the 11-point numerical rating scale to measure pain intensity. Unfortunately, this same information was not obtained from the comparison group.

Results

This review used 2 randomized, double-blind placebo controlled trials and 1 cohort study to look at the efficacy of marijuana and its relation in improving pain intensity for patients with

chronic pain. The inclusion and exclusion criteria for all of these studies can be referenced from Table 1.

Wilsey et al. utilized 42 participants randomized into 1 of 3 treatment groups: 2.9% delta 9-THC, 6.7% delta 9-THC, and visually matched placebo. Since this study was a crossover design study, all patients received all 3 treatment options on different study days. At baseline, there was no reported significant mean pain intensities differences between the 3 groups ($p > 0.6$).⁵ After 1 hour of administration of the first treatment dose, it was found that pain intensity was significantly lower for the 2 experimental groups compared to control ($p < 0.05$) with 6.7% delta 9-THC retaining significance for the next 2 hours ($p < 0.01$).⁵ After administration of the second treatment dose, this also showed that pain intensity was lower for both experimental groups compared to control ($p < 0.05$), although the effect on pain showed no significant distinction between 2.9% delta 9-THC and 6.7% delta 9-THC ($p > 0.11$) at hour 7.⁵ Using a reduction of pain intensity of $\geq 30\%$ as clinically important, it was determined that 18 placebo patients, 26 lower dose THC patients, and 35 higher dose THC patients met this criteria.⁵ The NNT to obtain 30% pain reduction was 4 for the lower dose and 3 for the higher dose when compared to placebo.⁵ These results are summarized in Table 2 below, which also include the 95% confidence intervals. No serious adverse events were reported in this study.

Table 2. Reduction of pain intensity by $>30\%$ [defined as clinically important]

Intervention	Placebo	Low	High
# patients	18	26	35
% patients	45%	70%	88%
95% CI	31-60%	54-83%	74-95%
NNT	N/A	4	3

Schimrigk et al. had a total of 240 participants randomized into 124 dronabinol and 116 placebo treatment patients. There was no significant differences at baseline for pain between the 2 groups, with pain intensity values being at 6.4 ± 1.49 (dronabinol) and 6.74 ± 1.41 (placebo).⁶ Although both experimental and control groups showed a clinically relevant pain reduction after 16 weeks, the mean change of pain intensity from baseline to mean of weeks 1-16 compared between dronabinol (1.92 ± 2.01 ; 30%) and placebo (1.81 ± 1.94 ; 27%) was not statistically significant ($p=0.676$).⁶ Serious adverse events were rare but reported in this study in 3 patients, which comprised of dysphoria, constipation, and exacerbation of preexisting pain.⁶

Vigil et al. had a total of 66 participants divided into 37 patients who enrolled in the MCP compared to 29 non-enrolled patients. By the end of the 21 month observation period, it was found that 83.8% of MCP patients were more likely to reduce daily opioid dosages compared to 44.8% non-enrolled patients ($p<0.001$), and 40.5% of MCP patients ceased filling opioid prescriptions altogether compared to 3.4% of non-enrolled patients ($p = 0.001$). The researchers also assessed pain reduction directly using the 11-point numerical rating scale to measure pain intensity. They found that 33 of the 34 respondents had a statistically significant change in pain intensity at 12 month post-enrollment (mean change = -3.4, $p<0.001$), shown in table 3. No serious adverse events were reported in this study.

Table 3. Survey responses at 12 months post-MCP enrollment

Variable	Mean \pm SD	Min	Max	P-value
Pain prior to MCP (0-10)	8.6 ± 1.4	4	10	<0.001
Pain after MCP (0-10)	5.3 ± 1.7	2	10	<0.001

Change in pain (post-prior)	-3.4 ±2.1	-7	3	<0.001
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Discussion

The 3 studies that were discussed in this EBM review show that marijuana can impart relief on pain intensity for patients with chronic pain. Research continues to prove hopeful for the advancement of marijuana to treat pain in addition to many other different medical conditions. Currently, there are other clinical trials showing benefit in the treatment of seizures, immunological diseases, inflammatory conditions, mental health/substance abuse disorders, and even cancer. ¹¹

There are several limitations noted in these studies as well as with marijuana in general. Both Wilsey et al. and Vigil et al. had sample sizes of less than 50 participants, leading to a question of validity to the general population. Wilsey et al. did not address long-term pain intensity changes as the studies performed were limited to separate single days. Furthermore, Vigil et al. did not obtain information regarding pain intensity changes from the comparison group, had 3 non-respondents from the experimental group regarding pain intensity changes, did not verify opioid and cannabis usage via drug screen, could not randomize participants, and could not monitor the type or amount of marijuana usage in their study. Even though marijuana dispensaries are mandated to report laboratory information regarding their marijuana products, there are just so many different types of options available (topicals, vaporizer, dried flower, edibles, drinks, tablets, sublingual etc.) with different potencies, psychoactive effects, and medical benefits, so it may be difficult for patients to find the products that work for them. For example, ingested products take longer to be absorbed in the body compared to inhaled products,

but they tend to exert their effects longer. With regards to long-term detrimental effects, it is known that marijuana may cause mental health disorders, including psychosis.⁹ There is also supporting evidence regarding long-term use being associated with respiratory issues, such as chronic bronchitis and lung cancer as well as risks associated with cardiovascular disease patients, such as increases in cardiac workload, increased catecholamine levels, and impaired blood oxygen carrying capacity.¹⁰ There is also the limitation of cost for patients, as marijuana itself is not a FDA approved drug at the time of this writing, so insurance companies are reluctant to offer coverage.⁸ This currently results in patients needing to pay out of pocket for this option if they wish to pursue it.

Conclusion

This EBM review has demonstrated that marijuana is an safe, effective treatment option for chronic pain patients looking to reduce pain intensity. The evidence gathered here from after July 2016 complements previous research performed addressing marijuana's ability to alleviate pain. Wilsey et al. found that inhaled marijuana was able to provide significant benefit in pain relief for at least 6 hours, when compared to placebo with 2 administered dosages.⁵ Despite the fact that Schimrigk et al. was unable to show a statistically significant difference between dronabinol and placebo, they were able to provide results revealing that dronabinol is a safe long-term treatment option for patients with chronic pain.⁶ Vigil et al. provided evidence that when given the option to use marijuana to self-manage pain over the course of a year, patients had improvements in pain intensity, which actually decreased their need to fill their routine opioid prescriptions.⁷

Future areas of research may prove beneficial to explore the different delivery methods mentioned above as well as include synthetically synthesized marijuana products in research to compare different efficacies. To that note, it would likewise be important to evaluate potency, dosing, and the effects of the individual components comprised in the makeup of marijuana. Dependence and tolerance are other issues to evaluate as it is with any drug. Another important consideration is the impact on marijuana on daily functioning and mood, which were not explicitly addressed in the 3 presented studies. Lastly, it is extremely important to increase validity and reliability by increasing sample size and having longer treatment times. Although marijuana should not replace current conventional medical therapies, it may serve as an alternative for patients willing to try other options for pain relief. Hopefully, ongoing research in the next couple years continues to shed more light on the benefits and disadvantages in using marijuana to manage pain, leading to wider acceptance by both patients and healthcare practitioners alike.

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