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RESEARCH ARTICLE

The Effectiveness of Topical Cannabidiol Oil in Symptomatic Relief of Peripheral Neuropathy of the Lower Extremities

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ARTICLE HISTORY

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Abstract: ***Background*:** Peripheral neuropathy can significantly impact the quality of life for those who are affected, as therapies from the current treatment algorithm often fail to deliver adequate symptom relief. There has, however, been an increasing body of evidence for the use of cannabinoids in the treatment of chronic, noncancer pain. The efficacy of a topically delivered cannabidiol (CBD) oil in the management of neuropathic pain was examined in this four-week, randomized and placebo-controlled trial.

***Methods*:** In total, 29 patients with symptomatic peripheral neuropathy were recruited and enrolled. 15 patients were randomized to the CBD group with the treatment product containing 250 mg CBD/3 fl. oz, and 14 patients were randomized to the placebo group. After four weeks, the placebo group was allowed to crossover into the treatment group. The Neuropathic Pain Scale (NPS) was administered biweekly to assess the mean change from baseline to the end of the treatment period.

***Results*:** The study population included 62.1% males and 37.9% females with a mean age of 68 years. There was a statistically significant reduction in intense pain, sharp pain, cold and itchy sensations in the CBD group when compared to the placebo group. No adverse events were reported in this study.

***Conclusion*:** Our findings demonstrate that the transdermal application of CBD oil can achieve significant improvement in pain and other disturbing sensations in patients with peripheral neuropathy. The treatment product was well tolerated and may provide a more effective alternative compared to other current therapies in the treatment of peripheral neuropathy.

Keywords: CBD, diabetic neuropathy, review, cannabis sativa, hemp, nerve pain.

1. INTRODUCTION

The hemp plant, Cannabis sativa and its derivatives have long been used in folk medicine for symptomatic treatment for many disorders such as anorexia and pain [1]. Cannabinoids are chemical compounds derived from the cannabis plant. There is now a growing body of evidence to suggest the beneficial effects of cannabinoids for a variety of clinical conditions including: pain control in cancer patients, down-regulating inflammation, and symptomatic relief of sleep disorders, epilepsy, anorexia, schizophrenia, multiple sclerosis and other conditions [2]. Over 80 phytocannabinoids have been identified and the major neuroactive components are Δ9-Tetrahydrocannabinol (Δ9-THC) and Cannabidiol (CBD) [1]. These are also the two best-studied cannabinoids that have shown analgesic effects, but little is known about the other cannabinoids [3]. Δ9-THC is the primary psychoactive compound of cannabis and promotes relaxation, altered perception, increased libido as well as perceptual distortions of time and space [4]. Side effects include impaired short-term memory and motor function, paranoia and anxiety [4]. CBD is the nonpsychoactive component and has been shown to have anti-inflammatory and antioxidant properties that are independent of THC [5]. The therapeutic effects of CBD have been demonstrated in various *in vivo* studies, particularly in pain control [6].

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The human endogenous cannabinoid system plays a major role in the regulation of homeostasis, neuroplasticity of the Central Nervous System (CNS), as well as in the modulation of pain transmission in the nociceptive pathway [4]. The cannabinoid receptors CB1 and CB2 are located throughout the central and peripheral nervous system, as well as in other organs and tissues [7]. It has been shown that the CB1 receptors are predominately expressed at neurons in the central nervous system while the CB2 receptors are expressed by microglial cells which are activated in many neuroinflammatory conditions [8-11]. Previous studies demonstrated that THC acts at both CB1 and CB2 receptors whereas CBD acts mainly on the CB2 receptor, further suggesting the potential anti-inflammatory effects of CBD [12].

Peripheral neuropathy is a type of chronic pain with complex pathophysiology and its treatment can be challenging, therefore it is an often undertreated condition [13]. It is characterized by weakness, paresthesia, burning sensation and sharp pain that usually begin in the hands and feet with proximal progression [14]. The majority of peripheral neuropathy cases include idiopathic, but diabetes mellitus, alcohol dependence, chemotherapy, Human Immunodeficiency Virus (HIV), autoimmune diseases and metal toxicity are some common underlying causes [13, 15]. It is estimated that over 20 million people in the U.S. are suffering from peripheral neuropathy and up to 30% of patients with diabetes mellitus are affected [15]. This disease significantly reduces one's quality of life and function and may have emotional and cognitive implications [16]. Current treatment modalities include topical local anesthetic patch, tricyclic antidepressants, anti-epileptic agents and opioids, but these have unwanted side effects and often fail to provide adequate symptomatic relief [17]. Considering its clinical and epidemiological significance, a paradigm shift is indicated in order to adequately treat chronic pain caused by peripheral neuropathy.

Recently there has been increasing attention to the use of cannabinoids for the treatment of chronic noncancer pain [6]. It has been theorized that CBD is able to antagonize the endogenous activation of the microglial cells in the dorsal spinal cord by acting at the CB2 receptors during an inflammatory state, and this may limit the development of neuropathic pain [12].

CBD compounded with organic oils such as emu oil can be an effective transdermal delivery method of CBD. Emu oil has moisturizing properties and has been shown in previous studies to be an effective transdermal vehicle [18, 19]. In this study, we aim to investigate the effectiveness of topical CBD-enriched emu oil in the symptomatic treatment of chronic pain from peripheral neuropathy of the lower extremities.

2. MATERIALS AND METHODS

2.1. Subjects

A total of 29 volunteer participants with symptomatic peripheral neuropathy were recruited, randomized and received either the study medication (CBD oil), or a placebo that was nearly identical to the active ingredient (emu oil). The participants were recruited from the local community at the senior author's (B.D.C.) private practice. The study took place from May 2018 to August 2018.

2.1.1. Inclusion Criteria

Eligible participants were aged 18 or older, including both males and females who have experienced at least a 3 month-course of symptomatic peripheral neuropathy. This study was not specific to diabetic individuals and eligible subjects had at least one of the following underlying conditions that caused the peripheral neuropathy: type 1 or type 2 diabetes mellitus, alcoholic neuropathy, idiopathic neuropathy, congenital hypomyelinating neuropathy or neuropathy as a result of syphilis or leprosy.

