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Is Tetrahydrocannabinol (THC)/Cannabidiol (CBD) oromucosal spray an effective adjuvant therapy for Multiple Sclerosis patients who suffer from central neuropathic pain?

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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
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ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not "Is Tetrahydrocannabinol (THC)/Cannabidiol (CBD) oromucosal spray an effective adjuvant therapy for Multiple Sclerosis (MS) patients who suffer from central neuropathic pain (CNP)?"

STUDY DESIGN: Systematic review of three randomized controlled trials published between 2005-2013, all English language.

DATA SOURCES: Three randomized controlled studies were obtained using PubMed and MedLine.

OUTCOMES MEASURED: The outcome of each study was the subject's incidence and severity of central neuropathic pain compared to their baseline at the beginning of the study. Outcomes were measured using an 11-point pain scale at various intervals. The average scores of these participants were used to compare the control group versus the intervention group.

RESULTS: Three randomized controlled trials and uncontrolled, extension trial were used in this review. Langford et al demonstrated a mean difference between the THC/CBD group and placebo-controlled group to be (odds ratio 1.31 [95% CI, 1.01-2.57 points]; *P*=0.046) after 10 weeks. Rog et al found that there was a statistically significant mean reduction of pain intensity (Mean change -2.7; 95% CI: -3.4 – 2.0 (p=0.005)) in the THC/CBD intervention group. Hoggart et al showed a significant mean reduction in pain scores (-0.96 points; 95% CI: -1.59, -0.32, (p=0.004)) when compared to control group. All of the results were observed in patients who were already on a stable regimen of analgesic medications to treat neuropathic pain related to MS.

CONCLUSIONS: All three studies demonstrated statistically significant reduction in mean central neuropathic pain with THC-CBD oromucosal spray as compared to baseline, as well as compared to a placebo-control group. The addition of THC/CBD oromucosal spray should be considered in MS patients who suffer from central neuropathic pain and do not receive pain relief from standard therapy.

KEY WORDS: Multiple sclerosis (MS), Tetrahydrocannabinol (THC)/Cannabidiol (CBD) oromucosal spray, central neuropathic pain (CNP)

INTRODUCTION:

Treating complex medical conditions, such as Multiple Sclerosis (MS), often leads to frustration of both the patient and the providers, because current biomedical therapies are not adequately treating the pain. There is no known cure for MS, and with current treatment regimens, patients are often left unable to perform normal activities of daily living. This leads to increased dependence of others, avoidance or interference of certain activities, increased difficulty sleeping, fatigue, depression, anxiety, increase use of narcotics, and a higher overall perception of pain.[1]

MS is an immune-mediated inflammatory disorder of the central nervous system, which leads to demyelination, glial scarring, and neuronal loss. [2] It is known to be a widely unpredictably disease with four different progression patterns. These include Relapsing-Remitting MS (85%), Primary-Progressive MS (10%), Secondary-Progressive MS (85%), Progressive-Relapsing MS (5%). Among all these types of MS, central neuropathic pain (CNP) is the most common pain syndrome. CNP is characterized by constant, extremity pain described as "burning or stabbing," and up to 32% rate this type of pain as "frequent, disabling, and inadequately managed." [3] It is estimated that approximately 63% of all MS patients suffer from central neuropathic pain. [4]

MS remains the most common cause of non-traumatic neurodisability in youth, with the average age of onset between 20-40 years old.[2] Approximately 400,000 in the US and 2.5 million worldwide have MS. There are several risk factors for developing MS; including genetics, female gender, Caucasian, residence further from the equator, low vitamin D, infection, and smoking. [2] They have identified the genetic marker HLA-DRb1*1501 haplotype. [3]

MS ranks 2nd to CHF for the most costly chronic disease.[5] When compared to their healthy counterparts, MS patients on average are 3.5 times more likely to be hospitalized (15.2% vs. 4.3%; $p< 0.001$), twice more likely to visit the ER (25.5% vs. 12.2%; $p< 0.001$) and 2.4 times more likely to require services from either a physical, occupational, or speech therapist (23.7% vs. 9.9%; $p < 0.001$) [5]. The average cost for MS disease-modifying therapies (DMT) alone range from $8,524 - $54,244, [4] and up to an additional $18,829 for other healthcare related costs, per year.[5] These economic estimates were derived from a systematic review of data from 1998-2008, and do not include some of the newer, more costly MS medications.[6]

