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ORIGINAL ARTICLE

Oral capsules of tetra-hydro-cannabinol (THC), cannabidiol (CBD) and their combination in peripheral neuropathic pain treatment

Kanita Zubcevic[1,2] | **Merete Petersen**[3] | **Flemming Winther Bach**[4,5] | **Aksel Heinesen**[6] | **Thomas Peter Enggaard**[7] | **Thomas Peter Almdal**[8] | **Jakob Vormstrup Holbech**[1,2] | **Lene Vase**[9] | **Troels Stahelin Jensen**[4,5] | **Christian Stevns Hansen**[6] | **Nanna Brix Finnerup**[4,5] | **Søren H. Sindrup**[1,2]

[1]Department of Neurology, Odense University Hospital, Odense, Denmark

[2]Department of Clinical Research, University of Southern Denmark, Odense, Denmark

[3]Multidisciplinary Pain Center, National Hospital, Copenhagen, Denmark

[4]Department of Neurology, Aarhus University Hospital, Aarhus, Denmark

[5]Department of Clinical Medicine, Aarhus University, Aarhus, Denmark

[6]Steno Diabetes Center Copenhagen, Copenhagen, Denmark

[7]Pain Center, University Hospital of Zealand, Køge, Denmark

[8]Department of Endocrinology, National Hospital, Copenhagen, Denmark

[9]Department of Psychology and Behavioral Science, Division for Psychology and Neuroscience, Aarhus University, Aarhus, Denmark

Correspondence
Søren H. Sindrup, Department of Neurology, Odense University Hospital, Odense, Denmark.
Email: soeren.sindrup@rsyd.dk

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Abstract

Background: Cannabinoids are often prescribed for neuropathic pain, but the evidence-based recommendation is 'weak against'.

Objectives: The aim was to examine the effect of two cannabinoids and their combination in peripheral neuropathic pain.

Methods: This was a randomized, double-blind, trial with treatment arms for cannabidiol (CBD), tetra-hydro-cannabinol (THC), CBD and THC combination (CBD/THC), and placebo in a 1:1:1:1 ratio and flexible drug doses (CBD 5–50 mg, THC 2.5–25 mg, and CBD/THC 5 mg/2.5 mg–50 mg/25 mg). Treatment periods of 8-week duration were proceeded by 1 week for baseline observations. Patients with painful polyneuropathy, post-herpetic neuralgia and peripheral nerve injury (traumatic or surgical) failing at least one previous evidence-based pharmacological treatment were eligible for inclusion. The primary outcome was the change in weekly average of daily pain measured with a numeric rating scale (NRS). Trail Making Test (TMT) was used as one of the tests of mental functioning.

Results: In all, 145 patients were included in the study of which 118 were randomized and 115 included in the intention-to-treat analysis. None of the treatments

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reduced pain compared to placebo (p = 0.04–0.60). Effect sizes as estimated in week 8 (positive values worse and negative better than placebo) were CBD mean 1.14 NRS points (95% CI 0.11–2.19), THC 0.38 (CI −0.65 to 1.4) and CBD/THC −0.12 (−1.13 to 0.89).

Conclusions: CBD, THC and their combination did not relieve peripheral neuropathic pain in patients failing at least one previous evidence-based treatment for neuropathic pain.

1 | INTRODUCTION

The recommended treatments of peripheral neuropathic pain are antidepressants and calcium-receptor $\alpha_2\delta$-ligands. The treatment options have not changed during the last two decades. Less than half of the patients obtain sufficient pain relief with the current treatments (Finnerup et al., 2015), and in clinical practice tramadol and pure opioids are often used as second-line treatment.

Cannabis and cannabis-based medicine has been suggested as treatment of neuropathic pain but clear-cut evidence lacks and there are concerns of risks (Finnerup et al., 2015; Fisher et al., 2021; Mücke et al., 2018). One randomized controlled trial showed that Sativex®, which includes tetra-hydro-cannabinol (THC) and cannabidiol (CBD) in approximately 1:1 ratio, was effective in the relief of peripheral neuropathic pain (Nurmikko et al., 2007). A small trial found a dose-dependent reduction in pain intensity, in response to inhaled cannabis in patients with diabetic polyneuropathy (Wallace et al., 2015). However, two other trials using THC/CBD spray (THC:CBD ratio approximately 1:1) (Selvarajah et al., 2010; Serpell et al., 2014) did not demonstrate any effect on the primary pain outcome, although there was effect on some secondary outcomes in one of the studies (Serpell et al., 2014). In a pilot study, Nabiximols (Sativex®) was used for treatment of chemotherapy-induced neuropathy pain, but there was no statistically significant difference in the pain intensity between the treatment and the placebo group (Lynch et al., 2014). There are no studies on the isolated cannabinoids CBD and THC in peripheral neuropathic pain. Negative outcome of several large un-published, randomized, controlled industry trials on Sativex® has together with the published data resulted in weak recommendation against the use of cannabinoids for peripheral neuropathic pain (Finnerup et al., 2015). A Cochrane systematic review that comprises studies on both central and peripheral neuropathic pain is slightly more positive (Mücke et al., 2018) as is a meta-analysis with studies on chronic pain (Wang et al., 2021).

Some of the active components of cannabis work via receptors, cannabinoid receptor-1 (CB_1) and cannabinoid receptor-2 (CB_2) (Finn et al., 2021). The cannabinoid receptors are widely distributed in the human body with CB_1 receptors present in high numbers in the central nervous system, and CB_2 receptors present on immune cells and peripheral nerve terminals (Lu & Mackie, 2016). The CB_1 and CB_2 receptors are the targets of THC, which is a partial agonist on the receptors (Finn et al., 2021). CBD has indirect antagonistic effect on CB_1 and CB_2 receptors (Finn et al., 2021; Mlost et al., 2020). Furthermore, it may enhance the effect of receptor agonists by increasing the number of CB_1 receptors. CBD has multiple effects besides the weak effect on cannabinoid receptors and these include some affinity for serotonergic, opioid, D2-dopaminergic and TRPV1 receptors (Mlost et al., 2020). THC is the most likely cannabis component to have an analgesic effect (Sachs et al., 2015). THC also has a psychoactive effect and may cause psychosis, whereas CBD may be anti-psychotic.

The objectives of this trial were to assess efficacy of the cannabinoids (CBD, THC and the combination CBD/THC) in patients with peripheral neuropathic pain as well as to investigate the effect on associated sleep disturbance and quality of life (QoL). Furthermore, we aimed at evaluating the effect on mental function.

2 | METHODS

2.1 | Study design

This was a 10-week (1-week baseline and 8-week treatment period, 1-week tapering), multicentre, double-blind, randomized, placebo-controlled trial with the aim to investigate the efficacy and tolerability of essential cannabinoids (THC, CBD and CBD/THC) in patients with peripheral neuropathic pain. An outline of the trial is shown in Figure 1.

