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An enriched-enrolment, randomized withdrawal, flexible-dose, double-blind, placebo-controlled, parallel assignment efficacy study of nabilone as adjuvant in the treatment of diabetic peripheral neuropathic pain

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ABSTRACT

Cannabinoids are emerging as potential options for neuropathic pain treatment. This study evaluated an oral cannabinoid, nabilone, in the treatment of refractory human diabetic peripheral neuropathic pain (DPN). We performed a single-center, randomized, double-blind, placebo-controlled, flexible-dose study with an enriched enrolment randomized withdrawal design. DPN subjects with a pain score $\geqslant 4$ (0-10 scale) continued regular pain medications and were administered single-blinded adjuvant nabilone for 4 weeks. Subjects achieving $\geqslant 30\%$ pain relief (26/37) were then randomized and treated with either flexible-dose nabilone 1-4 mg/day (n = 13) or placebo (n = 13) in a further 5-week double-blind treatment period, with 30% (11/37) of subjects deemed run-in-phase nabilone nonresponders. For nabilone run-in-phase responders, there was an improvement in the change in mean end-point neuropathic pain vs placebo (mean treatment reduction of 1.27; 95% confidence interval 2.29-0.25, $P = 0.02$), with an average nabilone dose at end point of 2.9 ± 1.1 mg/day, and improvements from baseline for the anxiety subscale of the Hospital Anxiety and Depression Scale, the Medical Outcomes Study sleep scale problems index, and the European Quality of Life-5-Domains index score (each $P < 0.05$). Nabilone run-in-phase responders reported greater global end-point improvement with nabilone than with placebo (100% vs 31%; $P < 0.05$). Medication-related confusion led to discontinuation in 2/37 subjects during single-blind nabilone treatment. Potential unmasking occurred in 62% of both groups. Flexible-dose nabilone 1-4 mg/day was effective in relieving DPN symptoms, improving disturbed sleep, quality of life, and overall patient status. Nabilone was well tolerated and successful as adjuvant in patients with DPN.

1. Introduction

Neuropathic pain (NeP) occurs as a result of damage or disease of the peripheral or central nervous system [1]. A common cause of NeP is diabetic peripheral neuropathic pain (DPN) [43] leading to distal extremity symptoms, disturbed sleep, and diminished quality of life [16,33]. Although symptomatic therapies such as gabapentinoids, antidepressants, and opioids are available for treatment of NeP, many of these therapies remain suboptimal for quantity of pain relief or due to adverse effects [15]. The availability of adjuvant or other therapies for refractory NeP management is important for both clinicians and patients. Whereas most current NeP medications act upon ion channels, the discovery of endocannabinoids and cannabinoid receptors has led to new understanding of pain pathophysiology in animal models. Two subtypes of the cannabinoid (CB) receptor exist: CB1 and CB2 [18]. Whereas CB2 is important within the immune system, the CB1 receptor is expressed upon neurons with a direct role in neuronal pain sensitivity [27]. Although scientific research has repeatedly demonstrated beneficial effects of cannabinoids upon NeP behaviours [3,9,21], clinical data for cannabinoids in the treatment of chronic pain conditions are conflicting. While submucosal delivery of tetrahydrocannabis and cannabidiol [36,37] has been effective in management of NeP in patients with multiple sclerosis, a study in patients with DPN-associated NeP failed to determine efficacy for cannabinoids [40]. A systematic review evaluating numerous pain states also concluded that cannabinoids were similar to codeine in pain relief and were associated with unwanted side effects [12]. A randomized comparison of the oral synthetic cannabinoid

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and CB1 agonist nabilone and tetrahydro-codeine in patients with various pain conditions [22] did not show greater benefit with cannabinoids, perhaps related to the underdosing of nabilone. Finally, an open-label comparison of nabilone to gabapentin showed similar outcomes for pain relief and possibly better outcomes for sleep efficacy with nabilone [6]. Thus, there has been uncertainty in the use of cannabinoids for management of NeP and its associated symptoms.

Nabilone, a synthesized CB1 predominant receptor agonist, has been used for NeP relief based upon anecdotal evidence and uncontrolled case series [2,4], with probable efficacy in fibromyalgia for pain [41] and insomnia [46]. With high bioavailability, rapid redistribution, metabolism, and excretion, nabilone also has a long half-life ($t_{1/2} \sim 20$ hours) with active metabolites potentially further prolonging its action [38]. Nabilone's side-effect profile is also acceptable in most studies when compared to other medications used for NeP.

The aim of this study was to compare the efficacy of nabilone as adjuvant treatment for NeP due to DPN vs placebo using a randomized double-blind, placebo-controlled, parallel-assignment, flexible-dose comparison using an enriched-enrolment randomized withdrawal design. Our primary hypothesis was that nabilone would improve average daily pain scores from average weekly baseline values as compared to placebo, but we also hypothesized that nabilone would benefit secondary outcome measures of associated features of NeP, including anxiety, depression, sleep efficacy, and quality of life.

2. Materials and methods

2.1. Subject assessment

This study was approved by the University of Calgary Conjoint Health Research Ethics Board and Health Canada. Subject recruitment occurred through both primary and tertiary care clinics in Calgary, Alberta, Canada with an intended equal distribution of recruitment. Subjects were assessed by one of 3 different neurologists throughout the study. Men or women aged 18-80 years with DPN-associated NeP were screened if their DN4 [7] questionnaire score was $\geqslant 4$. The presence of DPN-associated NeP was confirmed by a neurologist. Pain must have persisted for at least 3 months and pain severity must have averaged scores of $\geqslant 40$ mm on the 100-mm visual analogue scale (VAS) of the Short-Form McGill Pain Questionnaire [32] at the time of the visit. Then, following completion of written informed consent, completion of daily pain diaries occurred over a 7-day screening period using an 11-point numerical rating scale (NRS) from 0 = no pain to 10 = worst possible pain. Those subjects continuing with enrolment in the single-blind phase of the study were required to have an average daily pain severity of $\geqslant 4$ during the week of these baseline scores (with at least 4 days completed during a 7-day period).

