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Is cannabis effective in reducing muscle spasticity and body pain amongst patients with Multiple Sclerosis?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

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In

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Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
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ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not cannabis is effective in reducing muscle spasticity and body pain amongst patients with Multiple Sclerosis (MS).

STUDY DESIGN: A systematic review of three peer-reviewed studies published between the years of 2003 and 2012.

DATA SOURCES: Three randomized control trials (RCTs) evaluating if cannabis can reduce muscle spasticity and body pain for patients diagnosed with Multiple Sclerosis. All three sources were selected from PubMed and examined for outcomes that were patient oriented.

OUTCOMES MEASURED: The two primary outcomes measured include: muscle spasticity measured by the Ashworth scale, and the patient's perception of body pain measured by a subjective Category Rating Scale (CRS).

RESULTS: The study conducted by Bloom et al.⁷ showed a significant reduction in muscle spasticity by an average of 2.74 points more than the placebo group on the Ashworth scale. Furthermore, the treatment reduced body pain by an average of 5.28 points more than the placebo group when assessed on a Visual Analogue CRS. The MUSEC trial conducted by Zajicek et al.⁸ showed the relief from muscle stiffness after 12 weeks was almost twice as high with cannabis extract than with placebo (29.4% vs 15.7%; OR 2.26; 95% CI 1.24 to 4.13; p=0.004, one sided). Patient-reported body pain was also improved. The CAMS study conducted by Zajicek et al.⁹ found that treatment with cannabinoids did not have a beneficial effect on spasticity when assessed with the Ashworth scale, but did find subjective improvement in spasticity and pain via CRSs and asking patients direct questions about their overall opinion of symptom improvement.

CONCLUSIONS: The result of three RCTs reveals conflicting evidence in regards to muscle spasticity assessed by the Ashworth scale. However, clinically significant improvements of patient-reported muscle spasticity and pain were recorded via use of CRSs in each trial. Due to the limitations of these studies, further research is warranted.

KEY WORDS: Cannabis, Multiple Sclerosis, Pain, and Muscle Spasticity

INTRODUCTION

Multiple Sclerosis (MS) is an autoimmune, inflammatory demyelinating disease of the Central Nervous System (CNS). The destruction of myelin impairs signal transmission within the CNS and results in areas that develop scar tissue, resulting in a variety of symptoms. Some of the most notable symptoms of this disease include: blurred vision, extreme fatigue, numbness, loss of coordination, spasticity, and body pain. There are three distinct types of MS, however, the most common type of MS follows a relapsing-remitting disease course. This is characterized by clearly defined attacks of new or increasing neurologic symptoms followed by periods of partial or complete recovery.¹ This paper evaluates three Randomized Control Trials (RCTs) that analyze the efficacy of cannabis as treatment for improving muscle spasticity and body pain for patients with MS.

MS currently affects more than 1 million individuals in the United States, and 2.3 million globally. In the southern U.S., the prevalence rate is 57-78 cases per 100,000 versus 110-140 cases per 100,000 in the northern U.S.² These statistics suggest that geographic location may be a risk factor for the development of MS. Since healthcare providers are not required to report patients diagnosed with MS, there is no definitive method to track how many patients have developed this disease.

Healthcare costs are difficult to estimate and are largely dependent upon the type and severity of the patient's symptoms. When specifically assessing the most common type of MS, relapsing-remitting, it is estimated to cost a patient approximately \$65,000 per year and \$4.1 million dollars over the course of a lifetime. In addition, data shows that patient's average 20 healthcare visits per year depending on the severity of their symptoms.³

The exact cause of MS is unknown, and it is unclear as to why it develops in some people and not others. Although genetic and environmental factors are thought to play a role, the disease is not contagious or inherited. The average age of onset is 20-50 years old and is at least two times more common in women than men.⁴ MS initially manifests as a Clinically Isolated Syndrome (CIS), which is an episode of neurologic symptoms caused by inflammation and demyelination of nerve fibers in the CNS. Patients may present complaining of fatigue, gait abnormalities, numbness/tingling, optic neuritis, pain, spasticity, and/or weakness. The diagnosis of MS is initially made clinically with a history of at least two discrete episodes of symptomatic exacerbations. Clinicians may confirm their suspicions of an MS diagnosis by ordering an MRI with gadolinium, which will reveal white matter plaques in the brain. In addition, a diagnosis of MS can also be supported via lumbar puncture to evaluate for the presence of oligoclonal bands and increased IgG production. Once a diagnosis of MS is made a patient will be further categorized as having 1 of 3 subtypes. These include: relapsing-remitting, primary progressive, or secondary progressive.¹