2.1.2. Exclusion Criteria

Participants meeting the following criteria were excluded: hypersensitivity to organic oils, history of recreational substance abuse, fibromyalgia, Chronic Regional Pain Syndrome (CRPS), psychiatric history including but not limited to schizoaffective disorder, bipolar disorder, chronic depression, suicidal ideation and psychosis; conditions affecting capacity and adherence to study regimen including but not limited to dementia/delirium, Alzheimer's, Down's syndrome and Parkinson's; a need for elective surgery involving preoperative or postoperative analgesics or anesthetics during the study period; pregnant and/or lactating women.

2.2. Procedures

This was a 4-week, single-center, double-blind, randomized, and placebo-controlled trial to evaluate the efficacy of topical CBD oil in patients with symptomatic peripheral neuropathy. The study was conducted in accordance with the principles of the Declaration of Helsinki. All volunteer participants provided written informed consent to participate in the study. The flow diagram for all subjects enrolled in the trial is shown in Fig. (**1**).

All the visits took place in the single designated study center at the senior author's (B.D.C) private practice. Following eligibility screening, a focal physical exam of the bilateral lower extremities was performed on all participating subjects. The physical exam included a vascular exam and a neurological exam. The vascular exam aimed to assess the presence of dorsalis pedis and posterior tibial pulses, the presence of brisk capillary refill (defined as less than 3 seconds), and the presence of pitting or nonpitting lower extremity edema. The neurological exam involved testing the protective pedal sensation by using a 5.07 g Semmes-Weinstein monofilament, and vibratory sensation was tested at three levels using a 128-Hz tuning fork: the first metatarsophalangeal joint, the medial malleolus, or the tibial tubercle. A sample of the physical exam form is provided in Fig. (**2**).

The subjects were then assigned to either the treatment group or the placebo group for the next 4-week, double-blind study period. Randomization schedule was generated by a computer using blocks of size 4 and subjects were assigned accordingly. Biweekly follow-ups and evaluations were conducted by phone and electronic mail on days 14 and 28 of the double-blind treatment phase. At the end of 4-weeks, the participants in the placebo group were then identified and

given the opportunity to cross-over to the treatment group to be evaluated for an additional 4 weeks. Participating subjects received either topical Theramu Relieve CBD compound cream (Theramu, Bakersfield, CA) containing 250 mg of CBD per 3 fl. oz container, or placebo emu oil cream (identical in appearance but without CBD), to be applied topically to the symptomatic areas up to four times per day during the study period.

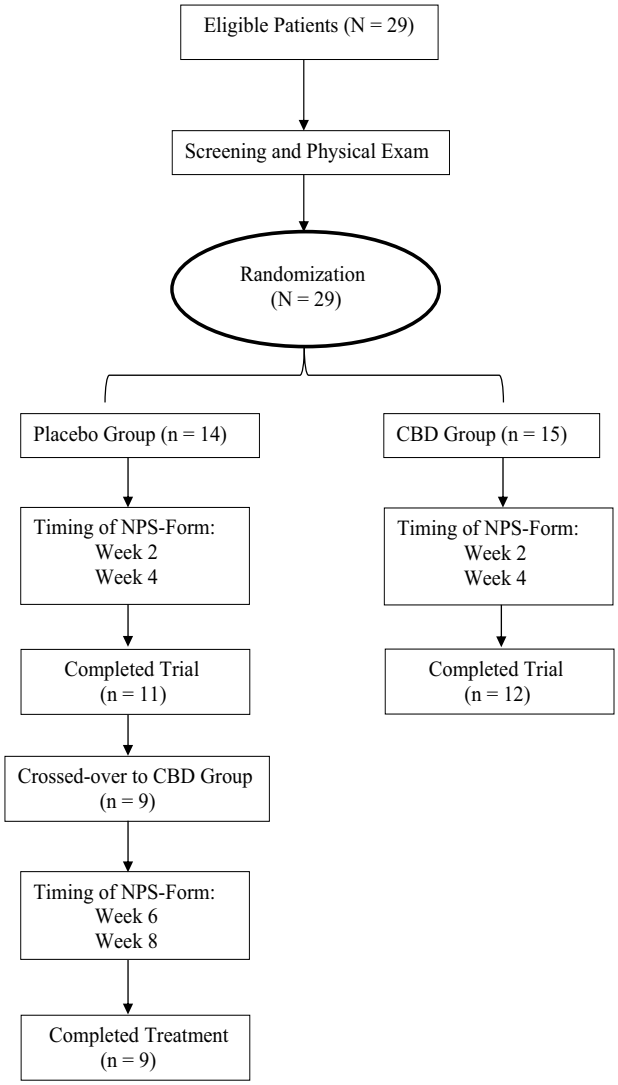


Fig. (1). Flow diagram for subjects enrolled in this study.

2.3. Study Measures

Pain and specific sensations were evaluated using the Neuropathic Pain Scale (NPS). The NPS was administered before treatment and again at week 2 and 4 during the double-blind treatment period. For patients crossed-over from the placebo group to the treatment group at the end of the double-blind study period, the NPS was also administered at week 6 and 8. This scale consists of 10 domains of pain assessing the qualities, locations and intensities of pain: sharp, hot, dull, cold, sensitive, itchy, deep and surface pain. Study subjects were asked to rate the pain on a scale of 0 to 10, with 0 being no pain or they were asked to describe sensation

Patient Name _____

Gender: □ Male □ Female

Date of Birth _____

Subject Number_____

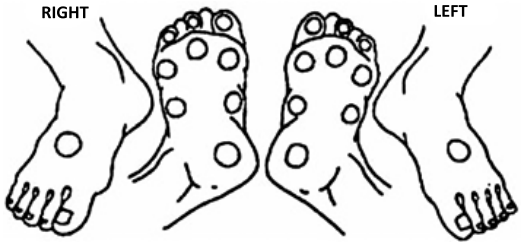
Have you ever used CBD oil for neuropathy?
□ Yes
□ No

Etiology of Peripheral Neuropathy
□ Diabetes mellitus □ Medication-induced (chemotherapy)
□ Hereditary □ Autoimmune/Connective Tissue Disorder
□ Environmental □ Idiopathic
□ Other _____

PHYSICAL EXAM:

	RIGHT	**LEFT**
Vascular:		
	□ DP pulse palpable (_/4)	□ DP pulse palpable (_/4)
	□ PT pulse palpable (_/4)	□ PT pulse palpable (_/4)
	□ Cap Refill <3 Seconds	□ Cap Refill < 3 Seconds
	__ (pitting/nonpitting) edema	__ (pitting/nonpitting) edema

Neuro:
Protective sensation intact to:



Vibratory (Less than 10 seconds)

□ 1st MTPJ	□ 1st MTPJ
□ Malleoli	□ Malleoli
□ Tibial tubercle	□ Tibial tubercle

Fig. (2). Sample of the screening and physical exam form used in this study.

and 10 being the most severe pain or sensation imaginable. A sample of the NPS form used is provided in Fig. (**3**).