Subjects with other causes of pain, including postherpetic neuralgia, lumbar radiculopathy, central neuropathic pain, complex regional pain syndromes I or II, or significant osteoarthritis, were excluded. Any skin conditions over the area of DPN which could hinder examination, led to exclusion. Any current diagnoses of schizophrenia, psychotic disorder, bipolar affective disorder, obsessive compulsive disorder, or major depressive disorder were also exclusionary. Clinically significant unstable medical conditions that could compromise participation, such as with poor diabetic control (haemoglobin A1C $\geqslant$ 11%), history of substance abuse or dependence, malignancy other than squamous cell carcinoma in the last 2 years, elevation of liver enzymes above 3 times the upper limit of normal, or an anticipated need for surgery or hospitalization within the next 16 weeks after screening led to exclusion at the discretion of the investigator. This was an adjuvant study – subjects were allowed to be taking other medications for their NeP, excluding cannabinoids, as long as their use had been stable for at least 1 month before the study and would remain so during the study. Those subjects previously exposed to nabilone were excluded. Any use of self-obtained cannabinoids or other illicit drugs during the study was prohibited, and subjects with a positive urinary illicit drug screen (including detection of 11-nor-delta-9-tetrahydrocannabinol-9-carboxylic acid) were excluded at screening. Women who were breastfeeding or pregnant were excluded, and female patients capable of conception were required to use reliable contraception.

During the assessment of DPN, other potential aetiologies of the polyneuropathy were also determined based upon laboratory investigations and clinical information. Other blood work was performed in order to determine the presence of other confounding medical conditions. These investigations included complete blood count, electrolytes, urea, creatinine, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transpeptidase, alkaline phosphatase, albumin, total bilirubin, international normalized ratio, thyroid-stimulating hormone, fasting glucose, haemoglobin A1C, erythrocyte sedimentation rate, antinuclear antibody, extracted nuclear antibody testing, serum protein electrophoresis, rheumatoid factor, vitamin B12 levels, fasting methylmalonic acid, urine toxicology screening, and beta-human chorionic gonadotropin. At completion of the study, repeated testing was performed for all of the above except for antinuclear antibody, extracted nuclear antibody testing, serum protein electrophoresis, rheumatoid factor, and fasting methylmalonic acid.

2.2. Study design, protocol, and intervention

This was a single-center, parallel-group, double-blind, placebo-controlled randomized clinical trial with a 4-week single-blind flexible-dose phase of nabilone use followed by a randomized double-blind maintenance phase. It was designed to compare 5 weeks of stable-dose nabilone 1-4 mg/day with placebo, taken as 2 daily doses 12 hours apart with 1:1 allocation. The study concluded with a 1-week taper phase incorporated to reduce the risk of potential withdrawal effects for the subjects assigned to the nabilone treatment arm; subjects receiving placebo also tapered their placebo use similarly during the last week of the study. The Clinical Trial Registration number for this study is NCT01035281 (www.clinicaltrials.gov).

After screening, when inclusion criteria were met and informed consent was completed, subjects were initiated on a 4-week flexible-dose single-blind run-in phase to receive adjuvant nabilone as part of an enriched enrolment randomized withdrawal (EERW) design using exclusion of nonresponders. Subjects were unaware of therapy allocation in this single-blind phase. Baseline data were collected prior to single-blind dosing. Prior to obtained consent, it was explained that the subjects could receive either nabilone or placebo during each of the single-blind and double-blind phases.

At baseline, patients were screened after informed consent completion. Efficacy assessments and questionnaires were completed, and no intervention was received during this baseline assessment week. The baseline week consisted of 1 week of completion of daily pain severity and sleep disruption severity diaries; after this, efficacy assessments and questionnaires were again completed prior to any intervention being provided. Next, the 4-week single-blind phase was initiated, with daily diaries evaluating pain severity and sleep disruption severity again completed. During the single-blind phase, subjects were initially prescribed nabilone 0.5 mg twice daily for 1 week, with weekly follow-up visits to determine efficacy, tolerability, and dosing adjustments. Nabilone was titrated up to 1.0 mg twice daily and as high as 2.0 mg

twice daily as tolerated over the subsequent 3 weeks until day 28 of the study. Adverse events were recorded during each visit. Only one dose reduction was allowed during the 4-week single-blind phase of the study.

In order to be randomized at day 28, subjects were required to have completed at least 75% of their daily pain diaries over the 4 weeks. If subjects did not achieve ⩾30% pain relief for daily pain scores for the 7 days prior to day 28 when compared to the baseline scores, or if subjects developed intolerable side effects, then these subjects were not randomized in the double-blind phase of the study; this requirement was explained to patients prior to informed consent. It was also explained to subjects that at randomization, if their intervention was switched, then titration either onto or off of nabilone over the first week of the double-blind phase would occur. During the double-blind phase, eligible subjects were randomly assigned to continue nabilone at the effective dose achieved in the flexible-dose single-blind phase or to receive placebo. For subjects receiving nabilone during the double-blind phase, the dose of nabilone achieved at day 28 was continued without change for 5 weeks. For subjects randomized to placebo, there was a 1-week blinded taper of either 0.5 mg daily or twice daily of nabilone regardless of dose achieved at day 28, followed by strict placebo use over the subsequent 4 weeks. However, the number of pills received remained unchanged from the amount received on day 28 to avoid unmasking of allocation, with a mixture of nabilone and placebo provided to patients allocated to placebo. No further titration occurred after day 28 regardless of allocation.

Medication was blinded for placebo using capsules of identical size, color, taste, and smell. An electronic randomization system was used to randomize individual subjects without block randomization as developed by an outside coordinator. Randomization was concealed from subjects, clinical coordinator, and assessing physicians. Clinic visits were scheduled for screening, baseline, and at the end of weeks 1, 2, 4, 5, 7, 9, and 1 week after completion of the study or at 1 week after early discontinuation. Telephone visits took place during the end of weeks 3, 6, and 8. There was a 1-week double-blind taper period at the end of the study for all subjects regardless of randomization to placebo or nabilone.

2.3. Efficacy assessments and questionnaires

The mean difference in the average daily pain score was the primary efficacy variable, based on the mean of the last 7 entries in the daily pain diary during the fifth week of the double-blind phase, with comparison to the mean of scores obtained in the baseline week prior to single-blind nabilone use. Pain severity and sleep disruption severity over the preceding 24 hours were rated daily using an 11-point NRS from 0 = no pain to 10 = worst possible pain, and 0 = pain does not interfere with sleep to 10 = pain completely interferes with sleep, respectively. Daily pain and sleep disruption severities were recorded from the baseline visit until the end of the tapering of intervention after completion of the double-blind phase.