The current accepted treatment regimens for MS includes disease-modifying agents such as Interferon Beta 1a and 1b (most common), Glatiramer acetate, Mitoxantrone, Natalizumab, Fingolimod, or Teriflunomid. [8] Relapses are often treated with high dose methylprednisone, 0.5-1g IV for 5 days. Initial treatment of CNP related to MS should be anticonvulsants, such as carbamazepine or gabapentin. Other first line agents include tri-cyclic antidepressants, serotonin-noepinepherine reuptake inhibitors, and lidocaine 12 hour transdermal patches.[8] When 1st line therapy fails, second line therapies such as Lamotrigine, buproprion, citalopram, baclofen, tizanidine, and short-acting opioid therapy may be used.[8] In several recent studies, THC/CBD oromucosal spray has been shown to decrease neuropathic pain and spasticity, and has recently been approved in Canada as an adjuvant therapy for central neuropathic pain in MS.[9] This systemic review will utilize three randomized control trials and evaluate the effectiveness of THC/CBD oromucosal spray on MS related CNP as an adjuvant therapy for patients who are currently optimized on other analgesic regimens without resolution of their pain.

OBJECTIVE

The objective of this systematic review is to determine whether or not Tetrahydrocannabinol (THC)/Cannabidiol (CBD) oromucosal spray is an effective adjuvant therapy for Multiple Sclerosis (MS) patients who suffer from central neuropathic pain (CNP)?

METHODS

This systematic review of three randomized control trials will investigate a patient population greater than 18 years old, who have been previously diagnosed with Multiple Sclerosis, and currently optimized analgesic therapy. This study will review three THC/CBD oromucosal spray interventions from 5-14 weeks. The comparison group is comprised of patients with MS of similar characteristics, all suffering from central neuropathic pain, currently optimized on analgesic therapy, and utilizing a visibly identical placebo oromucosal spray. Outcomes were measured using an 11-point numerical pain scale. Preliminary baseline assessments were made prior to initiation of the intervention, and reassessments took place at various intervals throughout each study.

The key words utilized in the searches were “Multiple sclerosis (MS)”, “Tetrahydrocannabinol (THC)/Cannabidiol (CBD) oromucosal spray”, and “central neuropathic pain (CNP).” All of the articles were researched by the author were published in peer-reviewed journals in the English language, and were found on PubMed and the Cochrane library. The articles were selected based off its clinical relevance to the question posed by the author. Inclusion criteria for this systemic review included publication date after 2005, were over 18 years old, have history of at least 6 months of unresolved, central neuropathic pain with evidence on clinical examination, a stable pain severity of at least 4 on the numerical pain scale, and had a stable analgesic medication

regimen for at least two weeks prior to initiation of the study. Exclusion criteria comprised of studies with patients who had severe non-neuropathic pain; psychiatric conditions that may alter pain severity such as schizophrenia and psychosis; history of substance or alcohol abuse; pregnancy or lactation; diabetes, hypertension, cardiovascular, hepatic, renal diseases; or any cannabinoid use at least seven days prior to the study were all excluded. The analytics used in this study were mean change from baseline, p-values, 95% CI, and NNT.