2.4. Statistical Analysis

All randomized volunteer participants who received at least one dose of the treatment product were included in the intention-to treat analysis set. All summaries and statistical analyses were performed using R (R: A Language and Environment for Statistical Computing, R Core Team, R Foundation for Statistical Computing, Vienna, Austria, 2018) by an independent statistician (M.T.). Each item on the NPS was evaluated using a repeated-measures Analysis Of Covariance (ANCOVA) to determine the effects of CBD oil on each of the 10 domains. The time effect associated with each ANCOVA determines whether the specific NPS item is sensitive to the expected changes in pain experience associated with treatment conditions. The treatment effect indicates whether the CBD oil has a significant impact on the NPS domain when compared to the placebo product. The significance

Name_____

DOB_____

Assigned Number_____

1. Please use the scale below to tell us how **intense** your pain is. Place an "X" through the number that best describes the intensity of your pain.

No pain	0	1	2	3	4	5	6	7	8	9	10	The most **intense** pain sensation imaginable

2. Please use the scale below to tell us how **sharp** your pain feels. Words used to describe "sharp" feelings include "like a knife," "like a spike," "jabbing " or "like jolts."

Not sharp	0	1	2	3	4	5	6	7	8	9	10	The most **sharp** sensation imaginable ("like a knife")

3. Please use the scale below to tell us how **hot** your pain feels. Words used to describe very hot pain include "burning" and "on fire."

Not hot	0	1	2	3	4	5	6	7	8	9	10	The most **hot** sensation imaginable ("on fire")

4. Please use the scale below to tell us how **dull** your pain feels. Words used to describe very dull pain include "like a dull toothache," "dull pain," "aching" and "like a bruise."

Not dull	0	1	2	3	4	5	6	7	8	9	10	The most **dull** sensation imaginable

5. Please use the scale below to tell us how **cold** your pain feels. Words used to describe very cold pain include "like ice" and "freezing."

Not cold	0	1	2	3	4	5	6	7	8	9	10	The most **cold** sensation imaginable ("freezing")

6. Please use the scale below to tell us how **sensitive** your skin is to light touch or clothing. Words used to describe sensitive skin include "like sunburned skin" and "raw skin."

Not sen-sitive	0	1	2	3	4	5	6	7	8	9	10	The most **sensitive** sensation imaginable ("raw skin")

7. Please use the scale below to tell us how **itchy** your pain feels. Words used to describe itchy pain include "like poison oak" and "like a mosquito bite."

Not itchy	0	1	2	3	4	5	6	7	8	9	10	The most **itchy** sensation imaginable ("like poison oak")

8. Which of the following best describes the **time** quality of your pain? Please check only one answer.

( ) I feel a background pain all of the time **and** occasional flare-ups (break-through pain) some of the time.

Describe the background pain:_____

Describe the flare-up (break-through) pain:_____

( ) I feel a single type of pain all the time. Describe this pain:_____

( ) I feel a single type of pain only sometimes. Other times, I am pain free.

Describe this occasional pain:_____

(Fig. 3) Contd….

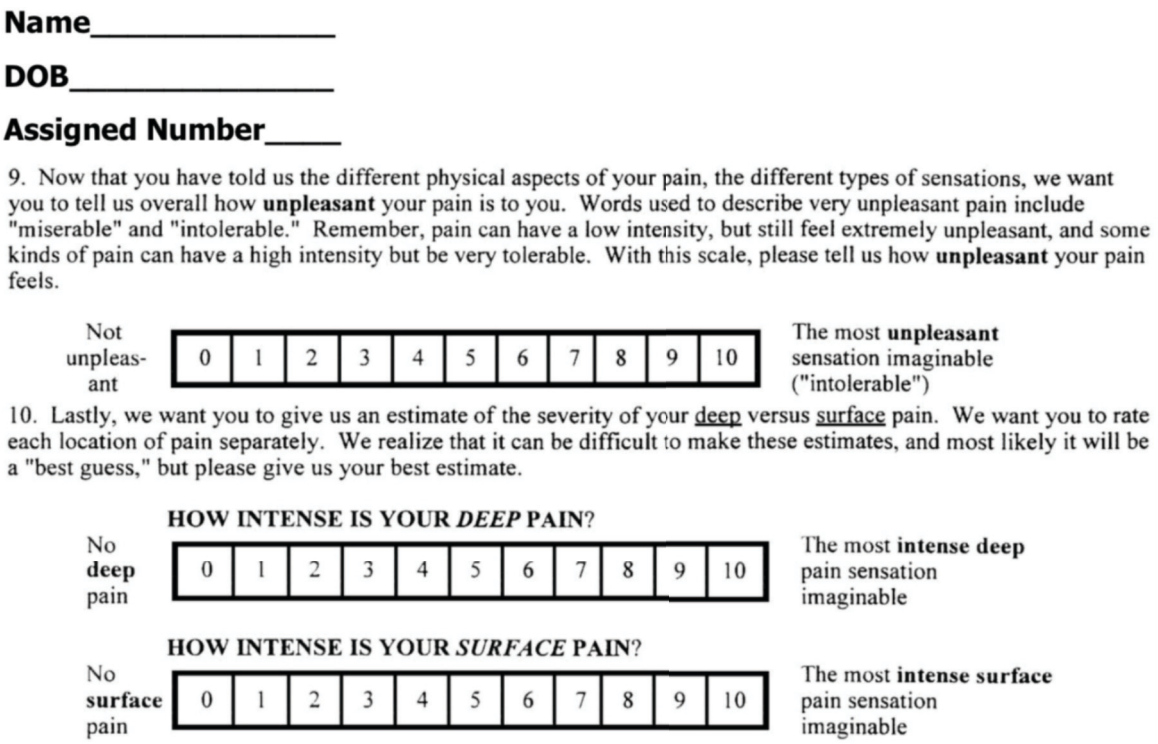


Fig. (3). Sample of the Neuropathic Pain Scale (NPS) form used to assess mean pain and sensation intensities in the placebo and treatment groups.

levels associated with each NPS item provide an indication of responses associated with CBD treatment. A p value < 0.05 is considered a significant change in each of the NPS item. Multiple linear regression between the different baseline screening variables and each of the NPS domain was also evaluated. The Pearson's r and the corresponding p values were calculated. A p value < 0.05 shows a significant correlation in each of the NPS domain.