Other efficacy assessments and questionnaires were completed at the baseline visit, after the baseline week (day 0), at the end of the single-blind phase (day 28), and at the end of the double-blind phase (end of week 9). These secondary efficacy assessments included the Medical Outcomes Study Sleep Scale (MOSSS) [25] based on a 1-week recall period, the Hospital Anxiety and Depression Scale (HADS) [50], the modified Brief Pain Inventory short form (MBPI) [47], the EuroQol 5 Domains (EQ-5D), the Pain Treatment Satisfaction Scale (PTSS), and the Neuropathic Pain Symptom Inventory (NPSI). The EQ-5D has 2 sections; the first section examines the health state in 5 dimensions: mobility, self-care, usual activities, pain/complaints, and anxiety/depression. We calculated EQ-5D utility scores and index VAS scores [44]. The PTSS is a 14-point scale used to provide subject-related evaluation of treatment effectiveness [19]. The NPSI [8] consists of 12 items regarding qualities and quantities of pain descriptions as well as subscores (burning, pressing [deep], paroxysmal, evoked, paresthesias/dysesthesias) and was administered at baseline, day 28, and at end point. We also used the VAS scale as a 100-mm unmarked line with subjects asked to indicate their level of pain severity during the week prior to evaluation, ranging from *no pain (0)* to *worst possible pain* (100) – the distance in millimetres measured from the left end of the scale (*no pain)* to the subjects' mark was recorded at baseline, day 28, and at the end of week 9. The Patient Global Impression of Change (PGIC) [20], during which subjects rate their overall status on a 7-point scale from 1 = very much improved to 7 = very much worse, was completed at day 28 and at the end of week 9.

2.4. Tolerability and safety assessments

All spontaneously reported and observed adverse events were recorded at each clinic visit and during telephone follow-up visits. Vital signs and body weight were monitored at all clinic visits. Electrocardiograms were completed at screening and at the end of study for all subjects. A full physical examination including a neurological component was completed at baseline and at end point for all subjects. Adverse events were coded using standard terminology [10].

2.5. Data analysis

Based upon our primary end point of mean pain reduction based upon weekly mean scores from the daily pain diary scales, sample size estimates were performed assuming a 2-sided comparison with tolerance for type I error set to be alpha = 0.05. Based on the results of 2 previous randomized controlled trials of cannabinoids in separate conditions [5,37], the effect size (difference from placebo in change of end-point mean pain score) was estimated to be 2.0, with an estimated SD of 1.0. A sample size of 20 subjects per group would provide 80% power to detect a treatment effect of 2.0. We assumed a dropout rate of 10%, meaning that a required group size of 44 total subjects in the randomized phase would be recruited. No interim analyses were planned.

All analyses were based on the intention-to-treat population. The proportions of subjects with a ⩾30% and ⩾50% reduction in pain score between baseline and end point (responder analyses) were calculated, and compared using analysis of variance (ANOVA) testing. Mean changes from baseline to end point in the secondary efficacy variables were also determined for each scale. All analyses were based on 2-sided testing without adjustment for testing multiple measures. The analysis of weekly mean pain and sleep interference scores was based on a mixed-model repeated-measures (MMRM) analysis and least squares (LS) means were compared between groups each week. The MMRM analysis used all of the available data from sequential observations. All other continuous variables were analyzed using analysis of covariance (ANCOVA), controlling for baseline values. Statistical significance was set to be $\alpha = 0.05$ in each case. Missing values were handled using imputation techniques using the last value carried forward technique. Categorical variables such as with the PGIC were analyzed using the Cochran-Mantel-Haenszel test.

Financial provisions for this study were discontinued by the sponsor earlier than anticipated, leading to suboptimal patient enrolment. Upon completion of the last study visit, database closure occurred and a post hoc analysis was performed using available data.

3. Results

3.1. Subjects

This study was concluded earlier than anticipated due to insufficient funding; as a result, we did not achieve the estimated total of 44 subjects in the second randomized phase of the study. Recruitment occurred between December 2006 and March 2011. A total of 51 subjects were screened for the study, with 27 of these subjects recruited from tertiary care clinics in the investigators' primary institution. A total of 37 subjects were enrolled in the single-blind phase of the study (Fig. 1). Of these subjects, 3 discontinued the study prior to day 28 due to lack of efficacy (n = 1) and intolerable side effects (ie, confusion; n = 2). At day 28, a total of 8 subjects were excluded from entry into the double-blind phase of the study due to <30% improvement in daily pain severity achieved during the 7 days prior to day 28 when compared to baseline data obtained. Therefore, 26 subjects were randomized and received either placebo (n = 13) or nabilone (n = 13). One subject from the placebo cohort discontinued the study at day 56 (prior to end of the double-blind phase) due to inefficacy of pain relief, but data were maintained for intention-to-treat population analysis. Baseline demographic and clinical characteristics were generally similar in the 2 randomized treatment cohorts, except for a greater proportion of women randomized to the nabilone group than in the placebo group (Table 1). Baseline and later timepoint characteristics between the subject groups receiving nabilone or placebo did not demonstrate any remarkable differences in concomitant medication use (including concomitant pain medication use) or comorbidities (Supplementary Tables 1 and 2).

3.2. Study medication

At day 28 (prerandomization), nabilone dosing was as follows: 21 subjects (62%) received 2 mg/day, 7 subjects (21%) received 4 mg/day, and 6 subjects received 1 mg/day. Subjects not achieving