Treatment for MS varies amongst patients. Typically, the first line medication for acute exacerbations are high dose IV corticosteroids. If patients are not responsive to corticosteroids, then plasmapheresis can be considered as a 2nd line treatment option.⁵ In regard to daily maintenance therapy, the first line treatment is β -interferon. If this medication is not adequately controlling the amount and severity of symptomatic relapses, then treatment with glatiramer acetate is indicated. Adjunct medications include amantadine for fatigue and diazepam for spasticity.⁶ Although these medications are useful in the treatment of MS, they are associated with a heavy cost burden and the potential for adverse side effects.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not cannabis is effective in reducing muscle spasticity and body pain amongst patients with multiple sclerosis.

METHODS

The studies were evaluated and selected based on their adherence to specific criteria: population studied, intervention used, comparison group, and outcomes measured. The studies selected for this review needed to focus on patients 18 years or older that had a confirmed diagnosis of MS. The intervention had to be cannabis, either smoked or oral administration. Comparison groups using a placebo drug were preferentially selected for this review. The outcomes measured needed to be patient-oriented evidence that matters (POEMs), which included improvement in spasticity and body pain using both objective and subjective rating scales. Each study used in this systematic review were RCTs comparing the effects of cannabis to a controlled, placebo group. Two of the three studies were double-blind RCTs.

PubMed was used to find RCTs published in peer-reviewed journals in the English language. The keywords “multiple sclerosis”, “cannabis”, “pain”, and “spasticity” were used when searching for these articles. Selection of each article was based on relevance to the clinical question, date of publication, generalizability, and outcomes that were patient oriented (POEMs). Inclusion criteria for all three studies included articles that were peer-reviewed RCTs and POEMs. Exclusion criteria were patients under the age of 18, disease-oriented evidence, and preexisting Cochrane systematic reviews. The reported statistics included p-value, mean change from baseline, and confidence intervals. Table 1 shows the demographics and characteristics of included studies that were selected for this review.

Table 1 - Demographics & Characteristics of included studies

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Intervention
Corey Bloom ⁷ (2012)	RCT	37	Average: 50 years old	Patients who were 18 years or older with MS	Patients with a history of major psychiatric disorder (other than depression), substance abuse, neurologic disease (other than MS), unstable medical illness, pregnant and breastfeeding women	7	Smoked cannabis cigarettes (4% delta-9-THC) VS. Placebo identical cigarette. After an 11-day washout interval, participants crossed over to the opposite group.
Zajicek ⁸ (2012)	RCT	279	18-64	Patients with stable MS for the past 6 months, who have ongoing muscle stiffness for at least 3 months before enrollment	Patients with active sources of infection or taking immunomodulatory drugs that might affect spasticity, fixed tendon contractures, severe cognitive impairment, major illness, pregnancy, cannabis use in the past 30 days, history of psychosis	53	Oral cannabis extract (titrated over 2 weeks to reach a maximum dose of 25mg daily) VS. placebo. Duration of treatment was 12 weeks. Patients were assessed at 2,4,8, and 12 weeks
Zajicek ⁹ (2003)	RCT	667	18-64	Patients with clinically definite or laboratory-supported MS. Disease must have been stable for the previous 6 months with problematic spasticity.	Ischemic heart disease, patients > 64 years old, active infection, severe cognitive impairment, pregnancy, use of cannabis in the 30 days prior to the start of the study, past history of psychotic illness, patients taking immunomodulator drugs that may affect spasticity, fixed tendon contractures	56	Oral Cannabis extract & delta-9-THC VS. Placebo. Duration of trial was 15 weeks