3. RESULTS

The study took place between May 2018 and August 2018. In total, 29 patients were recruited and randomized and analyzed at a single study center. One subject in the placebo group was lost to follow-up after the baseline screening. Two subjects in the placebo group did not complete the study during the double-blind study period and were crossed over to the CBD group at the end of the 4-week double-blind study period. Three subjects in the CBD group failed to complete the survey forms at week 4 during the double-blind study period. A total of 9 subjects in the placebo group elected to cross over to the CBD group at the end of the 4-week double-blind trial. Of the study subjects, 15 (51.7%) received the CBD oil and 14 (48.3%) received the placebo during the double-blind study period. The study population had a mean age of 68±8.9 (range 35-79) years and consisted of 18 males (62.1%) and 11 females (37.9%). Seven (24.1%) participants had previously used either a topical or oral CBD product. Eighteen (62.1%) participants of the study subjects had peripheral neuropathy that was secondary to diabetes mellitus, 6 (20.7%) participants had idiopathic peripheral neuropathy, and 3 (10.3%) participants had neuropathy secondary to medications such as chemotherapy. Embolism and sciatica were also less common causes of peripheral neuropathy in this study population. One (3.4%) participant had nonpalpable pulse and 2 (6.9%) participants had capillary refill time greater than 3 seconds. All the study subjects had diminished neurological status of the lower extremities confirmed by the Semmes-Weinstein monofilament test and the vibratory sensation test. Twenty-three (79.3%) of all volunteer participants presented with no lower extremity edema, 5 (17.2%) participants had 1+ pitting edema and 1 (3.4%) participant had 2+ pitting edema. The demographics and baseline characteristics of all participating subjects are shown in Table **1**.

An ANCOVA analysis on the 10 different dimensions of the NPS over the treatment period was performed. The ANCOVA analyses of the differences in time from pretreatment to post treatment (time effect) were also computed. Table **2** presents the 10 NPS domains and their mean values at baseline.

The mean value of baseline scores across all weeks in both the placebo and CBD groups was 3.93 ± 1.91 (range 0.50 to 8.64), with a medium baseline score of 3.76. The top scoring baseline sensations were surface pain, deep pain, and unpleasant pain. A statistically significant ($p < 0.05$) decreasing trend was observed in the following mean values of the NPS domains of the CBD group when compared with the placebo: intense, sharp, cold and itchy sensations. In particular, the mean decrease was significantly larger in the CBD treatment group compared with the placebo group in these 3 domains: intense ($p = 0.009$), sharp ($p < 0.001$), and itchy ($p = 0.001$) sensations. A statistically significant reduction in

Table 1. Demographics and baseline subject characteristics.

Characteristic	Placebo n=14 (48.3%)	CBD Group n=15 (51.7%)	Total n=29
Gender			
Male, n (%)	7 (50%)	11 (73.3%)	18 (62.1%)
Female, n (%)	7 (50%)	4 (26.7%)	11 (37.9%)
Age, years, mean (SD)	66.6 (11.3)	69.5 (5.6)	68.1 (8.9)
Previous CBD use	5	2	7
Etiology of PN			
Diabetes Mellitus	9	9	18 (62.1%)
Medication-induced	2	1	3 (10.3%)
Idiopathic	2	4	6 (20.7%)
Sciatica	0	1	1 (3.4%)
Embolism	1	0	1 (3.4%)
Pulses			
Palpable	13	15	28
Nonpalpable	1	0	1
Capillary Refill			
< 3 seconds	12	15	27
> 3 seconds	2	0	2
SWM intact spots			
Right (SD)	6.2 (3.9)	5.5 (3.5)	-
Left (SD)	6.1 (3.6)	5.7 (3.4)	
Vibratory Sensation			
Intact to 1st MTPJ	8	15	23
Right	4	7	11
Left	4	8	12
Intact to malleoli	14	5	19
Right	7	3	10
Left	7	2	9
Intact to tubercle	6	10	16
Right	3	5	8
Left	3	5	8
Edema			
No edema	10	13	23 (79.3%)
1+ pitting edema	3	2	5 (17.2%)
2+ pitting edema	1	0	1 (3.4%)

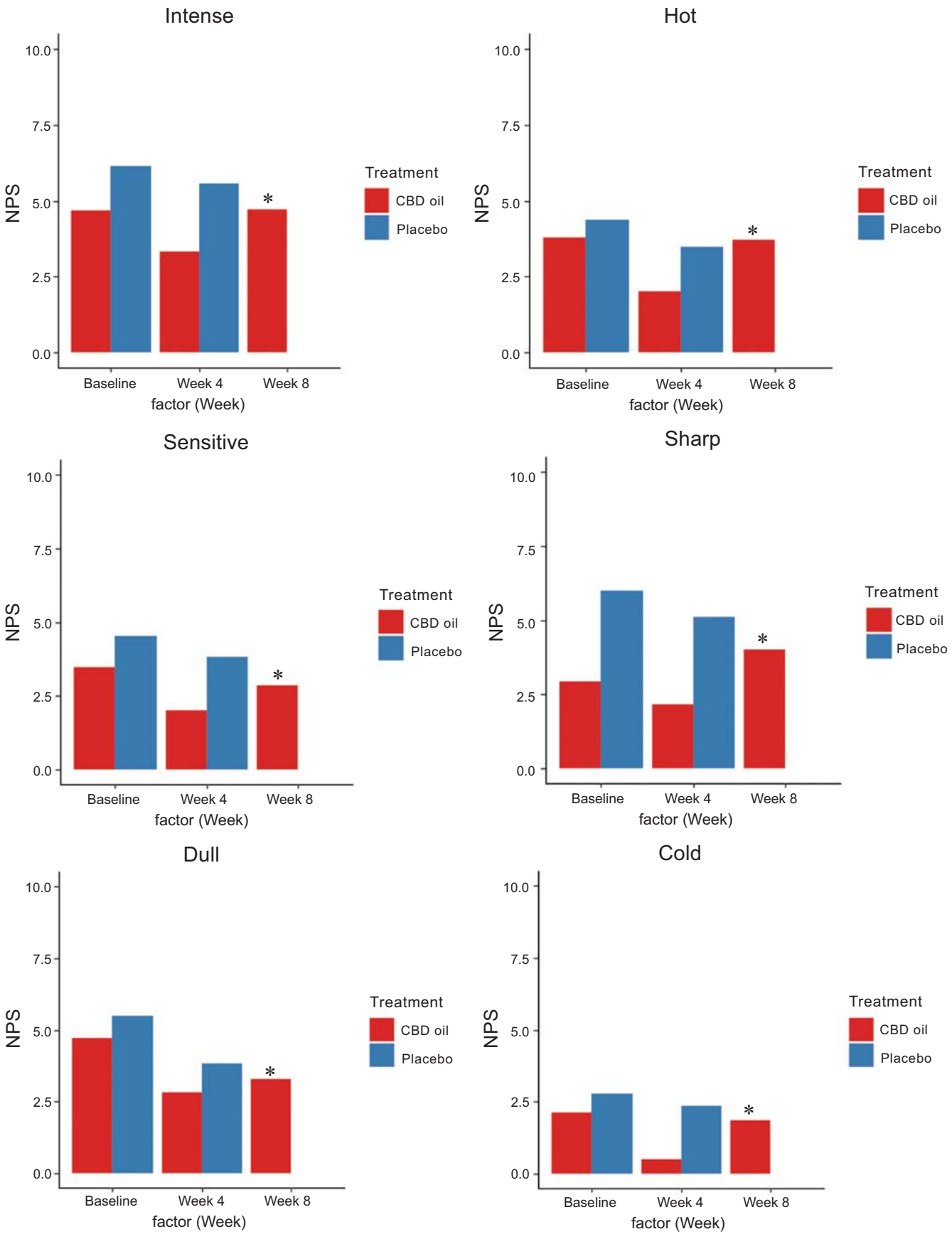
n = number of subjects enrolled in the study; SD = standard deviation; PN = peripheral neuropathy; SWM = Semmes-Weinstein monofilament; MTPJ = metatarsophalangeal joint.