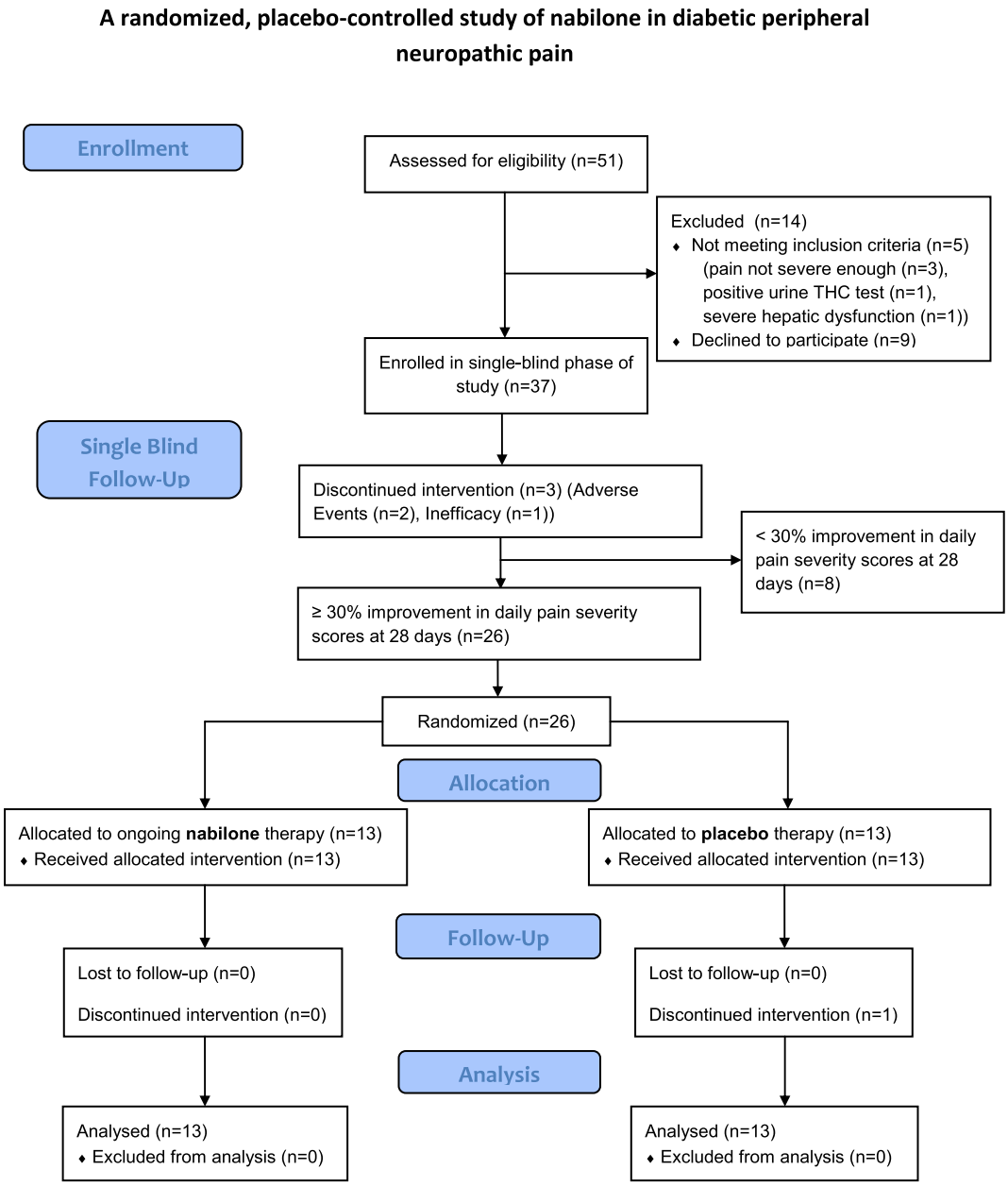

Fig. 1. Subject disposition throughout both phases of the study using the CONSORT (Consolidated Standards of Reporting Trials) guidelines.

Table 1
Subject baseline characteristics.

	Characteristics			
	Baseline data for all patients screened	Baseline data for all patients at day 0 prior to single-blind phase of study	Baseline data for all patients receiving nabilone in the double-blind phase of study	Baseline data for all patients receiving placebo in the double-blind phase of study
Age	62.2 ± 9.3 years		60.8 ± 15.3 years	61.6 ± 14.6 years
Sex (males)	23/51 (45%)		5/13 (38%)	9/13 (69%)*
Weight (kg)	96.9 ± 22.3 kg		86.4 ± 29.2 kg	92.1 ± 27.5 kg
Ethnicity	Caucasian 48/51 Asian 2/51 African-Canadian 1/51		Caucasian 12/13 Asian 1/13	Caucasian 12/13 African-Canadian 1/26
Duration of diabetes mellitus	10.5 ± 9.2 years		9.7 ± 13.1 years	10.0 ± 12.6 years
Type 1 diabetes mellitus	6/51 (12%)		1/13 (8%)	2/13 (8%)
Haemoglobin A1C (%)	7.7 ± 1.7		7.1 ± 1.8	7.2 ± 1.6
Duration of neuropathic symptoms	7.1 ± 7.3 years		7.2 ± 8.5 years	7.1 ± 7.9 years
Concomitant diabetic complications				
Retinopathy	15/51 (29%)		4/13 (31%)	4/13 (31%)
Cataracts	15/51 (29%)		3/13 (23%)	4/13 (31%)
Nephropathy	2/51 (4%)		0/13 (0%)	0/13 (0%)
Cardiovascular	14/51 (28%)		4/13 (31%)	3/13 (23%)
Cerebrovascular	4/51 (8%)		1/13 (8%)	2/13 (16%)
Limb/digit amputation	1/51 (2%)		0/13 (0%)	0/13 (0%)
Concomitant vascular risk factors				
Hypertension	24/51 (47%)		6/13 (46%)	7/13 (54%)
Hyperlipidemia	25/51 (49%)		7/13 (54%)	6/13 (46%)
Supine blood pressure				
Systolic	141.2 ± 19.8 mm Hg	138.1 ± 15.4 mm Hg	140.8 ± 21.6 mm Hg	140.2 ± 24.2 mm Hg
Diastolic	79.3 ± 11.6 mm Hg	79.6 ± 8.8 mm Hg	78.4 ± 14.2 mm Hg	79.0 ± 13.8 mm Hg
Standing blood pressure				
Systolic	135.2 ± 21.3 mm Hg	135.6 ± 14.8 mm Hg	136.0 ± 23.0 mm Hg	135.6 ± 24.1 mm Hg
Diastolic	79.7 ± 12.4 mm Hg	80.5 ± 8.7 mm Hg	79.9 ± 15.7 mm Hg	79.6 ± 14.0 mm Hg
Supine heart rate (beats/minute)	72.7 ± 11.6	73.8 ± 8.8	72.4 ± 13.6	73.1 ± 14.0
Standing heart rate (beats/minute)	74.9 ± 13.0	75.6 ± 12.0	75.1 ± 14.1	75.4 ± 14.3
Baseline daily average for pain severity visual analogue scale	5.4 ± 2.7	5.7 ± 2.2	5.8 ± 1.8	5.8 ± 1.6
Baseline daily average for sleep disturbance visual analogue scale	4.7 ± 2.6	4.9 ± 2.5	5.0 ± 1.7	5.1 ± 1.8
Hospital Anxiety and Depression Score (HADS)				
Anxiety (HADS-A)	6.7 ± 3.9	7.2 ± 4.5	6.9 ± 4.6	7.1 ± 5.2
Depression (HADS-D)	5.1 ± 3.1	5.4 ± 3.2	5.4 ± 4.0	5.5 ± 3.8
Medical Outcomes Study Sleep Score (MOSSS) sleep problems index score	35.2 ± 9.7	40.4 ± 14.5	38.3 ± 11.5	39.4 ± 12.2
European Quality of Life – 5 Domains (EQ-5D)				
Utility score	60.4 ± 14.6	60.2 ± 15.2	55.8 ± 17.2	58.4 ± 16.7
Index score	0.61 ± 0.17	0.60 ± 0.21	0.58 ± 0.20	0.58 ± 0.20
Visual analogue scale (VAS) (pain severity)	61.1 ± 17.2	65.9 ± 18.3	65.4 ± 19.1	65.9 ± 20.3

Values shown are means ± SD.
* Indicates $P < 0.05$ analysis of covariance for baseline data with comparison of subjects randomized to nabilone use as compared to those subjects randomized to placebo use prior to the initiation of the double-blind phase.