OUTCOMES MEASURED

The outcomes measured were patient oriented (POEMs) and assessed by similar methods across each study. Bloom et al.⁷ assessed muscle spasticity via the modified Ashworth rating scale. Investigators combined ratings for both elbows, hips and knees for a total possible score of 30 points. Participants were assessed using this scale before and approximately 45 minutes after treatment (cannabis or placebo) at each visit. In order to assess perceived pain, investigators administered a subjective visual analogue scale to their participants.⁷

In the MUSEC trial, Zajiek et al.⁸ measured both muscle spasticity and body pain with subjective category rating scales (CRS). Muscle spasticity was measured with an 11-point CRS to evaluate perceived change in muscle stiffness after 12 weeks of treatment compared with the premedication phase. At the final visit, participants answered the following question on a symptom questionnaire: “Compared with before the study started, my muscle stiffness over the last week has been...” providing a rating on an 11-point numerical CRS where 0 = very much better, 5= no difference, and 10= very much worse. Ratings of 0-3 on the rating scale were classified as a clinically relevant response.⁸ Body pain was also measured on a CRS at 4, 8, and 12 weeks. Participants would answer the question, “Over the last week, the body pain I have had is...” providing a rating in categories between “no body pain and “extreme body pain”.⁸

The CAMS study, also conducted by Zajiek et al.⁹ measured muscle spasticity with the Ashworth rating scale. Assessments were made at six visits: two pre-treatment (visits 1 and 2), three while on treatment (visits 5, 6, and 7), and one after discontinuation of treatment (visit 8). At each visit, 10 muscle groups were evaluated on each side of the body while participants were lying supine on a couch (or as close to this position as was tolerated) after resting for 15 minutes. CRSs were also used in this study to subjectively measure muscle spasticity and pain. They were

administered at the end of the treatment phase only. Participants were asked to assess their symptoms over the previous week and compare them with how they were just before the study began. At the end of the 15 weeks, the treating doctor asked the participants specific questions about the overall effect of the medication on spasticity and pain (visit 8).⁹

RESULTS

This review consists of three RCTs that assessed whether cannabis is an effective treatment for reducing muscle spasticity and body pain amongst patient with MS. Each trial presented their outcomes as continuous data.

In the study conducted by Bloom et al.⁷, 196 patients were recruited for screening from a regional MS clinic and by referral from specialists. Inclusion criteria included patients greater than 18 years old and a baseline Ashworth score of at least 3 points. Patients were excluded if they had a history of a major psychiatric disorder (other than depression), substance abuse, neurologic disease (other than MS), pregnant or breastfeeding women, or an unstable medical illness.⁷ Of the 196 patients recruited, 37 were randomized into either a smoked cannabis or placebo group. Pre-rolled cannabis and placebo cigarettes were identical in appearance and weight. Cannabis cigarettes contained 4% delta-9-tetrahydrocannabinol (delta-9-THC) by weight while placebo cigarettes contained the same material with delta-9-THC removed.⁷ The Ashworth scale was used to evaluate muscle spasticity and a visual analogue scale was administered to evaluate body pain. By the end of the trial, 7 patients withdrew due to adverse side effects (n=4) or unavailability for time commitment (n=3).⁷

Results show that smoking cannabis reduced Ashworth scale scores by an average of 2.95 points from baseline, which was 2.74 points more than placebo group (95% CI 2.20 to 3.14). P-value was calculated to be < 0.001. Smoking cannabis reduced patient scores on the visual

analogue scale by an average of 8.27 points from baseline, which was 5.28 points more than placebo (95% CI 2.48 to 10.01). The calculated p-value for this scale was 0.008.⁷ Overall, this trial showed a large and beneficial effect of smoked cannabis on spasticity and pain associated with MS.

Although smoked cannabis was well-tolerated adverse effects were noted. These included: dizziness, headache, fatigue, nausea, throat irritation, and feeling “too high”. As mentioned previously, 4 patients withdrew from the trial due to intolerable side effects. However, none of the participants experienced episodes of hypertension, hypotension, tachycardia, or bradycardia that required medical intervention.