Table 2. Mean NPS domain scores over treatment period: CBD versus placebo group. Arrows indicating the crossing over from the placebo group to the treatment group after four weeks.

NPS Domain	Baseline (SD)	Week 2 (SD)	Week 4 (SD)	Cross-Over	Week 6 (SD)	Week 8 (SD)	*p* Value Time Effect	*p* value Treatment Effect
Intense								
CBD	4.67 (2.44)	3.46 (2.33)	3.33 (2.02)	↗	3.57 (2.30)	4.71 (2.06)	0.0785	**0.00901**
Placebo	6.14 (2.51)	4.00 (3.06)	5.55 (2.81)					
Sharp								
CBD	2.93 (2.40)	1.54 (2.26)	2.17 (2.33)	↗	3.00 (2.31)	4.00 (2.16)	**0.0254**	**0.00000255**
Placebo	6.00 (2.91)	3.60 (3.27)	5.09 (3.05)					
Hot								
CBD	3.80 (2.91)	2.46 (2.73)	2.00 (2.22)	↗	2.43 (2.37)	3.71 (3.20)	0.079	0.332
Placebo	4.36 (2.53)	3.00 (2.94)	3.45 (2.54)					
Dull								
CBD	4.73 (3.17)	4.08 (2.96)	2.83 (1.99)	↗	2.86 (1.77)	3.29 (2.06)	0.109	0.243
Placebo	5.5 (2.50)	3.10 (3.41)	3.82 (2.36)					
Cold								
CBD	2.13 (3.72)	1.00 (1.78)	0.50 (1.17)	↗	1.86 (1.57)	1.86 (2.04)	0.670	**0.0434**
Placebo	2.79 (3.09)	1.80 (2.70)	2.36 (3.11)					
Sensitive								
CBD	3.47 (2.29)	3.00 (2.89)	2.00 (1.95)	↗	2.71 (1.70)	2.86 (2.12)	0.315	0.199
Placebo	4.50 (3.01)	2.00 (2.83)	3.82 (3.06)					
Itchy								
CBD	0.73 (1.39)	0.54 (1.12)	0.83 (1.40)	↗	1.00 (1.00)	1.71 (2.06)	0.737	**0.00108**
Placebo	2.79 (2.86)	1.20 (2.57)	2.00 (2.65)					
Unpleasant								
CBD	7.67 (1.99)	6.15 (2.79)	5.58 (2.57)	↗	5.86 (2.41)	5.71 (2.14)	**0.0184**	0.366
Placebo	8.64 (2.68)	5.00 (2.58)	6.73 (3.04)					
Deep								
CBD	6.80 (3.03)	6.00 (3.21)	5.17 (2.92)		5.57 (2.82)	6.29 (2.69)	0.297	0.0635
Placebo	8.07 (3.29)	5.40 (2.50)	6.64 (2.91)					
Surface								
CBD	6.80 (2.86)	5.46 (2.63)	4.17 (2.33)	↗	4.57 (1.99)	5.29 (2.75)	**0.0131**	0.119
Placebo	7.79 (2.86)	4.10 (2.96)	5.91 (2.70)					

mean baseline scores over time was also observed in the CBD group in the following NPS domains: sharp ($p = 0.025$), unpleasant ($p = 0.018$) and surface pain ($p = 0.013$) sensations. Although not statistically significant, a large mean baseline reduction in deep pain was observed in the CBD treatment group compared with the placebo group, and this reduction approached statistical significance ($p = 0.064$). Results at screening baseline and at 4 weeks and 8 weeks are shown in Fig. (**4**).

No adverse events were reported in this study. The results of the multiple linear regression analysis are presented in Table **3**. There appeared to be a significant negative correlation of palpable pulses with the scores in the following NPS domains: intense ($p = 0.0095$), sharp ($p = 0.0014$), hot ($p < 0.001$), dull ($p = 0.046$), cold ($p = 0.0039$), sensitive ($p < 0.001$), itchy ($p < 0.001$), unpleasant ($p = 0.035$), deep ($p = 0.025$) and surface pain ($p = 0.030$). The delayed capillary refill greater than 3 seconds was positively correlated with the following NPS scores and achieved statistical significance: intense ($p < 0.001$), sharp ($p < 0.001$), hot ($p = 0.0067$), dull ($p = 0.015$), sensitive ($p < 0.001$), itchy ($p < 0.001$), unpleasant ($p = 0.0012$), deep ($p = 0.0012$) and surface pain ($p < 0.001$).