Table 1: Demographics and Characteristics of Included Studies

Study	Type	#Pt	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Langford[1] (2013)	Double blind RCT	339	48.97 $\pm$ 10 yrs	- CNP due to MS x 3 months with pain of $\geq$ 24 last 6 days - Therapies must be stable x 2 week prior to study	- Severe pain from other conditions - Psychiatric disorder, renal, hepatic, CVD, or convulsive disorder - Recent cannabis use	42	THC 2.7mg/CBD 2.5mg oromucosal spray PRN. Maximum 12 sprays per 24h.
Rog[2] (2005)	Double blind RCT	66	48.1 $\pm$ 10 yrs	-Diagnosed MS x 6 months. Stable central pain x 3 months.	- Patient's with chronic visceral pain, on TCA's or have psych disorder, Current cannabis users, Pregnant, lactating, or on levodopa.	2	THC 2.7mg/CBD 2.5mg oromucosal spray PRN. Self –titrated with maximum spray 48 per 24h
Serpell[3] (2011)	Double blind RCT	125	54.3 $\pm$ 15 yrs	>18 y.o., 6 months of pain, baseline pain scale 4, stable medications x 2 weeks	- Cannibis use, Psych disorder, non-neuropathic pain, Diabetes, CVD, HTN, cancer, terminal ill	20	THC 2.7mg/CBD 2.5mg oromucosal spray PRN Self-titrated with maximum spray 48 per 24/h

OUTCOMES MEASURED

The three randomized controlled studies' outcomes utilized in this study was the average perceived pain, described on an 11-point pain numerical rating scale (NRS) score. A mean pain score for the experimental group was calculated and compared to baseline scores at the beginning of the study. Then the mean pain scores of the experiment group were compared to the placebo-controlled group.

RESULTS

Langford et al conducted a randomized, double blind, placebo-controlled, parallel-group study, which comprised of 339 patients with MS, and were randomized into an interventional group (n= 167) and a placebo-controlled group (n=172).[10] Each participant was instructed on proper medication delivery during a 1-week baseline period, followed by a 14 week treatment phase, where they self-titrated to a maximum of 12 sprays per 24 hours.[10] Participants were required to do daily self-reporting of their CNP using an 11-point numerical rating pain scale (NPS). At the end of the 14-week treatment phase, all participants were invited to begin a open treatment phase (n=58), which consisted of a 2-week re-titration and 12-week stable dose phase with THC/CBD spray.[10] At the end of the open trial, participants were entered in a double-blind, randomized withdrawal trial to determine the long term efficacy of THC/CBD, and the presence and severity of any side effects. [10]

Results of the study determined that there was no significant difference between the placebo-controlled and intervention group at baseline. [10] After 10 weeks of treatment, there was a statistically significant difference between the intervention and control group's in favor of the THC.CBD spray (odds ratio 1.61 [95% CI: 1.01-2.57]: p= 0.046).

[10] At the end of the 14-week treatment phase, there was not a statistically significant difference between interventional and placebo-controlled group, with a difference of -0.17 points in favor of THC/CBD spray (odds ratio 1.31 [95% CI: 0.84 – 2.04]: p= 0.234).[10] At the end of the open-trial phase, there was a statistically significant change in mean pain scare, with a difference of -0.79 points in favor of THC/CBD spray (90% CI: -1.37 to – 0.21 points; p=0.028). [10]. Statistically significant data was considered in p-values less than 0.05. 3% of the THC:CBD, and 1% of the placebo groups developed sever adverse events (AE) that led to cessation of the treatment, but did not reach a statistically significant difference (p = 0.69).[10] The most common reported AE was GI discomfort. Data was provided by Langford et al, and NNT and NNH (tables 4 and 5) were calculated by the author.

Table 2: Comparison of Control vs. THC/CBD Intervention after 10 and 14 weeks [10]

	10 weeks	14 weeks
Number of Responders with at the 30% improvement level in mean CNP NPS	THC ~ 50% Placebo ~ 40%	THC- 50% Placebo- 45%
p-value; 95% CI	**P = 0.046**	P = 0.234

Table 3: Comparison of Primary and Secondary Endpoints [10]

	Baseline CNP NPS	14 week CNP NPS from baseline	Randomized- Withdrawal CNP NPS from baseline
Control	6.61 (+/- 1.29)	-1.76 (6.61 ± 1.29-4.73 ± 2.26)	-0.03 (6.21 ± 1.37)
THC/CBD Intervention	6.55 (+/- 1.35)	-1.93 (6.55 ±1.35-4.54 ± 2.24)	+0.76 (6.49 ± 1.31)
p- value	N/A	P = 0.47	**P= 0.028***
Mean Change in NPS	+0.06	-0.17	-0.79