The treatment period was 8 weeks, preceded by 1 week for baseline observation. The participants were to participate in four visits, visit 1 (inclusion), visit 2 (after baseline week/randomization), visit 3 (after 4 weeks of treatment) and visit 4 (after 8 weeks of treatment). During week 9,

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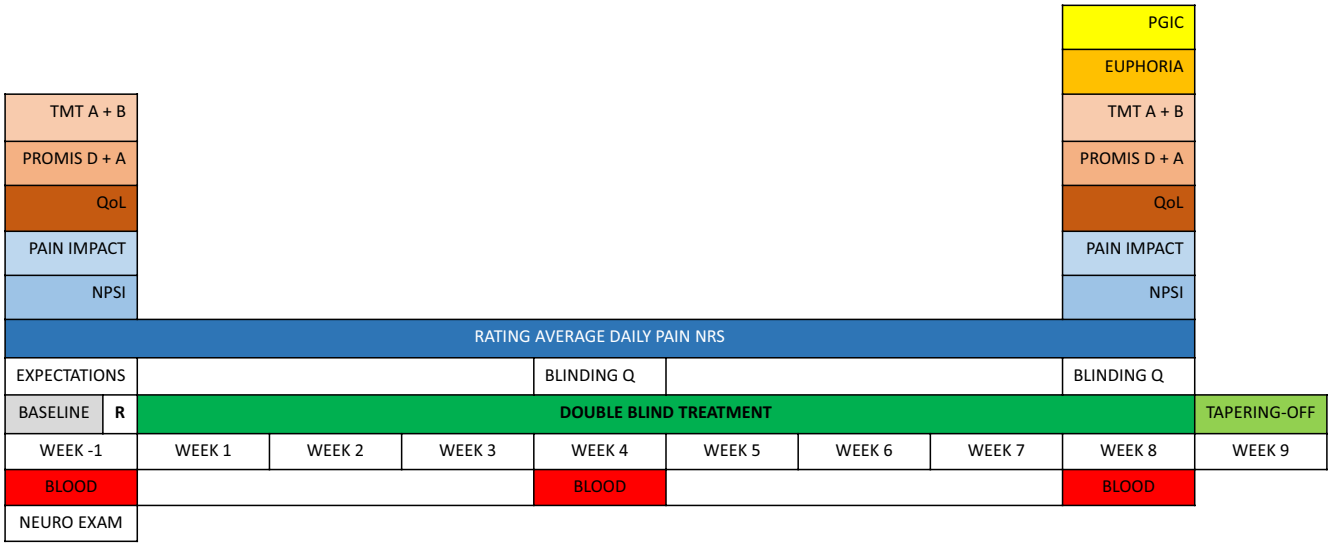

FIGURE 1 Study outline and timing of procedures, ratings and questionnaires. R, Randomization; EXPECTATIONS, Questions on expectations to treatment; NEURO EXAM, Neurological examination including sensory testing; Blinding Q, Questions regarding blinding; NPSI, Neuropathic pain symptom inventory; PAIN IMPACT, Pain impact on daily activities, mood and sleep; QoL, Quality of life; PROMIS D + A, PROMIS questionnaire on depression and anxiety; TMT A + B, Trail making test part A and B; EUPHORIA, NRS score on euphoria; PGIC, Patient global impression on change.

the participants tapered and discontinued the study medication.

Patients who were on concomitant pain treatments with antidepressants or anticonvulsants for neuropathic pain were allowed to continue the treatment, but it was required to maintain a stable dose throughout the study. Paracetamol at a maximum dose of 4 g daily was used as escape medication.

The patients were thoroughly informed about the study design and they were explicitly explained that 25% would receive placebo and that the evidence for the cannabis components included in this study was equivocal. This was done since it has been hypothesized that this procedure could reduce the size of the placebo response. Visits to the clinic were kept at a minimum, since a high number of visits may increase placebo response (Vase et al., 2015).

2.2 | Patient population

The study took place at three centres: the Department of Neurology, Odense University Hospital, the Danish Pain Research Center, Aarhus University Hospital and the Multidisciplinary Pain Center, the National Hospital in Copenhagen. Patients with peripheral neuropathic pain were recruited from December 2018 to May 2021 from the out-patient clinics of the departments and centres, and posts in diabetes out-patient clinics and on Facebook.

The inclusion criteria were patients aged ≥18 years with peripheral neuropathic pain for more than 6 months due to polyneuropathy, post-herpetic neuralgia or traumatic/surgical peripheral nerve damage. For patients with polyneuropathy, the diagnosis had to be confirmed by clinical signs, and either abnormal nerve conduction (ENG) or abnormal intraepidermal nerve fibre density as determined from a skin biopsy. Patients with diabetes were required to have had a stable metabolic control for at least 3 months with the HbAlc <100 mmol/L. Furthermore, all patients should fulfil the criteria for probable or definite neuropathic pain (Finnerup et al., 2016). The patients were required to have failed at least one previous evidence-based pharmacological treatment for peripheral neuropathic pain, and they were required to have a median pain intensity ≥4 on a 0–10 point numeric rating scale (NRS, 0 = no pain and 10 = worst possible pain) during 1 week (baseline) before finally being randomized.

Patients with other causes of pain (arthrosis, spinal stenosis, fibromyalgia) were excluded, as were patients with cardiac contraindications (recent myocardial infarction, conduction disturbances), severe kidney and liver disease, systemic neurological conditions (recent stroke, epilepsy, multiple sclerosis, dementia), severe psychiatric diseases (severe depression and schizophrenia) and abuse of alcohol or drugs during the last 2 years. Previous use of cannabinoids was not an exclusion criterion. Other exclusion criteria were previous allergic reactions to the study medication and pregnancy. Concomitant use of opioids, cannabinoids and

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benzodiazepines was not allowed, but other pain treatment that could not be tapered off was accepted in a stable dose throughout the study.

2.3 | Randomization and treatment

The study medication was capsules with identical appearance, taste and smell containing CBD 5 mg, THC 2.5 mg, combination of CBD 5 mg and THC 2.5 mg, and placebo. Participants were randomized to receive THC, CBD, CBD/THC or placebo in a 1:1:1:1 ratio. The study drugs were manufactured and packed at Glostrup Apotek (Hovedvejen 101, 2600 Glostrup, Denmark). Participants who met the study criteria were given a participant number. If they met the criteria of NRS ≥4 points during the baseline period, they were given a randomization code, which assigned them to a treatment. Assignment to treatment sequences was random through a computer-generated randomization list with a block size of 4. Participants were allocated to the next available randomization number. Participants and the clinicians were blinded to the randomization code, which was not broken until completion of the study. Envelopes containing the treatment sequence for each patient were kept at the respective study sites for emergency situations.

The participants increased the dose of study medication during the first 4 weeks (weeks 1–4) to a maximum dose of 10 capsules per day corresponding to CBD 50 mg, THC 25 mg, CBD/THC 50 mg + 25 mg. The participants were told to stop increasing the dose prematurely in case of sufficient effect or non-acceptable side effects. Once the dose was established at the end of the first part of the treatment period, participants continued on this dose for another 4 weeks (weeks 5–8). The study medication was dosed twice daily.

2.4 | Assessments

In Figure 1, timing of measurements, ratings and examinations are shown in relation to the study outline.

2.5 | Primary outcome

The primary outcome was the average daily pain intensity recorded each morning in a pain diary by a NRS, where 0 = no pain and 10 = worst possible pain. This rating covered the preceding 24 h. Pain ratings were performed during 1 week for baseline observations and during 8 weeks of treatment; no recordings were done in the week for tapering off study medication.