Table 2: Efficacy of smoked cannabis on muscle spasticity and body pain measured by the Ashworth Scale and Visual Analogue Scale conducted by Bloom et al.⁷

Study: Bloom et. al ⁷	Mean Change from Baseline	CI (95%)	P-value
Smoked cannabis: spasticity (Ashworth Scale)	-2.95	2.20 – 3.14	<0.001
Smoked Cannabis: body pain (Visual Analogue Scale)	-8.27	2.48 – 10.01	0.008

In 2012, Zajicek et al.⁸ conducted the MUSEC trial with a sample size of 279 patients. Patients ranged from 18-64 years old and were required to have a diagnosis of MS according to the McDonald Criteria. In addition, their disease had to have been stable for the previous 6 months with ongoing muscle stiffness for at least 3 months before the trial began.⁸ Exclusion

criteria included patients with active sources of infection or taking immunomodulatory drugs that might affect spasticity, fixed tendon contractures, severe cognitive impairment, major illness, pregnancy, cannabis use in the past 30 days, or history of psychosis.⁸

Patients were randomized to either an oral cannabis extract or placebo group via a computer-generated voice response system. Both study groups received identical oral capsules and all investigators and participants were blinded to treatment distribution throughout the trial. The starting dose was 2.5mg of delta-9-tetrahydrocannabinol (Δ^9 THC) twice daily. Patients were titrated up by 5mg every 3 days until a maximum dose of 25mg Δ^9 THC was achieved.⁸

Investigators administered CRSs to assess muscle spasticity and body pain. Results show that the proportion of participants experiencing muscle relief after 12 weeks of oral cannabis was nearly 2x higher than the placebo group (29.4% vs 15.7%; OR 2.26; 95% CI 1.24 to 4.13; $p=0.004$, one sided). The mean reduction of muscle stiffness from baseline = -1.8 ± 2.6 .⁸ This indicates a large treatment effect. Similar results were found when evaluating body pain. After 12 weeks, 28% of patients allocated to the cannabis extract group reported decreased body pain as compared to 18.7% of patients in the placebo group ($p=0.028$). The mean reduction of body pain from baseline = -1.2 ± 2.6 . This indicates a large treatment effect.⁸

Adverse events were most notable during the upward titration phase of Δ^9 THC. In the cannabis extract group, 46.2% of patients experienced dizziness vs. only 6.7% in the placebo group. In addition, 14% of cannabis patients reported feeling fatigued in comparison to only 6% of placebo patients. Of the 279 patients randomized, 39 withdrew due to adverse events.⁸

Although side effects were noted, they were consistent with the known effects of cannabinoids. No new safety concerns were detected, and the study achieved its goal to demonstrate the usefulness of oral cannabis extract to treat muscle spasticity and body pain in patient with MS.

Table 3: Efficacy of oral cannabis extract on muscle spasticity and body pain measured by Category Rating Scales conducted by Zajicek et al.⁸

Study: Zajicek et. al ⁸	Mean change from baseline (Mean change \pm SD)	P-value
Oral cannabis: spasticity	-1.8 \pm 2.6	0.004
Oral cannabis: body pain	-1.2 \pm 2.6	0.028

The CAMS study conducted by Zajicek et al.⁹ enrolled 667 patients with MS. Of these patients, 630 of them were randomized into one of the following groups: oral cannabis extract (n=211), Δ^9 THC (n=206), or placebo (n=213).⁹ Eligible patients were those between the age of 18-64 years old, clinically definite or laboratory-supported MS, and stable disease state for the previous 6 months with problematic spasticity. Exclusion criteria included: ischemic heart disease, active infection, severe cognitive impairment, pregnancy, use of cannabis in the 30 days prior to the start of the study, history of psychotic illness, patients taking immunomodulator drugs that may affect spasticity, and fixed tendon contractures. Throughout the duration of the study 56 patients withdrew, leaving 611 to be assessed for efficacy and outcome measurements over the next 10 weeks.⁹

Compared to baseline assessments, results show a mean reduction in total Ashworth score for patients taking oral cannabis extract vs. placebo to be 0.32 (95% CI -1.04 to 1.67; p=0.40). For those patients taking Δ^9 THC vs. placebo the mean reduction in total Ashworth score was 0.94 (95% CI -0.44 to 2.31).⁹ The results of the Ashworth scale indicate that cannabinoids did not have a clinically significant effect on reducing muscle spasticity. However, there was evidence of treatment effect on patient-reported spasticity and pain measured by an 11-point CRS. Improvement of spasticity was recorded in 61% of patients on cannabis extract