Table 4: Numbers needed to treat [10]

Relative risk reduction (RRR)	**Absolute risk reduction**	**Number needed to treat (NNT)**

	(ARR)	
$\frac{\text{EER – CER}}{\text{CER}}$	EER - CER	1/ARR
0.11	0.05	**20**

Table 5: Numbers needed to harm (rate of adverse events) [10]

Relative risk increase (RRI)	**Absolute risk increase (ARI)**	**Number needed to harm (NNH)**
$\frac{\text{EER- CER}}{\text{CER}}$	EER - CER	1/ARI
0.29	0.02	**50**

Rog et al., conducted a study evaluating 66 patients with MS CNP and their response to THC:CBD oromucosal spray as an adjuvant therapy. In this 5-week, randomized, double blind, placebo-controlled, parallel-group study, 64 patients were randomized into an interventional group (n=34) and a visually identical placebo group (n=32). [11] Each participant underwent a toxicity screening, using up to 4 sprays over 2 hours. Patients who passed the intoxication screening were entered in a 1-week dosing optimization period, where they titrated up to a maximum of 48 sprays in a 24-hour period.[11] The baseline mean pain score was recorded in the 7 days prior to the intoxication screening, using an 11-point pain NRS score.[11] During weekly telephone follow-ups, patient's reported pain severity was averaged, then compared to the average pain recorded the last week of treatment.

Results of the study determined that there was no significant difference between the placebo-controlled and intervention group at baseline. [11] After the 5 week, the study demonstrated a statistically significant difference between the placebo-controlled and the interventional group, in favor of the THC:CBD oromucosal spray (-1.25 [95% CI: -2.11 to -0.39]; p=0.005).[11] The study also collected data to determine their numbers needed to

treat and numbers needed to harm (tables 7 and 8). During the study 88.2% of CBD:THC vs 68.8% of placebo groups developed AE's. The most common AE's were dizziness and confusion, which did not reach a statistically significant difference (0.19; 95% CI: 0.00-0.39; p=0.053).[11] Statistically significant data was considered in p-values less than 0.05. The data in tables 6-8 were provided by Rog et al. [11]

Table 6: Comparison of Control vs. THC:CBD intervention after 5 weeks [11]

	Baseline (95% CI)	Primary Endpoint (95% CI)
Placebo-Controlled	6.37 (5.77- 6.97)	4.96 (4.19 – 5.72)
THC:CBD Intervention	6.58 (6.00 -7.15)	3.85 (3.13 –4.58)
p-value		**p = 0.005**

Table 7: Numbers needed to treat (NNT)[11]

Odd's Ratio: 3 (95% CI: 2.2 to 13)

Table 8: Numbers needed to harm (NNH)[11]

	1/ Risk Difference; Odds Ratio; CI; p-value
At least 1 Adverse Event	1/0.19 = 5 (0.19; CI: 0.00-0.39; p = 0.53)

Serpell et al., conducted a 5 week randomized, double-blind, placebo-controlled parallel-group study which evaluated 125 patients with MS CNP, and their response to THC:CBD oromucosal spray as an adjuvant therapy. Patients were randomized into the THC:CBD intervention group (n=63) and visibly identical placebo-controlled group (n=62). [12] Patients entered in a one-week dose optimization period, where they titrated up to a maximum of 48 sprays in 24 hours. An average baseline pain NRS score was collected in the 7 days prior to the first dosing and was compared to the mean pain score of each week, or 3 days prior to withdrawal. [12]

Results of the study determined that there was no significant difference between the placebo-controlled group and the intervention group at baseline. [12] After the 5 week intervention, the study demonstrated a statistically significant difference between the placebo-controlled and the intervention group, in favor of the THC:CBD oromucosal spray (-0.96 [95% CI: -1.59 to -0.32] p= 0.004). [12] AE's reported reached a statistical significance difference between the two groups was reported for nausea (THC/CBD 49% vs placebo 32%; p= 0.003). The study also collected data to determine the numbers needed to treat at 30% and 50%, as well as the numbers needed to harm (tables 10 and 11). Statistically significant data was considered in p-values less than 0.05. The data in tables 9-11 were provided by Serpell et al. [12]