⩾30% pain relief consisted of 5 subjects receiving 1 mg/day and 3 subjects receiving 2 mg/day. The mean end-point nabilone dose was 2.85 ± 1.14 mg/day, consisting of 1 subject taking 1 mg/day, 6 subjects taking 2 mg/day, and 6 subjects taking 4 mg/day. There was no difference in change in weight between baseline and end point for subjects receiving nabilone as compared to those subjects receiving placebo (+0.8 ± 0.2 kg vs +0.6 ± 0.3 kg, P = NS).

3.3. Efficacy

For the primary end point, nabilone adjuvant therapy was statistically more effective than placebo in improving pain at end point (MMRM analysis with LS means, $P < 0.05$) (Fig. 2). The number of subjects with ⩾30% reduction in pain from baseline to end point was 11/13 (85%) in the nabilone group, compared to 5/13 (38%) in the placebo group (ANOVA, $P < 0.05$). The percentage of subjects achieving ⩾50% reduction in pain from baseline to end point was 4/13 (31%) in the nabilone group, compared to 1/13 (8%) in the placebo group (ANOVA, P = NS). For the 37 subjects enrolled in the single-blind phase, the NRS was 6.6 ± 1.8, as compared to 3.6 ± 2.0 at day 28 ($P < 0.01$, MMRM analysis with LS means). At the end of the double-blind phase, the NRS was 3.5 ± 1.3 in the nabilone cohort, as compared to 5.4 ± 1.7 in the placebo cohort, giving a mean difference of 3.0 ± 1.2 in the nabilone cohort, as compared to 1.1 ± 1.5 in the placebo cohort ($P < 0.01$, MMRM analysis with LS means). For the single-blind phase (with comparison to baseline), an effect size of 1.10 was calculated using the standardized mean difference (using baseline SD values), while for the double-blind phase, an effect size of 0.67 was calculated for nabilone compared to placebo use.

In the MMRM analysis of weekly mean pain scores, pain relief favouring nabilone was first apparent at week 6 after baseline ($P < 0.05$, MMRM analysis with LS means), and then present weekly from week 6 to week 9 ($P < 0.05$ for each week, MMRM analysis with LS means) (Fig. 2). Assessment of sleep disruption scores showed less sleep disruption with nabilone at weeks 6, 8, and 9 ($P < 0.05$ for weeks 6, 8, and 9, MMRM analysis with LS means) (Fig. 2).

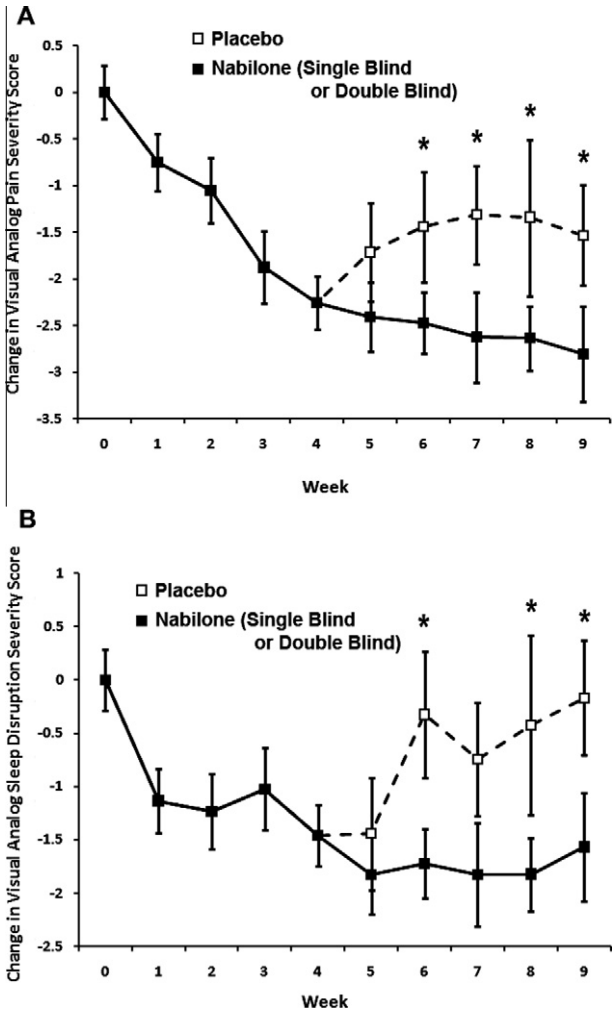

Fig. 2. The effects of nabilone and placebo upon visual analogue scoring for pain severity (A) and sleep disruption (B). Randomization to the double-blind phase began at week 4 (day 28). *Indicates significant differences with $P < 0.05$ for the mixed-model repeated-measures with least squares means analysis. Values shown are means ± SE.

A total of 9/37 (24%) subjects at baseline had a baseline HADS anxiety subscale score of ⩾10, indicating moderate anxiety levels (Table 2). A total of 4/37 (11%) subjects at baseline had a baseline HADS depressive symptoms subscale score of ⩾10, indicating mild depressive levels. There was a modestly significant improvement in HADS anxiety scores at end point for subjects receiving nabilone, as compared to subjects receiving placebo ($P < 0.05$, ANCOVA, F = 2.24) (Table 2). There was no significant change from baseline or difference between nabilone and placebo cohorts for the HADS depressive symptoms scale score at end point.

The evaluation of sleep using the MOSSS indicated an improvement in the overall sleep problems index of the MOSSS in the nabilone-receiving group (Table 2) ($P < 0.05$, ANCOVA, F = 1.91). The mean MOSSS sleep problems index score at end point of the double-blind phase was improved for the nabilone cohort compared to the placebo cohort (27.2 ± 2.5 vs 33.0 ± 2.8).

Quality of life was assessed using the self-reported EQ-5D utility score and the composite EQ-5D index score. Although there was no significant difference in the EQ-5D utility score reported at end point (Table 2), a significant improvement in the composite index score occurred, with nabilone subjects reporting a significantly improved quality of life as compared to subjects receiving placebo ($P < 0.05$, ANCOVA, F = 2.55).

The VAS was also administered at intervals of baseline, 28 days, and at double-blind phase end-point visits using a continuous nonmarked line, identifying a significant improvement in VAS at the end of the single-blind phase ($P < 0.05$, ANCOVA, F = 1.92), as well as significant improvement for VAS in patients receiving nabilone at the end of the double-blind phase (Table 2) ($P < 0.05$, ANCOVA, F = 2.67).