(n=121, 95% CI 54.6 – 68), 60% of patients receiving Δ^9 THC (n=108, 95% CI 52.5 – 66.8), and 46% of patients in the placebo group (n=91, 95% CI 39.0 - 52.90). In regard to body pain, reductions were seen in 57%, 50%, and 37% of participants on cannabis extract, Δ^9 THC, and placebo respectively.⁹ Episodes of adverse events were most commonly seen in the active treatment groups and were consistent with the known side effects of cannabinoids. These included: dizziness, lightheadedness, increased appetite, dry mouth, urinary tract infection, and diarrhea.⁹

Table 4: Efficacy of oral cannabis extract and Δ^9 THC on muscle spasticity measured by Ashworth scale conducted by Zajicek et al.⁹

Study: Zajicek et. al ⁹	Mean change from baseline	CI
Oral cannabis extract vs. placebo- spasticity (Ashworth scale)	0.32	-1.04 to 1.67
Δ^9 THC vs. placebo- muscle spasticity (Ashworth Scale)	0.94	-0.44 to 2.31

DISCUSSION

Medical cannabis is legal in over 50% of the United States and is currently used by patients who suffer from muscle spasms, severe pain, glaucoma, seizures, headaches, cancer, HIV/AIDS, and Chron’s disease.¹⁰ Since cannabis is classified as a Schedule I substance, health insurance companies will not help pay for the medication. Therefore, patients suffering from debilitating diseases are forced to pay the full price.¹¹ Research has resulted in the production of three synthetic cannabinoid products: dronabinol, nabilone, and epidiolex. Epidiolex was recently FDA-approved in June 2018 to treat Lennox-Gastaut syndrome and Dravet syndrome in patients 2 years or older.¹⁰ Cannabis and synthetic cannabinoids are contraindicated in patients

with previous history of hypersensitivity reactions to medications, hepatic disease, cardiovascular disease, women who are pregnant, history of substance abuse, and coadministration with other CNS depressant medications.¹⁰

The three RCTs discussed in this review show statistical evidence that cannabinoids, whether smoked or taken orally, are efficacious in reducing muscle spasticity and body pain for patients with MS. Although one study did not show clinically significant improvement of spasticity when assessed by the Ashworth scale⁹, subjective patient-oriented rating scales consistently showed reductions in spasticity and body pain across all three studies. Future studies would benefit by evaluating efficacy of this treatment method in elderly patients greater than 65 years old. Due to the newly approved FDA drug, Epidiolex, clinical trials assessing a pediatric population is now warranted.

A notable limitation of each study discussed in this review is the ability to completely blind participants from psychoactive substances. Participants could often tell which treatment they were receiving. However, investigators noted that this limitation was unlikely to affect objective spasticity scores. A second limitation is the reliability of the Ashworth scale. This measurement tool was implemented for these clinical trials because it is the most widely used in clinical practice. However, it is too insensitive to identify small but clinically significant effects on spasticity. This may explain why the CAMS study failed to show clinically significant improvement in muscle spasticity when assessed by the Ashworth scale.

CONCLUSION

The evidence presented in this review is conflicting as to whether or not cannabis is an effective intervention for muscle spasticity and body pain. When measured via the Ashworth

scale, the study conducted by Bloom et al.⁷ showed a mean reduction of 2.95 points compared to baseline scores. However, the CAMS study by Zajicek et al.⁹ did not show a clinically significant effect with either oral cannabis extract or Δ^9 THC as they both reduced spasticity scores by less than 1 point when compared to the placebo group. Data from the CRSs in each study consistently proved that patient's perceived the treatment to be effective in reducing muscle spasticity and body pain.

When conducting future research on this topic, slower dose-titration of the oral cannabis capsules need to be initiated. The MUSEC trial by Zajicek et al.⁸ titrated their oral cannabis treatment over two weeks. Similarly, the methods of the CAMS study involved a short 5-week titration period.⁹ This does not reflect normal clinical routine where dose titration can take a more gradual course and side effects can be minimized. Future studies should also explore the possibility of administering this treatment method via sublingual route. This would allow investigators to more effectively achieve desired blood concentrations of the drug and increase bioavailability, which may result in further reductions of muscle spasticity and body pain.

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