2.6 | Secondary outcomes

Different pain dimensions were recorded with Neuropathic Pain Symptom Inventory (NPSI) (Bouhassira et al., 2004) with in total 10 NRS comprising spontaneous pains (burning, pressing, squeezing), paroxysmal pains (lancinating, pins and needles), and evoked pains (touch, pressure, cold), and non-painful paresthesia. The ratings with NPSI were done at the end of the baseline period and at the end of week 8 of the treatment period, and each recording covered the preceding 24 h.

Pain impact on daily activities, mood and sleep was rated with NRS (0 = no impact, 10 = maximal possible impact) (Jensen et al., 2010). The ratings were performed at the end of the baseline week and the end of week 8 of the treatment period and covered the preceding week.

The daily use of paracetamol as escape medication was recorded during the baseline week and the 8 weeks of treatment with study medication.

At the end of week 8 of the treatment period, patient global impression of change (PGIC) was rated (3 = much improvement, 2 = some improvement, 1 = slightly improved, 0 = not changed, −l = slightly worse, −2 = moderately worse and − 3 = much worse).

2.7 | Mental function and symptoms

Trail Making Test (TMT) was performed to assess psychomotor speed, attention and cognitive sequencing (Tombaugh, 2004). The test consists of two parts, A and B. In part A, patients were required to connect series of randomly arranged numbers from 1 to 25 in ascending order. In part B, the patients were asked to arrange a series of randomly arranged numbers and letters in sequential order (1 to A, 2 to B, etc.). The time to complete each task was recorded at the first and last visit.

The Patient-Reported Outcome Measurement Information System (PROMIS) was used to rate anxiety and depression (Pilkonis et al., 2011) at baseline and end of week 8 of treatment, and at the latter time point euphoria was rated as 'present all the time', 'more than 50% of the time', 'less than 50% of the time' or 'not present at any time'. These ratings covered the preceding week.

General QoL was rated with a NRS (0 = worst possible QoL and 10 = best possible QoL) (Gill & Feinstein, 1994) at baseline and end of week 8.

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Prior to the treatment, the participants were asked two questions regarding their expectations to the treatment (Vase et al., 2003). The first question was about the general expectations to cannabis treatment and its effect on pain. Their expectations were rated on a 0–10 NRS, where 0 = no expected effect and 10 = greatest possible effect. The second question was addressed to their specific expectations to treatment, that is, how many percent they expected their own pain to be reduced while treated with the study medication.

After 4 and 8 weeks of treatment, questions concerning blinding were posed. The patients were asked if the thought they were on active or placebo treatment and if this was because of effect, side effects, both effect and side effects, or something else.

At the time of inclusion, the clinician (a neurologist or an anaesthesiologist) performed a full clinical examination. The neurological examination consisted of the following; strength, deep tendon reflexes, vibration sensation, touch sensation (hypoesthesia), pinprick sensation (hypoalgesia or hyperalgesia), temperature sensation and dynamic mechanical allodynia. Blood samples were collected at visits 2, 3 and 4, while ECG was recorded at baseline and at the end of treatment (4th visit). From blood collected, fructosamin and HbA1c were determined in patients with diabetes, and liver enzymes, renal function and lipids, and serum concentrations of the study medication were determined in all patient categories.

Any adverse events were recorded at each clinical visit. The participants were presented a list of possible side effects and asked to describe the intensity of each as not present, mildly present or present. The list comprised side effects commonly reported of cannabis (please confer results section). Other events were verbally described and recorded but not rated for intensity.

2.8 | Data analysis

The weekly average of daily rating of average pain was determined for the baseline period and the 8-week treatment period. The values of all 8 treatment weeks were included in the data analysis of effect. If the patient stopped the treatment prematurely due to lack of effect, side effects or other causes of drop out, last observation carried forward (LOCF) was used to determine the median score of the remaining weeks. The primary analysis was performed on the intention-to-treat (ITT) population with real scores combined with LOCF data. Analysis was also performed on the per protocol population (PP).

The weekly pain score during treatment was the primary outcome, and all other scores and ratings were secondary outcomes.

The primary efficacy variable was analysed in a general linear model (mixed effects model) with treatments as factors, baseline pain and treatment week as covariates, and patient as random effect. Secondary variables with scores at baseline and end of treatment were analysed by linear regression. Variables with discrete measurements were analysed with chi-square test. Response analysis (50% pain relief) was performed with Fisher's exact test and calculation of numbers needed to treat (NNT) with 95% confidence intervals (reciprocal value of absolute risk reduction). Significance level for the primary outcome was for comparisons of the treatments with placebo and, if relevant, combination treatment with single treatment set at $p = 0.0125$ corresponding to correction for multiple comparisons.

With a planned number of 35 participating patients in each treatment arm, we expected to be able to detect a 1.25-point difference in NRS for the primary outcome (SD for NRS rating of pain 1.6 points (Demant et al., 2014), $\alpha = 0.0125$, $\beta = 0.80$).

2.9 | Ethics and authority approvals

The trial was approved by the Ethics Committee of Southern Denmark (S-20170220) and by the Danish Medicines Agency (2018010146). It was registered at the Danish Data Protection Agency and the European Clinical Trial Database (Eudract nr: 2017–005198-38). The local Good Clinical Practice unit (GCP) was responsible for monitoring the trial.

3 | RESULTS

3.1 | Patients

A total of 169 patients were screened for participation of which 145 patients met the inclusion criteria and were included (Figure 2). In all, 27 were excluded before randomization, because of consumption of opioids, alcohol or cannabis, the driving ban, comorbidities, the inclusion criteria of a minimum total pain score of 4 on the NRS, or withdrawn consent. Of 145 included patients, 118 were randomized, but 1 never started on treatment and 2 did—without notice to the study team—not start treatment and delivered no pain rating. Therefore, 115 patients were included in the ITT population. Out of the 115 patients, 27 were treated with CBD, 28 with THC, 30 with the combination of CBD and THC, and 30 had placebo. The study was ended before the planned 135 patients had been randomized for logistic reason. There had been delays during the study period because of problems with supplies and