The PTSS subject self-evaluation of their satisfaction with treatment demonstrated improvement in subjects' feelings about the form, frequency, and amount of pain medications taken at the end of the single-blind phase when compared to baseline values (Table 3). There was also greater satisfaction with level of pain relief at the end of the single-blind phase. For the end point of study, subjects taking nabilone had greater satisfaction with amount of pain medication used when compared to subjects taking placebo ($P < 0.05$, ANCOVA, F = 2.41).

The MBPI pain interference scores identified a number of improvements at the end of the single-blind phase when values were compared to baseline values: levels of worst pain, least pain, average pain, current pain, and degree of pain relief were all significantly improved, as was the level of pain interference with sleep (Table 3). At study end point, subjects taking nabilone reported significantly better responses for levels of worst pain, least pain, average pain, current pain, and for interference with sleep when compared to subjects taking placebo (P < 0.05, ANCOVA, F = 1.47-5.05).

Table 2
Secondary end points.

Assessment	Characteristic	Timepoint			
		Day 7 values (pre-single blind) (n = 34)	End of single blind phase (n = 34)	End point (nabilone) (n = 13)	End point (placebo) (n = 13)
Medical Outcomes Study Sleep Scale (MOSSS)					
	MOSSS sleep problems index	34.3 ± 1.6	28.9 ± 3.4	27.1 ± 2.1**	33.0 ± 2.6
Hospital Anxiety and Depression Scale (HADS)					
	HADS-A (Anxiety)	7.4 ± 0.8	6.8 ± 1.3	5.0 ± 0.7**	7.9 ± 1.4
	HADS-D (Depression)	5.8 ± 0.5	5.3 ± 1.1	5.2 ± 0.9	5.6 ± 1.2
European Quality of Life - 5 Domains (EQ-5D)					
	EQ-5D utility score	60.2 ± 3.8	64.2 ± 5.2	72.6 ± 4.7	61.4 ± 6.7
	EQ-5D index score	0.60 ± 0.04	0.73 ± 0.04	0.74 ± 0.03**	0.60 ± 0.08
Interval Visual Analogue Scale					
	Continuous 100-mm visual analogue scale (VAS) (pain severity)	61.1 ± 3.0	35.6 ± 4.6*	35.4 ± 4.0**	54.3 ± 4.5

Values shown are means ± SDs.
* Indicates $P < 0.05$ (analysis of covariance [ANCOVA]) from baseline to end of single blind phase timepoint.
** Indicates $P < 0.05$ (ANCOVA) between nabilone and placebo cohorts at double blind phase end point.

Table 3
Other secondary end points.

Assessment	Characteristic	Timepoint			
		Baseline values (n = 34)	End of single blind phase (n = 34)	End point (nabilone) (n = 13)	End point (placebo) (n = 13)
Pain Treatment Satisfaction Scale (PTSS)					
	1-Physical health	2.6 ± 1.2	1.7 ± 1.0	2.1 ± 1.1	2.5 ± 1.2
	2-Outlook on life	2.5 ± 1.2	2.0 ± 1.0	2.2 ± 1.1	2.6 ± 1.3
	3-Daily activities	2.4 ± 1.3	1.9 ± 0.8	2.4 ± 1.1	2.6 ± 1.2
	4-Leisure activities	2.5 ± 1.4	2.4 ± 1.1	2.6 ± 1.3	2.7 ± 1.4
	5-Perform Independently	2.4 ± 1.2	2.3 ± 0.9	2.3 ± 1.1	2.4 ± 1.2
	6-Relationships with others	2.4 ± 1.1	2.3 ± 0.9	2.2 ± 1.1	2.8 ± 1.2
	7-Mood	2.6 ± 1.1	2.3 ± 1.1	2.4 ± 1.0	2.7 ± 1.3
	8-Concentration	2.6 ± 1.1	2.4 ± 1.1	2.5 ± 1.0	2.8 ± 1.3
	9-Form of Medication	2.0 ± 0.8	1.2 ± 0.4*	1.5 ± 0.7	1.8 ± 0.8
	10-Frequency of Medication	2.2 ± 1.0	1.5 ± 0.5*	1.6 ± 0.5	1.9 ± 1.0
	11-Amount of pain medication	2.7 ± 1.1	1.7 ± 0.9*	1.8 ± 0.6**	2.8 ± 0.8
	12-Time for medication to work	2.9 ± 1.1	2.2 ± 1.0	1.9 ± 0.7	2.5 ± 0.9
	13-Level or amount of pain relief	3.2 ± 0.6	2.0 ± 0.6*	2.6 ± 1.2	3.1 ± 0.9
	14-Duration of pain relief	3.4 ± 1.0	2.3 ± 0.9	2.5 ± 1.0	3.0 ± 0.9
Modified Brief Pain Inventory (MBPI)					
	1-Worst pain	6.8 ± 2.1	4.0 ± 1.6*	3.9 ± 1.2**	6.7 ± 1.1
	2-Least pain	3.5 ± 2.7	1.7 ± 1.4*	1.0 ± 0.4**	3.7 ± 1.2
	3-Average level	5.3 ± 2.0	2.9 ± 1.5*	2.5 ± 1.9**	5.2 ± 1.3
	4-Right now	4.4 ± 2.7	2.6 ± 1.5*	1.9 ± 1.5**	5.0 ± 1.2
	5-Degree of Relief	3.6 ± 1.8	6.2 ± 2.1*	6.1 ± 1.9	4.3 ± 2.2
	6-Interference with general activity	4.6 ± 2.9	3.1 ± 2.7	2.5 ± 1.6	3.6 ± 0.9
	7-Interference with mood	4.5 ± 2.5	3.5 ± 3.1	1.9 ± 1.3	3.1 ± 1.2
	8-Interference with walking ability	5.4 ± 3.4	4.8 ± 2.9	3.5 ± 2.6	4.1 ± 1.9
	9-Interference with normal work/ housework	4.5 ± 3.2	3.9 ± 3.6	3.2 ± 2.4	3.5 ± 1.4
	10-Interference with relations with other people	3.2 ± 2.6	2.6 ± 2.3	1.9 ± 1.7	2.2 ± 1.4
	11-Interference with sleep	5.4 ± 2.0	3.4 ± 2.2*	1.8 ± 1.3**	4.1 ± 0.8
	12-Interference with enjoyment of life	4.8 ± 2.6	4.1 ± 3.4	3.5 ± 2.6	4.1 ± 0.9
Neuropathic Pain Symptom Inventory (NPSI)					
	1-Pain feels like burning	5.5 ± 3.0	3.4 ± 2.1	3.1 ± 3.0	4.8 ± 3.0
	2-Pain feels like squeezing	2.9 ± 2.8	2.3 ± 2.2	2.0 ± 2.6	1.7 ± 2.6
	3-Pain feels like pressure	4.4 ± 2.7	3.3 ± 2.0	3.0 ± 2.7	4.3 ± 2.5
	4-Spontaneous pain	2.5 ± 1.5	2.6 ± 1.3	2.9 ± 1.4	2.1 ± 1.5
	5-Pain feels like electric shocks	5.2 ± 3.2	4.2 ± 2.7	2.8 ± 2.3**	6.0 ± 2.9
	6-Pain feels like stabbing	4.8 ± 3.0	3.3 ± 2.5	3.1 ± 2.9	4.6 ± 3.0
	7-Pain attacks	3.1 ± 1.3	3.4 ± 1.2	3.8 ± 0.8	3.1 ± 1.1
	8-Light touching	3.7 ± 3.2	3.1 ± 2.1	1.3 ± 2.1**	4.1 ± 3.9
	9-Pressure	4.7 ± 3.2	3.5 ± 2.3	3.0 ± 2.7	3.2 ± 3.2
	10-Contact with something cold	2.2 ± 3.1	2.6 ± 2.8	1.1 ± 1.4	2.5 ± 3.1
	11-Feels like pins and needles	5.4 ± 3.2	4.4 ± 2.8	4.3 ± 3.0	4.9 ± 3.0
	12-Feel tingling	5.5 ± 2.9	4.4 ± 2.5	4.2 ± 2.8	5.4 ± 2.8

