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Does Routine Use of Medical Cannabis (Marijuana) Decrease the Intensity of Chronic Neuropathic Pain in Adults?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

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Abstract

Objective: The objective of this selective EBM was to investigate the question, "Does routine use of medical cannabis (marijuana) decrease the intensity of neuropathic chronic pain in adults?

Study Design: systematic review of 3 English language primary studies, published between 2005 and 2009.

Data Sources: Three Randomized Controlled Trials (RTC's) published on or after 2005 were selected based on their relevance to the proposed question via PubMed. All three RTC's compared cannabis use vs. placebo for chronic neuropathic pain, with two RTC's focusing on HIV neuropathic pain and the third focusing on MS.

Outcome(s) Measured: The outcomes measured in these trials were by how much medical cannabis decreases the intensity of chronic neuropathic pain. This was accomplished using three techniques depending on the study: A self-reporting visual analog scale; a Descriptor Differential Scale (DDS); and an 11-point numerical sliding scale.

Results: Ronald Ellis and co-authors demonstrated that the proportions of subjects with HIV achieving at least 30% pain relief with cannabis versus placebo were 0.46 (95%CI 0.28, 0.65) and 0.18 (0.03, 0.32). Abrams and co-authors demonstrated that smoked cannabis reduced daily pain with HIV by 34% vs 17% with placebo ($p = 0.03$). Greater than 30% reduction in pain was reported by 52% in the cannabis group and by 24% in the placebo group ($p = 0.04$). Rog and co-authors demonstrated that cannabis was superior to placebo in reducing the mean intensity of pain of MS (CBM mean change -2.7, 95% CI: -3.4 to -2.0, placebo –1.4 95% CI: -2.0 to -0.8, comparison between groups, $p = 0.005$).

Conclusions: There is a significant benefit to patients with chronic neuropathic pain when using medical cannabis vs. placebo in HIV and MS. While the risks and benefits to daily use of medical marijuana needs to be further investigated, medical cannabis can be an effective alternative to standard treatments in those who can't tolerate their side effects.

Key Words: Chronic Pain; Cannabis

INTRODUCTION

For those with lifelong multisystem medical conditions such as HIV or Multiple Sclerosis, chronic neuropathic pain characterized by nerve and/or tissue damage causing recurrent pain over a prolonged period of time is a constant debilitating problem. Multiple sclerosis is a disease which causes the development of primary lesions on different areas of the brain, leading to downstream CNS neuropathic pain in an unpredictable manner in 17-52% of patients. The symptoms largely depend on the individual, but they more frequently involve the peripheral extremities and can including the sensations of burning, aching, prickling, stabbing, or squeezing.[1] Nearly 32% of MS patients confirm the notion that MS is "frequently disabling and inadequately managed".[1] For HIV, one of the most common HIV-associated sensory neuropathy found in as many as 30% of patients is chronic neuropathic pain in the form of aching, burning, or painful numbness.[2,3] Hyperalgesia, or an abnormally heightened sense of pain, is common in the HIV population as well.[3]

Chronic pain affects more than 50 million patients annually.[4] While there is no clear data depicting just how many visits there were to health institutions annually, when comparing the cost of chronic pain to other common ailments, there was a significantly higher cost associated with chronic pain ($635 billion) than the estimated annual costs of heart disease ($309 billion), cancer ($243 billion), and diabetes ($188 billion). The $635 billion in annual costs include healthcare expenses, loss of income, and loss of productivity, which makes this one of the leading costs in our healthcare system today.[5]

These chronic neuropathic pains can be quite debilitating which prompts the use of standard treatments such as NSAIDs and opioid medications as well as biofeedback and topical

remedies. Treatment for HIV-associated sensory neuropathy also includes anticonvulsants such as lamotrigine and gabapentin, however some patients fail to respond or are unable to handle the side effects of such treatments.[3] This has led researchers to explore alternative forms of medicine for patients with chronic neuropathic pain.

Of the alternative medicines researched, the use of medical cannabis, or marijuana, has become an important and controversial center of debate. Cannabis is an illicit recreational drug that causes users to enter a mild state of euphoria. The most abundant active ingredient in cannabis, tetrahydrocannabinol(THC), and its synthetic derivatives, produce effective analgesia in most animal models of pain. The antinociceptive effects of THC are mediated through cannabinoid receptors(CB1, CB2) in the central and peripheral nervous systems, which in turn interact with noradrenergic and k-opioid systems in the spinal cord to modulate the perception of painful stimuli. The endogenous ligand of CB1, anandamide, itself is an effective antinociceptive agent.[2]

There is a huge stigma associated with cannabis due to it not only being an illegal substance, but also due to it being in the DEA scheduling category 1; along with LSD, peyote, and ecstasy. Recently there has been a major movement to decriminalize cannabis for medicinal use due to its analgesic and euphoric properties. Since 1996, 23 states have legalized medicinal marijuana, indicating that this will increasingly become more common within the healthcare field: directly impacting physician assistants and their colleagues.