Intense
Hot
Sensitive
Sharp
Dull
Cold
NPS
10.0
7.5
5.0
2.5
0.0
Baseline
Week 4
Week 8
factor (Week)
Treatment
CBD oil
Placebo
*

(Fig. 4) Contd….

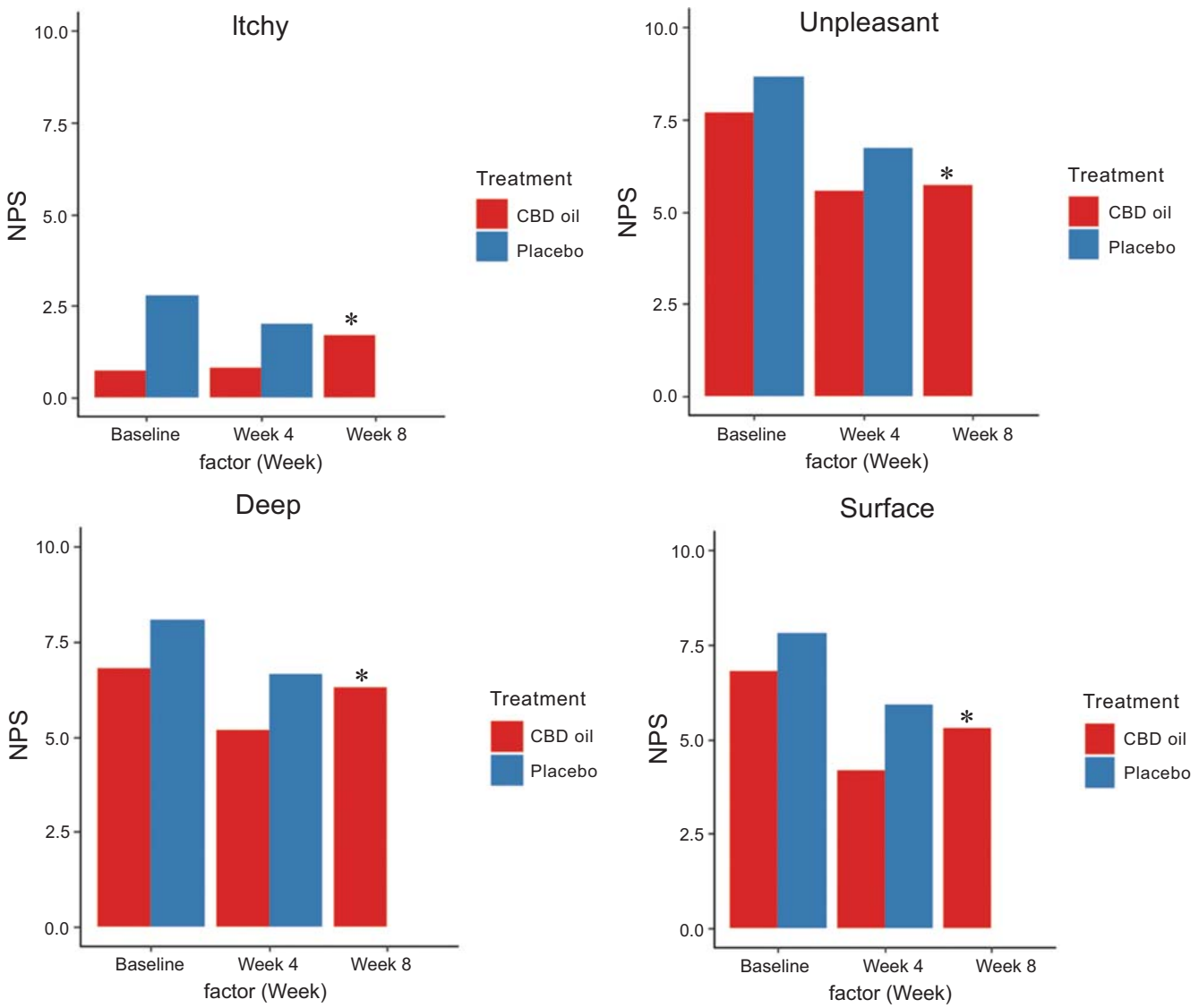


Fig. (4). Mean NPS domain scores at screening baseline, at the end of week 4, and at week 8. *Note that week 8 is the crossed-over group from the placebo group.

The presence of lower extremity edema was negatively correlated with the scores of cold ($p = 0.042$) but positively correlated with the score ofitchy ($p < 0.001$) sensation with statistical significance. The SWM testing had a negative correlation with the scores of intense, sharp, dull, itchy, unpleasant, deep and surface pain on both extremities. Interestingly, the level of diminished vibratory sensation on the left lower extremity was found to have a weak positive correlation with the scores in intense ($p = 0.002$), dull ($p < 0.011$) and unpleasant sensation ($p = 0.0097$), while the findings of the right lower extremity did not achieve statistical significance. The use of previous CBD products appeared to have a weak positive correlation with the scores in all NPS domains but this was not statistically significant. The presence of peripheral neuropathy secondary to Type II DM seemed to be negatively correlated with the score in intense, hot, cold, unpleasant and deep pain, while the presence of medication-induced peripheral neuropathy was positively correlated with the scores of intense, sharp, hot, dull, sensitive, unpleasant, deep and surface pain. Idiopathic peripheral neuropathy appeared to have a negative correlation with the scores in hot, sensitive and surface pain. It was difficult to interpret the correlation between peripheral neuropathy secondary to sciatica or embolism and the different NPS domains, as only one case was identified in each etiology.

4. DISCUSSION

4.1. The Validity of NPS

In recent years, various screening tools for distinguishing neuropathic pain from nociceptive pain have been developed [20]. Some of them rely on interview questions (NPS, ID Pain, and Pain DETECT), while others use both interview questions and physical tests such as The Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) and Douleur Neuropathique en 4 Questions (DN4) [21]. The Neuropathic Pain Scale (NPS) was first developed by Galer and Jensen to assess the various pain qualities in patients suffering from

Table 3. Correlational analysis between the NPS domains and the physical exam findings. Pearson's coefficient with corresponding *p* value were reported.