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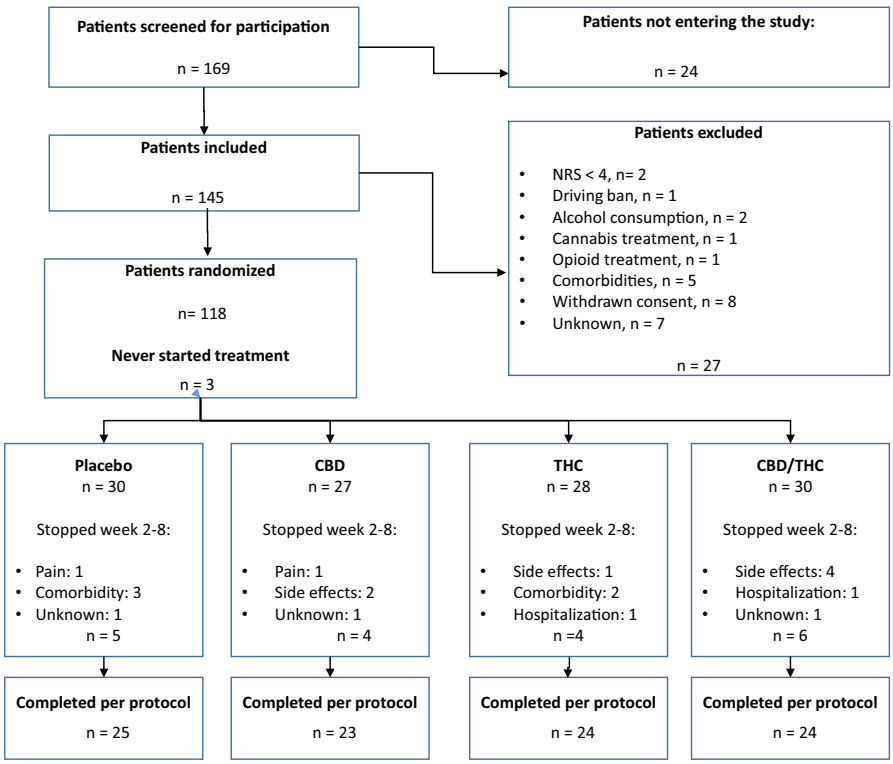

FIGURE 2 Overview of patient flow. CBD, Cannabidiol; THC, 9-delta-tetra-hydro-cannabinol.

documentation of study medication, and the COVID-19 pandemic. Furthermore, one of the grant agreements requested that the study should be completed within a certain timeframe, and production of new study medication to replace out-dated study medication could not be covered by the available grants.

The number of patients completing PP was in total 96, and the number of completers in each treatment group ranged from 23 to 25 (Figure 2). Side effects was the most frequent reason among the participants who discontinued the treatment during weeks 2–8, and the number was highest in the combination group (Figure 2).

The 115 patients included in the data analysis ranged in age from 22 to 95 years and there was nearly the same number of females and males (Table 1). The neuropathic pain condition was in most cases painful polyneuropathy and fewer had post-herpetic neuralgia and other localized neuropathies (Table 1). The baseline pain level was on average 6.5 NRS points (SD 1.3) and most patients had experience with other medications for neuropathic pain. About 50% of the patients were currently treated with another drug or drugs for their peripheral neuropathic pain. In all, 28 patients (24%) had previous experience with non-specified cannabis-based medicine or cannabinoids, or cannabis for their pain. The four treatment groups were rather similar with respect to age, sex, baseline pain, distribution among neuropathic pain diagnosis and fraction with current neuropathic pain treatment (Table 1).

The daily dose of study medication during week 8 was placebo median 10 capsules (range 3–10 capsules), CBD median 10 capsules (range 6–10 capsules), THC median 10 capsules (range 6–10 capsules) and CBD/THC combination median 6 capsules (6–10 capsules). This corresponds to median doses CBD 50 mg, THC 25 mg, and combination CBD 30 mg and THC 15 mg.

Treatment code correctness and compliance was confirmed by serum drug concentrations measured at the end of the treatment period. Blinding as assessed by questions on which treatment the patients believed they had received revealed that the patients only guessed correctly overall in about 50% of the cases, although correctness was higher with CBD treatment and at the 8-week evaluation for THC (Table 1). Guess of treatment was most often made on the background of the effect experienced by the patients.

At baseline before treatment, the patients had high expectations to the effect of treatment and specifically that their pain would be reduced by mean 60% and no difference in expectations between treatment groups.

3.2 | Primary outcome, numbers needed to treat and PGIC

Pain intensity decreased over time in all groups and mean reduction at week 8 of the treatment period was: CBD −0.6 NRS points, THC -1.4 NRS points, combination of

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TABLE 1 Demographics and baseline characteristics

	Total sample	Placebo	CBD	THC	CBD/THC
Patients, *n*	115	30	27	28	30
Age, years, median (range)	65 (22–95)	66 (39–78)	64 (43–79)	62 (27–83)	68 (22–95)
Sex, *n*, female/male	64/51	17/13	13/14	13/15	21/9
Aetiology of neuropathic pain					
Polyneuropathy	95	25	24	23	23
Diabetic polyneropathy	26	7	6	5	8
Postherpetic neuralgia	9	2	1	3	3
Nerve damage	11	3	2	2	4
Pain					
Duration, mo., median (range)	60 (10–360)	60 (10–360)	72 (24–156)	60 (12–264)	72(15–264)
Pain (baseline), NRS, mean (SD)	6.5 (1.3)	6.6 (1.3)	6.2 (1.3)	6.5 (1.2)	6.4 (1.4)
Sensory signs					
Hyperalgesia	39	12	7	11	9
Dynamic mechanical allodynia	31	11	6	6	8
Previous pain treatment, *n*					
TCA	44	13	7	10	14
SNRI	30	4	4	9	13
Gabapentin/pregabalin	115	29	30	22	35
Tramadol	32	5	7	11	9
Opioids	23	6	4	7	6
Current pain treatment, *n*					
TCA	14	3	5	2	4
SNRI	19	6	5	3	5
Gabapentin/pregabalin	32	9	7	8	8
No treatment	57	14	12	18	13
Expectations cannabis treatment					
General, NRS (mean [SD])[a]	6.9 (2.0)	6.6 (2.3)	7.1 (2.2)	6.8 (1.9)	7.0 (1.7)
Specific, % (mean [SD])[b]	62 (22)	56 (23)	69 (21)	61 (22)	63 (19)
Effectiveness of blinding, *n* (%)					
After 4 weeks, *n* total 115					
Guessed correct active versus placebo	53 (46)	13 (48)	6 (22)	13 (52)	21 (72)
Foundation of correct guess					
Effect/lack of effect		10	2	4	8
Side effects		0	1	2	5
Effect and side effects		1	3	6	6
Other		2	0	0	1
After 8 weeks, *n* total 102					
Guessed correct active versus placebo	57 (56)	12 (48)	5 (21)	19 (73)	21 (78)
Foundation of correct guess					
Effect/lack of effect		12	4	7	6
Side effects		0	0	3	7
Effect and side effects		0	0	8	8
Other		0	1	1	0

Abbreviations: CBD/THC, combination CBD and THC; CBD, Cannabidiol; THC, 9-delta-Tetra-Hydro-Cannabinol.

[a]General expectations to treatment efficacy, NRS: 0 = no pain relief, 10 = total pain relief.

[b]Expected reduction in patients own pain (%).