OBJECTIVE:

The objective of this selective EBM was to investigate the question, "Does routine use of medical cannabis (marijuana) decrease the intensity of neuropathic chronic pain in adults?

METHODS:

Research for this review was performed using PubMed using keywords Chronic Pain; and Cannabis. Articles were selected based on their relevance to the proposed question and whether they were patient oriented outcomes (POEMS). All articles were Randomized Controlled Trials (RTC's), published scholarly peer reviewed articles, and were published in English between 2005 and 2007.

Three studies were included in this review: Randomized, controlled trial of cannabis-based medicine in the central pain in multiple sclerosis by Rog et al[1]; Smoked Medical Cannabis for Neuropathic Pain HIV by Ellis et al[2]; and Cannabis in Painful HIV-Associated Sensory Neuropathy: A randomized Placebo-Controlled Trial by Abrams et al[3]. Criteria used for selection of these studies included chronic neuropathic pain in male and female adults due to MS or HIV and intervention using cannabis with a comparison to placebo to decrease the intensity of chronic neuropathic pain. Inclusional criteria varied slightly by trial but typically included adults with chronic pain, prior lifetime cannabis used, and a negative toxicology screening prior to start of trial. Exclusional criteria also varied slightly by trial but typically included a negative history of substance abuse, psychiatric disorders, or unstable disease. Each article used a different style of measurement to determine clinical significance (visual analog scale, descriptor differential scale, and an 11-point numerical scale) between intervention and control and included p-values, RRR,

ARR, and NNT in their statistical analysis. The demographics and characteristics of the included studies are displayed in Table 1.

Table 1 - Demographics & Characteristics of included studies

Study	Type	#Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Rog[1] (2005)	RCT	64	Mean: 49.2 y/o	1. Adult patients with central neuropathic pain syndrome due to multiple sclerosis for at least 6 months	1. Unstable Health 2. Substance abuser 3. Psychiatric disorder 4. Current MS exacerbations including positive Lhermitte's sign	2	Oromuscosal Cannabis Spray vs. Oromuscosal Placebo Spray
Ellis[2] (2009)	RCT	26	Mean: 49.1 y/o	1. Adults with HIV with neuropathic pain refractory to at least two previous analgesics	1. Unstable Health 2. Substance abuser 3. Psychiatric disorder 4. Positive urine toxicology screen	6	Smoked Cannabis vs. Placebo
Abrams[5] (2007)	RCT	50	Mean: 48.5 y/o	1. Adults with HIV infection and chronic pain 2. Had a stable medication regimen	1. Unstable Health 2. Substance abuser or smoker 3. Have never had prior experience smoking cannabis	5	Smoked Cannabis vs. Placebo

OUTCOMES MEASURED

In the study by Rog et al, outcomes were measured daily using an 11-point numerical scale, with 0 being no pain and 10 being the worst possible pain. Every day, participants were randomly assigned either an oromucosal spray containing plant derived cannabis-based medicine THC:CBD or a placebo that contained compounds to mimic the appearance, taste and smell of the THC:CBD spray with no active components. Participants were blinded to whether they received the cannabis or the placebo. After a 7 day baseline period, daily results were recorded over the course of 4 weeks.[1]

In the study by Ellis et al, outcomes were measured by a Descriptor Differential Scale (DDS). The DDS is a ratio scale containing 24 words describing pain intensity. Ratings are averaged to provide a summary score on a 0- to 20- point scale. Members participated in a 5 phase study over the course of 7 weeks. Phase 1 lasted one week and was meant to secure a baseline. During Phase 2 and 4, participants were blindly and randomly given either a placebo or cannabis to smoke under the observation of a study nurse four times a day for 5 days. During Phase 3 and 5, participants weren't given any cannabis or placebo to achieve a "wash-out" period and allow for the cleansing of cannabis from their system while also observing secondary affects. These two phases lasted two weeks each. The effects were recorded using the DDS.[2]

In the study by Abrams et al, outcomes were measured with a self-reported visual analog scale from 0- to 100-points, with 0 being no pain and 100 being the worst amount of pain, and recorded in a daily diary. Members participated in a 4 phase study: Phase 1 was a pre-intervention phase; Phase 2 was an acclimation phase; Phase 3 was the intervention phase; and Phase 4 was the post-intervention phase. Baseline measurements were obtained during Phase 2.