NPS Domains	Pulses	Cap Refill	Edema	R SWM	L SWM	R Vibratory	L Vibratory
Intense	-0.2377625 (p = 0.0095)	0.3259636 (p = 0.0003)	0.05669343 (p = 0.5420)	-0.2977824 (p = 0.0011)	-0.3136493 (p = 0.0005)	0.09327804 (p = 0.3151)	0.2818287 (p = 0.0020)
Sharp	-0.2911294 (p = 0.0014)	0.4455532 (p <0.0001)	0.1491522 (p = 0.1070)	-0.2659416 (p = 0.0036)	-0.229239 (p = 0.0125)	0.08731533 (p = 0.3471)	0.1504864 (p = 0.1038)
Hot	-0.3233624 (p = 0.0004)	0.2484076 (p = 0.0067)	-0.0141665 (p = 0.8790)	-0.1625118 (p = 0.0787)	-0.1478995 (p = 0.1100)	-0.127727 (p = 0.1681)	-0.1530063 (p = 0.0981)
Dull	-0.1837191 (p = 0.0464)	0.2233488 (p = 0.0151)	0.01190042 (p = 0.8982)	-0.2328037 (p = 0.0112)	-0.3050679 (p = 0.0008)	0.08140472 (p = 0.3809)	0.2343393 (p = 0.0106)
Cold	-0.263958 (p = 0.0039)	0.05406357 (p = 0.5609)	-0.187799 (p = 0.0417)	-0.110144 (p = 0.2351)	-0.1402948 (p = 0.1297)	-0.1774931 (p = 0.0545)	0.005932439 (p = 0.9492)
Sensitive	-0.3825051 (p < 0.0001)	0.2026641 (p = 0.0277)	-0.05020607 (p = 0.5893)	-0.08285588 (p = 0.3724)	-0.1163287 (p = 0.2097)	0.03078281 (p = 0.7407)	-0.08630991 (p = 0.3527)
Itchy	-0.5299474 (p < 0.0001)	0.353689 (p < 0.0001)	0.3079453 (p = 0.0007)	-0.3315793 (p = 0.0002)	-0.325751 (p = 0.0003)	0.04577412 (p = 0.6226)	0.06902733 (p = 0.4576)
Unpleasant	-0.1956116 (p = 0.0353)	0.2964861 (p = 0.0012)	0.02442087 (p = 0.7947)	-0.2927618 (p = 0.0014)	-0.3422994 (p = 0.0002)	0.01524088 (p = 0.8710)	0.2392241 (p = 0.0097)
Deep	-0.2081354 (p = 0.0250)	0.2979136 (p = 0.0012)	0.06649785 (p = 0.4782)	-0.3910642 (p < 0.0001)	-0.4503937 (p < 0.0001)	-0.006404286 (p = 0.9456)	0.1758407 (p = 0.0590)
Surface	-0.2736324 (p = 0.0030)	0.3689433 (p < 0.0001)	-0.0104763 (p = 0.9111)	-0.2181828 (p = 0.0186)	-0.2317739 (p = 0.0123)	0.01001906 (p = 0.9150)	0.003217727 (p = 0.9727)

NPS Domains	CBD Use	DM II	Medication-Induced	Idiopathic	Sciatica	Embolism
Intense	0.09526079 (p = 0.3048)	-0.277469 (p = 0.0024)	0.3867817 (p < 0.0001)	-0.02401372 (p = 0.7963)	-0.1199169 (p = 0.1959)	0.2377625 (p = 0.0095)
Sharp	0.01778197 (p = 0.8484)	-0.1562743 (p = 0.0910)	0.2658978 (p = 0.0036)	-0.1015108 (p = 0.2741))	-0.1262064 (p = 0.1733)	0.2911294 (p = 0.0014)
Hot	0.1349845 (p = 0.1450)	-0.1953334 (p = 0.0340)	0.3167391 (p = 0.0005)	-0.1952134 (p = 0.0341)	0.1064581 (p = 0.2512)	0.3233624 (p = 0.0004)
Dull	0.1049413 (p = 0.2581)	-0.1451471 (p = 0.1168)	0.3320252 (p = 0.0002)	-0.09934681 (p = 0.2845)	-0.1561067 (p = 0.0914)	0.1837191 (p = 0.0464)
Cold	0.1743269 (p = 0.0590)	-0.2358774 (p = 0.0101)	0.07442066 (p = 0.4232)	0.1361205 (p = 0.1416)	-0.1103572 (p = 0.2342)	0.263958 (p = 0.0039)
Sensitive	0.1541164 (p = 0.0957)	-0.1104555 (p = 0.2338)	0.2369931 (p = 0.0098)	-0.2489112 (p = 0.0066)	0.06322197 (p = 0.4964)	0.3825051 (p < 0.0001)
Itchy	0.1109656 (p = 0.2316)	-0.08040254 (p = 0.3868)	0.07673366 (p = 0.4089)	-0.1875602 (p = 0.0420)	-0.07493279 (p = 0.4200)	0.5299474 (p < 0.0001)
Unpleasant	0.1147147 (p = 0.2201)	-0.3532726 (p = 0.0001)	0.4092806 (p < 0.0001)	-0.01838578 (p = 0.8447)	0.1060311 (p = 0.2573)	0.1956116 (p = 0.0353)
Deep	0.1068519 (p = 0.2536)	-0.2275691 (p = 0.0140)	0.3501343 (p = 0.0001)	-0.006284701 (p = 0.9466)	-0.2175229 (p = 0.0190)	0.2081354 (p = 0.0250)
Surface	0.08061197 (p = 0.3897)	-0.1597215 (p = 0.0868)	0.4444034 (p < 0.0001)	-0.3094277 (p = 0.0007)	0.1150438 (p = 0.2188)	0.2736324 (p = 0.0030)

peripheral neuropathy [22]. A total of 10 domains of pain associated with peripheral neuropathy were included in the NPS. Both the pain intensity and unpleasantness were assessed in this scale. In addition, the NPS contains six pain qualities including sharp, hot, dull, cold, sensitive, and itchy sensations. Locations of the pain (deep and surface) are also addressed in the NPS. Because the 10 domains in the NPS are weakly correlated with one another and able to exhibit different levels of responsivity to treatments of neuropathic pain, the authors of the NPS believe the scale is able to detect treatment effects that could not be otherwise detected by the existing pain intensity scales [22]. The NPS has since been validated by other studies including its efficacy in assessing central pain caused by multiple sclerosis (MS) as well as its easier identification and assessment of patients with predominantly neuropathic pain symptoms [23, 24]. A hallmark study by Jensen *et al.*, in 2006 further demonstrated and validated the utility of the NPS in its sensitivity to determine treatment effects of neuropathic pain in patients with painful diabetic neuropathy [25]. As a result, the authors of the current study elected to choose the NPS as the measurement tool to assess the efficacy of CBD in the treatment of symptomatic peripheral neuropathy.