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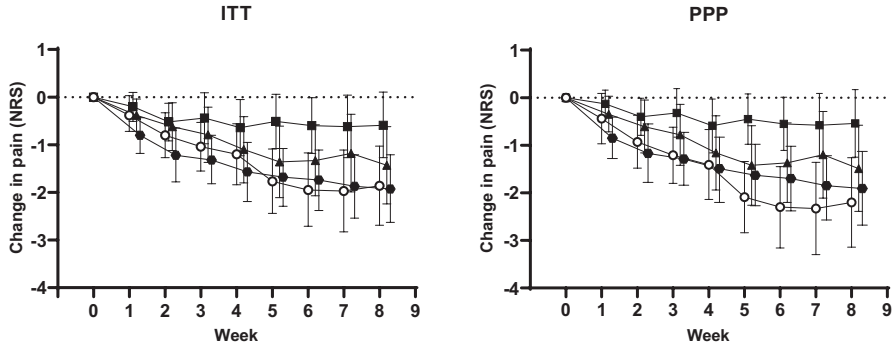

FIGURE 3 Mean (95% confidence interval) change in weekly mean of daily pain during the trial from baseline (0) through weeks 1 to 8. NRS: Numeric rating scale 0–10, ITT: Intention-to-treat population, PPP: Per protocol population. Cannabidiol (CBD): larger?, 9-delta-tetra-hydro-cannabinol (THC): ▲, combination CBD/THC: ⬣ Placebo: ○

CBD and THC −1.9 NRS points, and placebo −1.9 NRS points (Figure 3). The statistical analysis showed that in both the ITT and the PP population, none of the active treatments were different from placebo except for CBD having significantly less pain reduction than placebo in the per PP (Table 2). Effect size as estimated as the difference between placebo and active treatments for NRS differences baseline minus week 8 ranged from -0.12 to 1.14 points for the ITT population and from 0.84 to 1.35 for the PP population (Table 2).

Response determined as more than 30% or 50% pain relief is detailed for each of the treatments in Table 3. The 50% pain relief response rate was slightly higher on the combination CBD/THC than on placebo, but this was not statistically significant. NNT were either high or could not be calculated since the number of responders on placebo was higher than on active treatments. PGIC was not significantly different between treatments ($p = 0.124$) (Table 3).

3.3 | Secondary outcomes and explorative analyses

The consumption of paracetamol as escape medication was very low with <25% of the patients using paracetamol during baseline and <5% using it during treatment. The change in number of paracetamol used from baseline to treatment week 8 did not differ between placebo and the active treatments (Table 2).

For specific pain symptoms as measured with NPSI, none of the active medications were superior to placebo with respect to pain reduction (Table 2). Evoked pains were actually less reduced by CBD than by placebo, and pressing and squeezing pain less by THC than by placebo. Similarly, pain impact on daily activities, mood and sleep, as well as QoL were not reduced or changed more by the active treatments than by placebo (Table 2).

Subgroups of patients with diabetic neuropathy, polyneuropathy, localized neuropathic pains, or with or without hyperalgesia or dynamic mechanical hyperalgesia showed a similar pattern with no superiority of active treatments over placebo (Table 4). The response was also with the same pattern and similar in males and females except for CBD being significantly worse than placebo in females (Table 4). Likewise, QoL, mood and pain-related sleep disturbance did not impact on response to the cannabinoids or their combination even though there was significantly less pain reduction with CBD as compared to placebo for patients with moderate depressive symptoms and for patients with high score for QoL (Table 4). Some of the subgroups were small with less than 50 patients.

Seventy-five percent of the patients expected that their pain would be reduced by at least 50% by cannabis-based medicine (specific expectations). For the total group of patients general and specific expectations to treatment response did not impact on pain reduction during treatment as compared to baseline pain (mean −0.11 NRS points, $p = 0.104$ and mean 0 NRS points, $p = 0.958$, respectively, in the general linear model). In the placebo group ($n = 30$), general expectations to treatment response had an impact on the treatment response (mean −0.3 NRS points, $p = 0.009$), whereas this was not the case for specific expectations in the placebo group (mean −0.01 NRS points, $p = 0.285$). In the active treatment group ($n = 85$), neither general nor specific expectations had an impact (mean – 0.02 NRS points, $p = 0.764$ and mean 0 NRS points, $p = 0.586$).

At the end of week 8, measurements of serum drug concentrations showed CBD treatment: CBD mean 7.69 ng/mL (range 1.53–26.51 ng/mL), THC treatment: mean THC plus 11-OH-THC 8.31 ng/mL (range 0.94–21.49 ng/mL), and CBD/THC treatment: mean THC plus 11-OH-THC 5.85 ng/mL (range 1.41–14.72 ng/mL) and CBD mean 3.80 ng/mL (range 0.54–11.77 ng/mL). Cannabinoids were

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TABLE 2 The effect on pain, use of escape medication, pain impact and quality of life of cannabidiol (CBD), 9-delta-tetra-hydro-cannabinol (THC) and their combination (CBD/THC) as compared to placebo in patients with peripheral neuropathic pain

	Treatment	Impact mean (95% CI)[a]	*p*[a]	Effect size mean (95% CI)[b]
Average weekly pain				
Intention-to-treat ($n = 115$)	CBD	0.76 (0.02–1.49)	0.042	1.14 (0.11–2.19)
	THC	0.31 (−0.42 to 1.03)	0.406	0.38 (−0.65 to 1.4)
	CBD/THC	−0.19 (−0.90 to 0.52)	0.603	−0.12 (−1.13 to 0.89)
Per protocol ($n = 96$)	CBD	1.06 (0.27 to 1.85)	0.009	1.51 (0.36–2.66)
	THC	0.55 (−0.22 to 1.32)	0.164	0.69 (−0.43 to 1.81)
	CBD/THC	0.09 (−0.67 to 0.85)	0.818	0.84 (−0.7 to 1.35)
Paracetamol consumption				
	CBD	−0.66 (−5.8 to 4.42)	0.798	
	THC	−3.4 (−8.4 to 1.6)	0.189	
	CBD/THC	0.35 (−4.6 to 5.3)	0.890	
NPSI				
Burning pain	CBD	0.86 (−0.90 to 2.49)	0.352	
	THC	1.28 (−0.39 to 2.95)	0.132	
	CBD/THC	0.61 (−1.03 to 2.26)	0.463	
Pressing and squeezing	CBD	1.18 (−1.56 to 3.92)	0.395	
	THC	3.28 (0.60–5.97)	0.017	
	CBD/THC	0.29 (−2.38 to 2.96)	0.831	
Pain paroxysms	CBD	1.76 (−0.99 to 4.50)	0.207	
	THC	2.46 (−0.25 to 5.16)	0.075	
	CBD/THC	2.28 (−0.39 to 4.95)	0.093	
Evoked pain	CBD	4.47 (1.44–7.49)	<0.001	
	THC	2.16 (−0.80 to 5.12)	0.150	
	CBD/THC	2.64 (−0.27 to 5.56)	0.075	
Pain impact				
Activity	CBD	1.24 (−0.32 to 2.81)	0.117	
	THC	0.36 (−1.19 to 1.91)	0.645	
	CBD/THC	0.89 (−0.64 to 2.42)	0.251	
Mood	CBD	0.53 (−0.95 to 2.01)	0.480	
	THC	0.96 (−0.53 to 2.42)	0.196	
	CBD/THC	0.82 (−0.63 to 2.27)	0.264	
Sleep	CBD	2.03 (0.35 to 3.71)	0.018	
	THC	0.36 (−1.31 to 2.03)	0.669	
	CBD/THC	0.93 (−0.72 to 2.58)	0.265	
Quality of life				
	CBD	−0.75 (−2.09 to 0.60)	0.272	
	THC	−0.35 (−1.66 to 0.97)	0.599	
	CBD/THC	−0.71 (−2.01 to 0.59)	0.283	

Abbreviations: CBD, cannabidiol; CBD/THC: combination cannabidiol and 9-delta-tetra-hydro-cannabinol; NPSI, neuropathic pain symptom inventory; THC, 9-delta-tetra-hydro-cannabinol.