During phase 3, participants were blindly and randomly given either a placebo or a cannabis cigarette under supervision. Data measurements were collected throughout all 4 phases.[3]

RESULTS

Three double blind, randomized placebo-controlled trials were used to compare whether medical cannabis vs placebo offered a decrease in pain intensity in patients with chronic neuropathic pain caused by systemic diseases such as HIV and MS.

Significant mean reductions favoring CBM were found for the primary outcome of pain in HIV patients as reported by Rog et al. Of the total 65 patients, 59 (89%) had dysesthetic pain and seven (11%) had painful spasms. In the patients with dysesthetic pain, the mean change in pain was -2.4 (SD = 1.5, n = 30) for CBM and -1.3 (SD = 1.7, n = 28) for placebo. In patients with spasm, the mean changes were -5.7 (SD = 3.5, n = 3) and -2.1 (SD = 1.6, n=4). 30% of CBM participants experienced at least one adverse event compared to the 22% of placebo participants. These adverse events included dizziness, dry mouth, weakness, fatigue, etc. No adverse events were serious; however two female patients had to be removed from the trial due to the severity of their adverse event. Table 2 breaks down the control event rate, experimental event rate, relative and absolute risk ratios, and the numbers needed to treat.[1]

Table 2: Analysis data comparing CBM and placebo use in patients with chronic neuropathic pain using an 11-point sliding scale reported by Rog et al

Rog	Patients	CER	EER	RRR	ARR	NNT
	64	.24	.52	1.17	.28	4

In the trial conducted by Ellis et al, pain reduction was significantly greater with cannabis compared to placebo (median difference in pain reduction =3.3 DDS points). The active cannabis group achieved pain reduction of 30% greater than the placebo cannabis week (0.46 (95%CI 0.28, 0.65) vs 0.18 (0.03, 0.32), p=0.043). The number needed to treat (NNT) to achieve 30% pain reduction was 3.5 (95% CI 1.9, 20.8). Also, the median change in pain scores from baseline was -17 (-58, 52) for cannabis as compared to -4 (-56, 28) for placebo (p=0.001). Adverse events were noted in the smoked cannabis group more-so than in the placebo group, but like the trial by Rog et al, they were mild and not serious. Table 3 breaks down the control event rate, experimental event rate, relative and absolute risk ratios, and the numbers needed to treat.[2]

Table 3: Analysis data comparing CBM and placebo use in patients with chronic neuropathic pain using the descriptor differential scale reported by Ellis et al

Ellis	Patients	CER	EER	RRR	ARR	NNT
	26	.18	.46	1.56	.28	4

In the trial conducted by Abrams et al, 13 of 25 patients who were given cannabis cigarettes had >30% reduction in pain from baseline to end of treatment as opposed to 6 of 25 patients receiving placebo cigarettes (52% vs 24%; difference of 28%, 95% CI 2% to 54%, p = 0.04). The median reduction in chronic neuropathic pain on the daily diary visual analog scale was 34% in the cannabis group and 17% in the placebo group; difference = 18%; p = 0.03. Adverse events were similar to the trails by Rog et al and Ellis et al, however no participants withdrew from the study due to them. Table 4 breaks down the data depicting baseline daily visual analog scale scores in both study groups as well as the average daily scores during the treatment phase.[3]

Table 4: Analysis data comparing CBM and placebo use in patients with chronic neuropathic pain using a daily diary of self-reported visual analog scale scores reported by Abrams et al

Abrams	Intervention	Patients	Baseline Score	Final Treatment	Mean Difference
	CBM	25	6.58 (6.00-7.15)	3.85 (3.13-4.58)	-1.25 (-2.11 to -0.39)
	Placebo	25	6.37 (5.77-6.97)	4.96 (4.19-5.72)	

DISCUSSION

In assessing the three randomized controlled trials comparing cannabis-based medicine to placebo in reducing chronic neuropathic pain, it's important to note the limitations of the studies. Complications arising from the use of CBM were minimal, with acute adverse events ranging from mild dizziness, nausea, weakness, dry mouth, and fatigue being few and far between with little impact on the overall outcome. Only 2 of the 65 participants in the Rog trial removed themselves from the study due to the adverse events, making them the only participants that were removed due to the effects of CBM from all three trials. However, the more notable side effects from chronic use of cannabis arise more in the long-term, making these complications appear less impactful than they really are. As an example, in an article published by The Journal of the American Medical Association, heavy chronic marijuana use is "associated with residual neurophysiological effects even after day of supervised abstinence".[6]

Also, while the aim of these trials were to demonstrate whether alternative therapy for chronic neuropathic pain existed for those who can't tolerate or are refractory to traditional therapy, there was no comparison made in the decrease in pain intensity between CBM and traditional therapy. Without knowing how CBM compares to opioids, NSAID's, and anticonvulsants, it is unclear whether CBM is the superior form of chronic pain management. Because of this, while CBM does decrease the intensity of chronic neuropathic pain, there is no evidence to suggest that it should be the primary form of pain management. Likewise, it would also be appropriate to determine whether CBM would be a suitable adjunctive therapy with traditional therapy to further decrease the pain intensity.