4.2. Current Evidence on Medical Cannabis and Pain Management

As mentioned previously, there is now a growing body of evidence for alternative management of chronic pain due to the inadequate current standards of treatment. The compounds THC and CBD from the family known as cannabinoids that are derived from the hemp plant species Cannabis sativa have received particular attention. These compounds can be administered *via* inhalation, orally as oils or capsules, oramucosally *via* sprays, or topically [26]. Although the exact mechanisms of cannabinoids-induced pain control remain elusive, one of the identified mechanisms is the interaction of these compounds with the host endogenous cannabinoid system including the aforementioned CB1 and CB2 receptors [27]. This system appears to act independently of the opioid pathway and is able to regulate pain control, immune activation and inflammation [28]. Nonetheless, the efficacy of medical cannabis has not been validated through high-quality clinical trials despite the several anecdotal evidence of its analgesic properties [27]. This is in part due to the unclear legal status of cannabis use in the U.S. Although medical cannabis is legal at the state level in 33 states and the District of Columbia, it is still illegal at the federal level, thus prohibiting potential large scaled quality clinical research [29]. In addition, the various existing forms and dosages of medical cannabis and cannabinoids further complicate any research efforts to translate them into clinical practices [27, 30]. Despite these potential barriers, medical cannabis remains as a viable treatment option for chronic pain [29]. In a systematic review conducted by Stockings *et al.*, in 2018 on the efficacy of medical cannabis in the treatment of noncancer pain, the pooled analyses indicated that a 30% reduction in pain was achieved in 29% of the cannabinoids groups, compared to 25.9% in placebo groups [6]. In a review by Blake *et al.*, cannabis has been shown to reduce chronic pain and neuropathic pain in cancer patients [27]. The results of this study was further validated by Pergolizzi *et al.*, with the authors suggesting that cannabinoids are most effective in the treatment of neuropathic pain, allodynia, medication-rebound headache and chronic noncancer pain, but do not seem to have an effect on acute visceral pain [29].

4.3. Evidence for CBD in the Treatment of Peripheral Neuropathy

Although the aforementioned studies indicate the potential utility of medical cannabis in the treatment of chronic pain, the undesired psychotropic effects of medical cannabis are a concern for many providers as well as patients. Unlike THC, CBD is a nonpsychoactive cannabinoid that has also been shown to have anti-inflammatory effects, making it a candidate for potential clinical applications with neuroinflammatory conditions, including peripheral neuropathy [4]. CBD is extensively metabolized by the liver and the metabolites are excreted mainly in the feces [31]. The half-life of CBD if administered systemically is estimated to be between 18-32 hours, and no significant adverse events of the central nervous system or host hemodynamics were identified in multiple clinical trials [1]. CBD has been shown to inhibit the accumulation and activation of microglial cells in the dorsal spinal cord in a murine model of diabetic peripheral neuropathy, and this was theorized to ameliorate the development of a neuropathic pain state, suggesting the potential mechanism and utility of CBD in the treatment of painful peripheral neuropathy [12]. A recent randomized, placebo-controlled and parallel group trial by Serpell *et al.*, examined the effects of a THC/CBD oromucocsal spray formulated in a 1:1 ratio on painful peripheral neuropathy [32]. The authors demonstrated that the use of THC/CBD spray reduced pain clinically and statistically improved sleep quality of study subjects [32].

Nonetheless, to date, there does not appear to be any quality clinical trials in the literature examining the effects of CBD alone in the treatment of peripheral neuropathy. The majority of the existing clinical trials examining the efficacy of medical cannabis on painful peripheral neuropathy are based On Treatments Using THC, A Combination Of THC And CBD, Or Inhaled Herbal Cannabis [4]. Furthermore, the pharmacokinetics and effects of topically delivered CBD are also poorly studied and understood. In a study conducted by Agu *et al.*, in murine models, transdermal gel application of CBD was shown to achieve a significant steady-state plasma concentration, and the level of tissue penetration was tripled with the use of an enhancer Transcutol HP, suggesting the effectiveness of this route of administration [33].

In the current study, the treatment group using the topically delivered CBD oil at 250 mg/3 fl. oz in an emu oil vehicle demonstrated statistically significant reduction in the following NPS domains when compared to the *placebo* emu oil group: intense pain, sharp pain, cold and itchy sensations. In particular, a larger reduction in ratings of intense pain, sharp pain and itchy sensation was noted. A greater overall reduction in the ratings of deep pain was also observed in the CBD group relative to the place group, although this did not achieve statistical significance ($p = 0.064$). In addition, a significant time effect was also observed in the CBD group in the reduction of ratings of sharp, unpleasant and surface pain

over the 4 weeks of study period. No statistically significant differences between the CBD treatment and placebo were found for hot, dull, sensitive, unpleasant, deep and surface pain. No local or systemic adverse events were reported in the study population. To our knowledge this is the first randomized, placebo-controlled trial examining the efficacy of a transdermally delivered CBD-enriched emu oil on the treatment of symptomatic peripheral neuropathy.

A potential study limitation is the small sample size. The current study may be underpowered and the treatment effects may be magnified due to the relatively small amount of study subjects. Another potential study limitation is the inclusion of multiple etiologies of peripheral neuropathy which may lead to clinical trial heterogeneity. As such, future larger-scaled randomized controlled, multi-center trials may be necessary to truly determine the potential clinical applications of topically delivered CBD.

CONCLUSION

In summary, the current pilot study demonstrated the potential clinical significance of CBD in the treatment of painful peripheral neuropathy. The transdermal delivery of cannabinoid may be a more effective alternative in comparison to current available modalities for management of this challenging condition. Further quality research is necessary in the hope of translating the use of topical CBD oil into clinical practice.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was not registered in an online repository. Due to the current status of marijuana and its derivatives listed as Schedule I substances on the federal level, we were not able to obtain approval from the Scripps Institutional Review Board.

HUMAN AND ANIMAL RIGHTS

No animals were used in this study. All reported human were experimented in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national), and with the *Helsniki Declaration* of 1975, as revised in 2013 (http://ethics.iit.edu/ecodes/node/3931).

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The authors confirm that the data supporting the findings of this study are available within the article [and/or] its supplementary materials.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to report and both equally contributed to the writing the manuscript. The named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval to the version to be published.

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SUPPLEMENTARY MATERIAL

Supplementary material is available on the publisher's website along with the published article.

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