[a]Impact on change in average daily pain from baseline week to treatment weeks 1 to 8 as compared to placebo in a general linear model with baseline pain as co-variate. Positive values correspond to less pain reduction on treatment than on placebo and negative values to more pain reduction. For the other variables, the change from baseline to week 8 was used and for these variables impact corresponds to effect size.

[b]Effect size estimated on the basis of differences from baseline to week 8 and each treatment compared to placebo (linear regression).

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TABLE 3 Number of responders with more than 30% and 50% reduction in pain score from baseline to end of treatment with corresponding numbers needed to treat (NNT), as well as improvement as measured with patient global impression of change (PGIC)

Response				
	>30%	≤30%	Total	NNT
Placebo	17	13	30	—
CBD	9	18	27	—
THC	12	16	28	—
CBD/THC	18	12	30	30 (3.5–∞)
	>50%	≤50%		
Placebo	11	19	30	—
CBD	5	22	27	∞
THC	8	20	28	∞
CBD/THC	16	14	30	6 (2.4–∞)
PGIC				
	Improvement		**No change or worse**	
Placebo	14		11	25
CBD	7		17	24
THC	16		10	26
CBD/THC	16		12	28

Abbreviations: CBD, cannabidiol; CBD/THC, cannabidiol and 9-delta-tetra-hydro-cannabinol combination; THC, 9-delta-tetra-hydro-cannabinol.

not measurable in blood samples for the placebo period and in periods with a single cannabinoid the other cannabinoid was not measurable.

3.4 | Side effects

Table 5 gives details with respect to TMT, mood and anxiety. The change in time for the TMT A did not differ between active treatments and placebo (5.15 s shorter, $p = 0.21$ (CBD), 0.1 s shorter, $p = 0.98$ (THC), and 4.3 s longer, $p = 0.30$ (CBD/THC combination)). For TMT B, there were also no significant differences between active treatments and placebo (0.1 sec. longer, $p = 0.41$ (CBD), 0.1 s shorter, $p = 0.24$), although the time during the CBD and THC combination was longer than during placebo (20 s, $p = 0.068$). Depression and anxiety scores were unchanged by the study medication. Euphoria was seen with low frequency and was a little more frequent with THC (5 of 21 patients) and CBD/THC combination (7 of 20 patients) than with placebo (2 of 23 patients) and CBD (0 of 24 patients) ($p = 0.037$).

TABLE 4 The effect on average weekly pain of cannabidiol (CBD), 9-delta-hydro-cannabinol (THC), and their combination (CBD/THC) as compared to placebo in relation to pain diagnosis, signs of hyperexcitability, quality of life, mood, and pain-related sleep disturbance

Treatment	Impact[a]	p[a]
Diabetic neuropathy ($n = 35$)		
CBD	0.95 (−0.29 to 2.20)	0.135
THC	0.67 (−0.59 to 1.94)	0.299
CBD/THC	−0.45 (−1.66 to 0.77)	0.474
Polyneuropathy ($n = 95$)		
CBD	0.56 (−0.21 to 1.33)	0.153
THC	0.06 (−0.72 to 0.83)	0.888
CBD/THC	−0.29 (−1.06 to 0.48)	0.463
Nerve injury/Postherpetic neuralgia ($n = 20$)		
CBD	2.80 (0.77–4.84)	0.007
THC	1.44 (−0.15 to 3.04)	0.076
CBD/THC	0.44 (−1.06 to 1.94)	0.568
Male ($n = 51$)		
CBD	0.06 (−0.84 to 0.97)	0.894
THC	−0.44 (−1.35 to 0.46)	0.335
CBD/THC	−0.30 (−1.32 to 0.71)	0.559
Female ($n = 64$)		
CBD	1.27 (0.22 to 2.31)	0.018
THC	0.89 (−0.16 to 1.93)	0.095
CBD/THC	0.13 (−0.79 to 1.05)	0.788
Hyperalgesia ($n = 42$)		
CBD	1.64 (0.34–2.94)	0.013
THC	0.63 (−0.52 to 1.78)	0.281
CBD/THC	0.07 (1.25–1.12)	0.912
No hyperalgesia ($n = 76$)		
CBD	0.47 (−0.40 to 1.33)	0.293
THC	0.21 (−0.69 to 1.11)	0.649
CBD/THC	−0.14 (−1.00 to 0.72)	0.750
Dynamic mechanical allodynia ($n = 33$)		
CBD	1.81 (0.55 to 3.07)	0.006
THC	1.26 (−0.02 to 2.54)	0.053
CBD/THC	−0.32 (−1.49 to 0.86)	0.60
No dynamic mechanical allodynia ($n = 84$)		
CBD	0.49 (−0.38 to 1.37)	0269
THC	0.08 (−0.78 to 0.94)	0.856
CBD/THC	−0.06 (−0.92 to 0.80)	0.884
High quality of life[b] ($n = 56$)		
CBD	1.37 (−0.33 to 2.42)	0.01
THC	0.89 (−0.18 to 1.95)	0.10
CBD/THC	−0.13 (−1.15 to 0.89)	0.80
Low quality of life[b] ($n = 59$)		

(Continues)

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TABLE 4 (Continued)

Treatment	Impact[a]	p[a]
CBD	0.33 (−0.68 to 1.35)	0.52
THC	−0.04 (−1.01 to 0.82)	0.93
CBD/THC	0.15 (−0.83 to 1.13)	0.76
Mild or no symptoms of depression[c] ($n = 49$)		
CBD	0.08 (−0.91 to 1.08)	0.87
THC	−0.69 (−1.72 to 0.35)	0.19
CBD/THC	−0.62 (−1.62 to 0.39)	0.23
Moderate depressive symptoms[c] ($n = 66$)		
CBD	1.29 (0.32–2.26)	0.009
THC	1.02 (0.11–1.94)	0.028
CBD/THC	0.24 (−0.68 to 1.16)	0.604
Low pain impact on sleep[d] ($n = 47$)		
CBD	0.40 (−0.51 to 1.30)	0.39
THC	0.05 (−1.00 to 1.11)	0.92
CBD/THC	−1.12 (−2.05 to 0.20)	0.018
High pain impact on sleep[d] ($n = 68$)		
CBD	0.87 (−0.20 to 1.94)	0.11
THC	0.47 (−0.46 to 1.40)	0.32
CBD/THC	0.43 (−0.53 to 1.39)	0.38

Abbreviations: CBD/THC, combination cannabidiol and 9-delta-tetra-hydro-cannabinol; CBD, cannabidiol; THC, 9-delta-tetra-hydro-cannabinol.

[a]Impact on change in average weekly pain from baseline week to treatment weeks 1–8 as compared to placebo in a general linear model with baseline pain as co-variate.

[b]Low quality of life score 0–5 and high quality of life score 6–10 on a 0–10 NRS.