Table 9: Comparison of Control vs. THC:CBD intervention after 5 weeks [12]

	Baseline (95% CI)	Estimated Mean Difference (95% CI)
Placebo-Controlled	7.2 (1.5)	- 0.52 (-1.59 to -0.32)
THC:CBD Intervention	7.3 (1.4)	-1.48 (-1.59 to -0.32)
p-value		**p = 0.004**

Table 10: Numbers needed to treat (NNT) [12]

NNT (30% pain reduction)	**8 patients**
NNT (50% pain reduction)	**8 patients**

Table 11: Numbers needed to harm (NNH) [12]

Relative risk increase (RRI)	**Absolute risk increase (ARI)**	**Number needed to harm (NNH)**
$\frac{EER - CER}{CER}$	EER - CER	1/ARI
0.90	.10	**10**

DISCUSSION

In this three-study review was able to show that THC:CBD oromucosal spray is an effective adjunctive therapy for MS related CNP. The Langford, 2013 study failed to

meet a statistically significant difference at their primary endpoint, however an intermediate endpoint, which more closely represented studys conducted by Rog et al. and Serpell et al, (10 weeks vs. 5 weeks), were able demonstrate a statistically significant difference in the THC:CBD oromucosal spray, suggesting a stronger placebo response after 10 weeks. [10]

These studies also indicated that THC:CBD oromucosal spray is a safe drug to use for adjuvant therapy in this population of MS patients with CNP.[11] Of those who suffered from AE's, most were considered mild to moderate, and at the completion of the study, the majority of AE's were no longer present. In the Langford 2013 study, a 14 week open-trial treatment using THC:CBD oromucosal spray, as well as a double blind, placebo-controlled 4 week withdrawal trial, was conducted to determine long-term efficacy of the spray, and identify any withdrawal symptoms that may present. They concluded that THC:CBD oromucosal spray had a statistically significant mean reduction in pain and time to treatment failure[10]

A limiting factor identified in these studies is a small sample size that was taken in the studies (339, 64, 125) [10,11,12] and the results may not accurately reflect the population's response to THC:CBD oromucosal spray therapy. Studies also indicate a strong placebo effect that may have taken place. This may be contributed to the unlimited daily dosing for the placebo controlled group in all the studies, versus a maximum daily dosage for the THC:CBD oromucosal spray groups.[10]. Statistical analysis may have also been affected by the maximum permitted daily dosage for the THC:CBD oromucosal spray which differed between the studies, (24 vs. 48 sprays), and may have altered the participant's perceived analgesic effect.

Another limiting factor to consider is the multiple etiologies of "neuropathic pain," and no accepted diagnostic criteria, or bed-side exams that exists to determine if the patient's pain is neuropathic in nature. [13] Some studies accept spasm-related MS pain as neuropathic while others do not. [13] Therefore, you could hypothesize that all etiologies of MS-related pain could benefit from THC:CBD oromucosal spray. To enhance homogeneity of future study subjects, a standardized, diagnostic criterion should be to determined to identify neuropathic pain from other pain etiologies.

Finally, it is important to note that THC:CBD oromucosal spray is currently in phase III clinical trials and is not currently available for purchase in the United States, and thus not covered by any US healthcare insurer. [8] Current Federal government regulations make marijuana use illegal in all 50 states, however state governments have approved medicinal marijuana in 24 states. [8]

CONCLUSION

This small systematic review was able to determine that the use of THC:CBD oromucosal in MS related pain, is an effective adjuvant therapy in patients who are currently optimized on pain medication. [10, 11, 12] Future studies should attempt to identify diagnostic criteria for neuropathic pain, provide a maximum daily dosage for both the THC:CBD oromucosal spray and placebo, and continue to investigate the safety and effectiveness of THC:CBD oromucosal spray in MS related pain. Currently there are no clinical trials using THC:CBD oromucosal spray on MS related CNP.

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