Probably the most important issue with the use of CBM for chronic pain is the legal ramifications of its use. While 23 states have legalized the use of CBM, marijuana is still a

category 1 drug as mandated by the DEA and it's still illegal according to federal law. So long as you're in a state that has a law which contradicts a federal law, you are protected by that state and in most cases will not be interfered with by the federal authorities. However, until CBM is downgraded in the DEA category list and is no longer illegal under federal law, the FDA will never approve its use for chronic neuropathic pain, which is just another pain these patients have to deal with.

CONCLUSION

The results from the three randomized controlled trials comparing oral or inhaled cannabis-based medicine (CBM) to placebo in decreasing the intensity of chronic neuropathic pain in chronic diseases such as HIV and MS reveals that there is a significant decrease in pain in those taking the CBM. For those individuals who are unable to take traditional therapy due to their side effects or ineffectiveness, CBM appears to be a suitable replacement to aid in the day to day lives of people with these debilitating disorders. As the individual states continue to legalize medicinal marijuana, the scope of its use will further broaden; making trials such as the three depicted in this review an important resource to guide future studies.

An interesting question that wasn't addressed in any of the three trials was whether CBM or homegrown marijuana displayed any changes to the outcomes of pain management. With any medical treatment, controlling the dosing is one of the most important variables. With purchased marijuana, depending on the provider the THC content can fluctuate, making no two marijuana cigarettes between different providers the same. This poses a problem for homegrown marijuana in the treatment of chronic pain because if the treatment is failing or serious side effects begin to

show there is no way to determine if the issues are being caused by the marijuana or by the dosing. However, should a provider instead give the means to grow their marijuana from the same germ line, then in theory the THC content should be equal amongst each marijuana cigarette should each cigarette contain the same amount of leaf content. It is important to consider homegrown marijuana as opposed to pharmacy administered marijuana, because if homegrown marijuana can be monitored and managed appropriately, it would cut down on the expenses to both the patient and the healthcare system dramatically, which would further aid to the credibility of CBM use for chronic neuropathic pain.

Acknowledging that the short-term side effects of CBM were minimal and lacking any serious impact on these trials is important, however the long-term effects of chronic use of CBM were never entertained and needs to be investigated further. While the question was successfully answered in regards to whether CBM can significantly decrease the intensity of chronic neuropathic pain, before a final conclusion can be made regarding CBM's placement in the hierarchy of the treatment plan, more research needs to be conducted.

References

1. Rog DJ, Nurmikko TJ, Friede T, Young CA. Randomized, controlled trial of cannabis-based medicine in the central pain in multiple sclerosis. *Neurology*. 2005; 65:812-819

2. Ellis RJ, Toperoff W, Vaida F, Brande G, Gonzales J, Gouaux B, Bentley H, Atkinson JH. Smoked Medical Cannabis for Neuropathic Pain in HIV: A Randomized, Crossover Clinical Trial. *Neuropharmacology.* 2009; 34:672-680

3. Abrams DI, Jay CA, Shade SB, Vizoso H, Reda H, Press S, Kelly ME, Rowbotham MC, Petersen KL. Cannabis in Painful HIV-Associated Sensory Neuropathy: A randomized Placebo-Controlled Trial. *Neurology.* 2007; 68:515-521

4. Olsen Y, Daumit GL, Chronic Pain and Narcotics: A Dilemma for Primary Care. *Journal of General Internal Medicine*. 2002;17(3):238-240. doi:10.1046/j.1525-1497.2002.20109.x.

5. Bisbee GE., Clark PA., Jones SL., Wang E., Watts CM. Profiling Best Practices: chronic pain management in the leading health systems. *The Health Management Academy Benchmarking Series.* 2011. Website: http://www.hmacademy.com/pdfs%5CChronic_Pain_Management.pdf. Accessed: 10/7/2015

6. Harrison PG., Yurgelun-Todd D. The Residual Cognitive Effects of Heavy Marijuana Use in College Students. *JAMA.* 1996;275(7):521-527.