[c]No or mild depression according to PROMIS mood score 0–5, moderate depression scores >5.

[d]Low pain impact on sleep NRS score 0–5 and high impact scores 6–10.

Other side effects in this study were recorded at baseline and during the treatment period as, not present, present to a lesser extent, and present (Table 6). Most of the side effects were reported with the same frequency during baseline/placebo and active treatment periods, except for dry mouth reported slightly more frequently with all active treatments, and drowsiness being reported more frequently during combination treatment.

Most of the dropouts during weeks 2–8 were due to side effects (Figure 2). Two out of 27 (7.4%) stopped in the CBD group, one out of 28 (3.6%) in the THC treatment group and four out of 30 (13.3%) in the treatment group with CBD/THC. One participant in the THC treatment group was hospitalized because of falls, which was not related to the study drug. There was one serious adverse event. One participant in the combination group CBD/THC was hospitalized during the treatment period because of infection. None of the participants in the placebo group stopped because of side effects (Figure 2).

TABLE 5 The effect on psychomotor function and mood as measured by the trail making test and the PROMIS questionnaire of cannabidiol (CBD), 9-delta-tetra-hydro-cannabinol (THC) and their combination (CBD/THC) as compared to placebo

Treatment	Change[a]	p[a]
Trail making test A (seconds)		
CBD	−5.15 (−13.3 to 3.0)	0.211
THC	−0.10 (−8.9 to 7.9)	0.980
CBD/THC	−4.3 (−3.8 to 12.3)	0.296
Trail making test B (seconds)		
CBD	−15.8 (−37.6 to 6.0)	0.155
THC	3.9 (−17.5 to 25.3)	0.718
CBD/THC	20.1 (−41.6 to 1.5)	0.068
PROMIS questionnaire		
Anxiety (score)		
CBD	−0.58 (−2.90 to 1.74)	0.620
THC	0.23 (−2.04 to 2.50)	0.843
CBD/THC	0.04 (−2.23 to 2.31)	0.975
Symptoms of depression (score)		
CBD	0.345 (−1.57 to 2.25)	0.722
THC	1.64 (−0.24 to 3.52)	0.086
CBD/THC	1.49 (−0.39 to 3.37)	0.119

Abbreviations: CBD/THC, combination cannabidiol and 9-delta-tetra-hydro-cannabinol; CBD, cannabidiol; THC, 9-delta-tetra-hydro-cannabinol.

[a]Change in score from baseline week to end of treatment week 8 as compared to change on placebo (linear regression).

Biochemistry and ECG recordings did not show any major changes or safety issues.

4 | DISCUSSION

This trial showed no beneficial effect of CBD, THC and their combination in patients with peripheral neuropathic pain that failed at least one previous first-line treatment of neuropathic pain. The treatments were generally well tolerated by the patients. This study confirms the lack of effect of THC and CBD combination for neuropathic pain. This is the first study to examine the effect of CBD alone in neuropathic pain and it found no better effect of CBD than of placebo. Actually, in the PPP, CBD reduced pain less than placebo, and less effect of CBD than of placebo was also seen with some secondary pain outcomes.

It can with the present results not be ruled out that there could be a small treatment response at a group level, that is, a small effect in most patients, or that a minor subgroup of patients could have a large treatment response. This study was powered to detect an active versus placebo difference of 1.25 NRS points and not

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TABLE 6 Side effects reported as "present" during the baseline period and during the treatment period

Side effect	Baseline ($n = 114$)	Placebo ($n = 25$)	CBD ($n = 24$)	THC ($n = 26$)	CBD/THC ($n = 27$)
Dry mouth, *n* (%)	28 (25)	7 (28)	7 (29)	8 (31)	9 (33)
Headache, *n* (%)	13 (11)	0	2 (8)	3 (12)	4 (15)
Nightmare, *n* (%)	3 (3)	0	0	0	0
Dizziness, *n* (%)	12 (11)	3 (12)	1 (4)	3 (12)	2 (7)
Tinnitus, *n* (%)	10 (9)	2 (8)	1 (4)	3 (12)	2 (7)
Anxiety, *n* (%)	0	0	0	1 (4)	0
Nervousness, *n* (%)	2 (2)	0	0	1 (4)	0
Drowsiness, *n* (%)	29 (25)	5 (20)	2 (8)	6 (23)	8 (30)
Palpitations, *n* (%)	3 (3)	0	0	0	1 (4)
Facial flush, *n* (%)	8 (7)	2 (8)	1 (4)	2 (8)	0
Abdominal pain, *n* (%)	3 (3)	0	0	0	1 (4)
Nausea, *n* (%)	1 (1)	0	0	1 (4)	3 (11)
Diarrhoea, *n* (%)	3 (3)	0	0	1 (4)	3 (11)
Muscle pain, *n* (%)	30 (26)	3 (12)	8 (33)	6 (23)	1 (4)
Blurred vision, *n* (%)	6 (5)	1 (4)	0	0	1 (4)

Abbreviations: CBD/THC, cannabidiol and 9-delta-tetra-hydro-cannabinol combination; CDB, cannabidiol; THC, 9-delta-tetra-hydro-cannabidiol.

smaller differences, and a non-significantly higher fraction of patients treated with the CBD/THC combination than with placebo treatment had more than 50% pain reduction. To finally settle this, larger treatment groups would have been required. Smaller treatment responses may not be worth pursuing, since what is needed in neuropathic pain is treatments with larger robust effect in a high percentage of patients. Large effect in a smaller subgroup of patients could be important if the subgroup had specific clinical characteristics so individualized therapy could be used.

Cannabis and cannabis-based medication is controversial in many areas also regarding treatment of peripheral neuropathic pain. Some published trials do indicate an effect of preparations containing THC, which is in the same range as some of the current pharmacological treatments of peripheral neuropathic pain (Nurmikko et al., 2007; Serpell et al., 2014). However, others did not find an effect and most importantly large unpublished trials performed by a pharmaceutical company on Sativex® failed to find an effect (Finnerup et al., 2015). With respect to CBD alone, a recent study found no effect of CBD in arthritis (Vela et al., 2021). The indication of CBD being pro-nociceptive has also been found in an analysis of experimental data (Mlost et al., 2020). Thus, overall this study adds to the evidence of no effect of cannabinoids or cannabis-based medication in general in peripheral neuropathic pain. In our opinion, the study medication did comprise the essential components of cannabis, that is, THC and CBD, alone or in combination. These components have the potential to interact with relevant receptors such as CB1, CB2 and TRPV1 receptors, and exert other relevant actions all of which in experimental studies have been linked to the pain-relieving action of cannabis (Finn et al., 2021, Mlost et al., 2021). It has been proposed that for the full effect of cannabis to be exerted, all or a large range of the more than 200 different components of cannabis, which besides CBD and THC, also includes minor components with interaction with cannabinoid receptors as well as a range of terpenes, are needed. Experts within the fields talks about an entourage effect of many of the components, that is, small contributions by each of many components (Ferber et al., 2020). Therefore, it cannot be ruled out that full-scale products of cannabis could have had an effect. However, there are large negative trials on Sativex® in neuropathic pain, and Sativex® contains both CBD and THC, as well as standardized amounts of some other components of cannabis, although not close to the more than 100 other cannabinoids and terpenes in cannabis.