Values shown are means ± SDs.
* Indicates $P < 0.05$ (analysis of covariance [ANCOVA]) from baseline to end of single blind phase timepoint.
** Indicates $P < 0.05$ (ANCOVA) between nabilone and placebo cohorts at double blind phase end point.

The NPSI categorizes symptomatic descriptors of pain. There were no significant differences between responses at the end of the single-blind phase and baseline amongst subjects enrolled in the single-blind phase. However, subjects receiving nabilone in the double-blind phase reported fewer symptoms of electrical shocks and less provocation or increase in pain with light touching when compared to subjects receiving placebo ($P < 0.05$, ANCOVA, F = 1.77-3.44) (Table 3).

At the end of the single-blind phase, a leftward shift in the subject global impression of change (PGIC) could be seen when compared to week 1 of the study, although 2/34 subjects regarded themselves to be much worse (Fig. 3). At end point, all subjects in the nabilone treatment group rated themselves as improved. In the placebo group, over half the subjects rated themselves as unchanged, while 4 subjects stated they were improved, and one subject rated their overall status to be worse. The distribution of responses across the 7 PGIC categories was statistically significant ($P < 0.05$) in favour of improvement in the nabilone cohort at end point.

After completion of the study, subjects were asked to speculate upon which treatment had been administered: 24/37 subjects (65%) correctly identified receiving nabilone during the single-blind phase. With respect to the double-blind phase, 8/13 (62%) subjects receiving placebo correctly identified receipt of placebo, while 8/13 (62%) subjects receiving double-blinded nabilone correctly identified receiving the active therapy.

Imputation of data using the last value carried forward technique was required for <0.5% of all data assessed in the study – this was required for data for 3 patients discontinuing during the single-blind phase and for one patient receiving placebo in the double-blind phase.

3.4. Tolerability and safety

At baseline, all 37 subjects participating in the single-blind phase had symptoms or adverse events possibly related to baseline medications (Supplementary Table 3). At day 28, with completion of the single-blind phase, there were new adverse events possibly

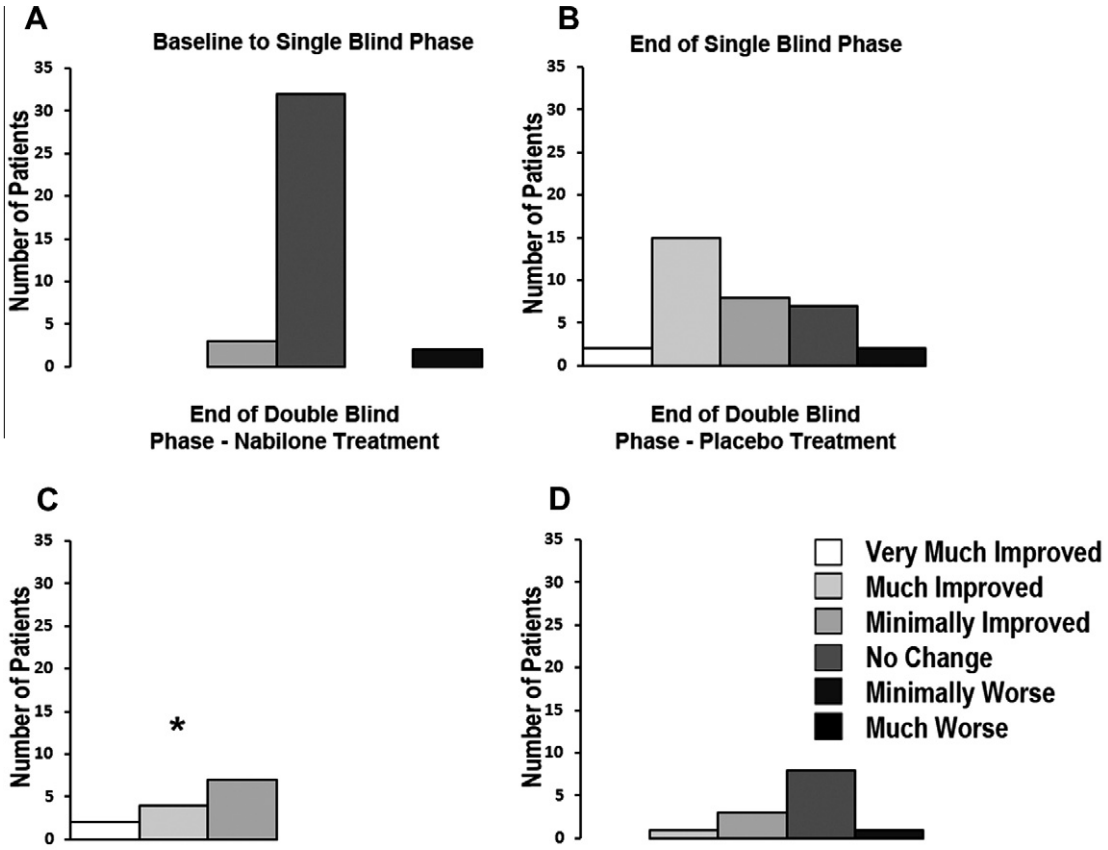

Fig. 3. Patient global impressions of change were analyzed using a Cochran-Mantel-Haenszel procedure, adjusting for center in each case. When compared to baseline data accumulated from day 0 (A), there was a leftward shift towards improvement seen at the end of the single-blind phase (B). Subjects reported a significant perceived overall improvement with adjuvant nabilone therapy (C) when compared to placebo group subjects (D) at end point ($^*P < 0.05$).