The study medications were generally well tolerated with few drop-outs due to side effects and many of the reported side effects did not show substantial difference in frequency across active treatment versus placebo. Dry mouth, drowsiness, headache and dizziness were the most common side effects, but also these were seen with active treatment at a frequency nearly corresponding to placebo or baseline observations.

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The optimal dose of the cannabinoids THC and CBD for neuropathic pain is unknown. This study used doses comparable to those used in a trial with a positive outcome (Nurmikko et al., 2007) and some studies using higher doses were in fact negative (Sativex® trials, clinicaltrials.gov), although the route of administration was different in both occasions. Doses used in clinical practice are often lower than those used in this and other trials. The bioavailability of per oral formulations of cannabis-based medications and cannabis is very variable (Huestis, 2007). We used a flexible dosing and the patients could increase doses to a rather high level. The low number of drop-outs and only few side effects could indicate that doses and serum drug levels could have been too low, and thereby be the reason for lack of effect. The measured serum concentrations of THC and its active metabolite indicated that we were within the effective range as estimated from previous trial data (Wallace et al., 2020), although that trial was of very short duration and used inhaled cannabis which, in contrast to our trial with oral dosing, will not involve first-pass metabolism. Effective serum concentration of CBD is unknown. The large Sativex® studies used higher maximally allowed doses and oral spray, that is, an application with more stable and higher bioavailability than the per oral application, and still these studies were negative (clinicaltrials.gov). In all, it is not likely that higher doses would have changed the outcome of this trial substantially.

Some patients did have a large response to THC and the CBD plus THC combination. However, it was not possible to identify a meaningful denominator for this group of patients neither with respect to disease entity, nor to pain severity, pain symptoms and signs, nor to mood and QoL. For patients in the placebo group high pre-study expectations to the effect of cannabis-based medication for their pain, there was a larger treatment effect than in patients with lower expectations. A similar relationship was not seen in the groups receiving active treatment. There is no obvious explanation for this difference.

This study had a large placebo response with an average reduction of pain scores on placebo of around 2 NRS points. Large placebo responses make it difficult to obtain statistically significant separation between active and placebo treatments (Finnerup et al., 2015; Finnerup et al., 2016). This was well known before we started our trial and we therefore implemented some measures to possibly reduce the risk of large placebo responses. One important factor in placebo response is expectations with larger placebo responses when the patients have high expectations for trial treatment (Vase et al., 2015). Thus, all the patients were as part of the protocol thoroughly explained that there was a fair possibility that they would be treated with placebo and that the evidence for the active components was equivocal. We did find that expectations had an impact on the placebo response. We also kept visits at the trial centres and examinations to a minimum. Thus, we tried to avoid that the patients had too high expectations to their pain relief in the present study. On the other hand, the study was performed at a time when there was a large public interest on cannabis-based medication in the community. In all, the expectations to own treatment response on cannabis-based medication was rather high with 75% of the patients expecting that cannabis-based medication would cause more than 50% reduction of their pain. Despite its size, the placebo response observed in the present trial is not supposed to have impacted the validity of the results with respect to effectiveness of cannabinoids. The rather effective blinding found in the present study may actually consequently have increased the placebo response. Another reason for a high placebo response is inflation of baseline pain score, which could be expected in trials, where patients are very interested in participating, which was the case in this study. In all, to possibly reduce placebo responses more it could be suggested to be even more conservative with respect to information of the patients on the potential effect of study drug, increase the chance of being treated in a placebo arm, and have a blinded placebo run-in period to exclude patients with too large placebo responses. Finally, using a cross-over design may also be a possibility, since placebo responses seem to be smaller in cross-over than in parallel group designs (Finnerup et al., 2018).

This study had several strengths. The randomized, controlled and double-blind design is the standard, which is required to adequately test for effect of drugs in neuropathic pain. Blinding of treatments was tested and found very effective, and this increases the validity of the results. The quality of the study, as such, was secured and maintained by Good Clinical Practice monitoring. The diagnosis of neuropathic pain was made by trained neurologists and was according to internationally accepted criteria. There were also some study limitations. A larger study would, of course, have been preferable especially in the search for effect in subgroups of patients. We had to stop patient inclusions prematurely for logistic reasons. Thus, we did not reach 150 randomized patients as planned to achieve data for statistical analysis from 140 patients, and the study did not have quite the desired statistical power. The study could, for this reason, have overlooked real placebo versus active treatment differences. However, there was not even a trend of effect of the cannabinoids so this is not very likely. Furthermore, a power calculation using the actual study data (SD of baseline pain 1.3 and of end of treatment pain 2.0) indicate that with around 30 subjects per group, we would be able to detect a 1.5 difference in pain score instead of a 1.25 difference. It cannot be ruled out that higher drug doses could have been effective, but

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as discussed above this is not very likely. In this study, it was an inclusion criterium that the patients had failed at least one of the evidence-based treatments for peripheral neuropathic pain either due to insufficient response or due to intolerable side effects. This may have biased the study to include a group of patients that were less responsive to pharmacological treatments of neuropathic pain. It is possible that the outcome of the study would have been different without this inclusion criterion. The study does not rule out an effect in treatment naïve patients and patients responsive to standard pharmacological treatments of neuropathic pain. This population should probably not be the target of cannabis or cannabis-based medicine with the well-known risks with this treatment, such as addiction, psychosis and altered mental functioning. Furthermore, the sensitivity of the study was reduced by the large placebo response and by the fact that many patients had the study medication as add-on treatment. However, only about 50% of the patients were actually treated with other drugs for peripheral neuropathic pain.

In conclusion, this study found no pain-relieving effect of the cannabinoids CBD, THC or their combination in peripheral neuropathic pain in patients failing at least one previous evidence-based treatment. The data support the evidence of no beneficial effect of cannabis-based medicine in neuropathic pain.

AUTHOR CONTRIBUTIONS

KZ, SHS. Conception and design, acquisition of data, analysis and interpretation of data, drafting article, revision of article and final approval of article. FWB Conception and design, acquisition of data, analysis and interpretation of data, revision of article, final approval of article. AH, MP. Acquisition of data, revision of article, final approval of article. TJS, NBF, LV, JH, TPE, TPA, CSH. Conception and design, analysis and interpretation of data, revision of article, final approval of article. All authors discussed the results and commented on the manuscript.

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CONFLICT OF INTEREST

KZ, SHS, AH, CSH, TPE, LV and TSJ has nothing to declare. Outside the submitted work, NBF has received consultancy fees from Merck, Almirall, NeuroPN, Vertex and Novartis Pharma, has undertaken consultancy work for Aarhus University with remunerated work for Biogen, Merz and Confo Therapeutics, and has received grants from IMI2PainCare, an EU IMI 2 (Innovative medicines initiative) public–private consortium and the companies involved are: Grunenthal, Bayer, Eli Lilly, Esteve and Teva. TPA holds stocks in Novo Nordisk A/S. Outside the submitted work, JH has received consultancy fee from UCB and MP do consultancy work for Institute Horsted.

ORCID

Søren H. Sindrup https://orcid.org/0000-0003-0357-8628

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