related to single-blind nabilone use, including dizziness, dry mouth, drowsiness, confusion or impaired memory, lethargy, euphoria, headache, and increased appetite. In total, treatment-emergent adverse events were reported in 13/37 (35%) subjects within the single-blind phase receiving nabilone. For the subjects participating in the double-blind phase, treatment-emergent adverse events were reported by 6/13 (46%) subjects receiving placebo and by 7/13 (54%) subjects receiving nabilone. Most adverse events were either mild or moderate in intensity. Two subjects receiving nabilone in the single-blind phase developed intolerable confusion (at doses of 2 mg daily and 4 mg daily) leading to discontinuation, constituting 2 serious adverse events; in one subject, confusion led to admission to the Emergency Department and work-up for delirium, with symptoms discontinuing after cessation of study medication. Weight gain was not self-reported by any subjects nor detected by study personnel during the study.

4. Discussion

This is the first clinical trial to examine a potential role for nabilone as an adjuvant in the management of diabetic peripheral neuropathic pain. Both in the single-blind phase and in the randomized double-blind phase, nabilone use was associated with improvements in pain relief, sleep efficacy, and quality of life. Nabilone demonstrated superiority to placebo with respect to a number of indices for neuropathic pain and its associated comorbidities for run-in phase nabilone responders. Adverse effects were few, but 2 subjects developed confusion, requiring discontinuation of nabilone during the single-blind phase of the study, while tolerable adverse effects included drowsiness and dizziness.

This study has several important strengths. The second half of the study compared nabilone to placebo using a randomization scheme with double blinding. Subjects were blinded as to intervention status throughout the study, permitting greater assessment of blinded use of nabilone in a larger population of subjects during the single-blind phase despite the lack of a placebo control. Flexible dosing assessment was analogous to typical use of pain medications in the clinical setting. Subjects recruited represented equally patients presenting to either primary or tertiary care clinics. Finally, multiple measures other than pain severity, including sleep, well-being, and quality of life, showed improvement with nabilone therapy when compared to placebo therapy.

The EERW design has been used in previous phase III analgesic studies [14,24]. Putative advantages of this design are the ability to show a larger effect size and avoid dilution of a true treatment effect between active drug and placebo, as well as reduced variance [26,30]. This may be due to greater ease in discerning a loss of pain control rather than a gain in pain control, as is usually investigated using conventional studies. As a result of its design, EERW permits study of time to efficacy failure end point, which may permit greater statistical power than do studies examining mean pain intensity [24]. Furthermore, nonresponding patients or those developing prominent adverse effects are rapidly discontinued from further treatment, analogous to the general clinical setting [28]. Potential criticisms of the EERW design [29,42] include the potential for reduced generalizability of study results to a larger population aside from responders, the potential for carryover medication effects

during the withdrawal phase in subjects randomized to placebo, underestimation of adverse event prevalence [23], and concerns of discernment, or unmasking, of blinded subjects to absence of treatment.

The effects of cannabinoids on pain have been recognized for millennia [34], but the knowledge of endocannabinoids and cannabinoid receptors in the nervous system spans only 2 decades [17]. Clinical trials of cannabinoids in chronic pain disorders have also reported improved sleep as either a primary or secondary outcome measure [39,46]. Preclinical studies have demonstrated the ability of CB1 receptor agonists to ameliorate pain in animal models of diabetic neuropathy and promote neurite outgrowth [11,45,48], effects that may be lost with downregulation of the CB1 receptor in models of diabetic neuropathy [49]. However, these findings are controversial as well, as CB1 receptor antagonists are also reported to relieve neuropathic pain behaviours in animal models of diabetic neuropathy [13,31]. It is possible that, in addition to interaction with the CB1 and CB2 receptors, interactions with the transient receptor potential vanilloid 1 channels may be important for the effects of cannabinoids [51].

4.1. Limitations

There are limitations associated with this study and its results. The greatest limitation was the relatively low number of subjects studied and the inability to randomize the numbers of subjects estimated by initial sample size calculations. The SD value of 1.0 used to obtain the sample size calculation was possibly underestimated, perhaps further contributing to an underpowered study. Also, there were more women than men randomized to the active intervention in the double-blind phase, which may have influenced outcomes. The exposure to the double-blind phase portion was limited to a 5-week interval, with the possibility of the first weeks of placebo use in the double-blind phase being contaminated by nabilone carryover effects with 1-week washout of nabilone use. NeP due to DPN is a chronic condition, and prolonged treatment over months to years is typically required clinically, but could not be studied with the present study. Dosing of nabilone was performed based upon individual subject tolerability and efficacy, but further dose-finding studies may be more appropriate for determination of safety and efficacy if doses higher than 4 mg per day are to be considered. This study was performed to study the adjuvant potential of nabilone in subjects already receiving pharmacotherapeutic management for NeP due to DPN; the use of concomitant medications leads to difficulty in determination of the individual effect of nabilone. Future studies to assess the efficacy of nabilone monotherapy requiring washout of medications for the study of primary efficacy of nabilone for chronic NeP would be informative. Discernment of study allocation was above chance, with the prevalence of potential cannabinoid-induced adverse effects, including dry mouth, dizziness, sedation, disturbed thinking, and euphoria possibly playing a role in unmasking [35]. Additionally, the absence of titration of the number of pills provided during the double-blind phase of the study may have contributed to unmasking. It was unclear why there was an absence of improvements in NPSI subscores at the end of the single-blind phase, with improvement in some subscales of the NPSI at the end point of the double-blind phase. Finally, although subjects enrolled in this study were referred from both primary care and tertiary care clinics, it is possible that they were not representative of the general population of subjects with DPN and DPN-mediated NeP.

4.2. Conclusions

In conclusion, we report that the synthetic cannabinoid nabilone is an effective drug in management of NeP and associated promotion of sleep and quality of life in patients with NeP due to DPN. Further studies on the effects of nabilone for long-term pain relief, as well as safety and efficacy in conditions of chronic pain, are warranted to verify our results, although the randomized double-blinded design and multiple positive indices are supportive of nabilone's efficacy in assisting the management of diabetic neuropathic pain. We suggest that nabilone should be considered as a potential adjuvant in the management of NeP due to DPN.

Conflict of interest statement

Dr. C. Toth has received honoraria from Valeant Canada for medical education presentations. The authors have no financial interests to disclose.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.pain.2012.06.024.

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