

## Sativex successfully treats neuropathic pain characterised by allodynia: A randomised, double-blind, placebo-controlled clinical trial

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### Abstract

Cannabinoids are known to have analgesic properties. We evaluated the effect of oro-mucosal sativex, (THC: CBD), an endocannabinoid system modulator, on pain and allodynia, in 125 patients with neuropathic pain of peripheral origin in a five-week, randomised, double-blind, placebo-controlled, parallel design trial. Patients remained on their existing stable analgesia. A self-titrating regimen was used to optimise drug administration. Sixty-three patients were randomised to receive sativex and 62 placebo. The mean reduction in pain intensity scores (primary outcome measure) was greater in patients receiving sativex than placebo (mean adjusted scores –1.48 points vs. –0.52 points on a 0–10 Numerical Rating Scale ( $p = 0.004$ ; 95% CI: –1.59, –0.32). Improvements in Neuropathic Pain Scale composite score ( $p = 0.007$ ), sleep NRS ( $p = 0.001$ ), dynamic allodynia ( $p = 0.042$ ), punctate allodynia ( $p = 0.021$ ), Pain Disability Index ( $p = 0.003$ ) and Patient's Global Impression of Change ( $p < 0.001$ ) were similarly greater on sativex vs. placebo. Sedative and gastrointestinal side effects were reported more commonly by patients on active medication. Of all participants, 18% on sativex and 3% on placebo withdrew during the study. An open-label extension study showed that the initial pain relief was maintained without dose escalation or toxicity for 52 weeks.

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**Keywords:** Sativex; Cannabinoid; Peripheral neuropathic pain; Allodynia

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### 1. Introduction

The treatment of chronic neuropathic pain is mainly pharmacological, with antidepressants, antiepileptic

drugs, opioids and topical local anaesthetics constituting the first-line therapy [2]. Despite differences in their mechanism of action, these agents appear similar in analgesic efficacy and tolerability. There is a well-recognised need for better pain relief than is currently available. This study reports the effect of the administration of a highly standardised THC:CBD endocannabinoid system modulator, sativex (Sativex<sup>®</sup>), on the severity of pain and allodynia, and associated sleep disturbance, mental distress and disability in patients with peripheral

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neuropathic pain. Identification of cannabinoid receptors [20] and encouraging results from preclinical and clinical studies [15,16] and change in the political and scientific scene in some countries, notably Canada, have led to revived interest in cannabinoids as a therapeutic modality. Two controlled trials on central pain associated with MS found short-term efficacy from them [26,30], whereas two other studies in which pain was not a primary outcome measure gave conflicting results [33,40]. Neuropathic pain of peripheral or mixed peripheral and central origin was reported to respond to ajulemic acid, sativex or smoked cannabis; however, treatment arms in these studies were short, between 5 and 14 days [1,6,19].

Sativex is derived from extracts of selected strains of cannabis plants (*Cannabis sativa*) which produce high and reproducible yields of the principal active cannabinoids, delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). It is administered as a spray for sublingual and oro-pharyngeal administration. Each 100 µl spray delivers 2.7 mg of THC and 2.5 mg of CBD.

Cannabinoids are thought to work via two types of receptors, CB1 and CB2. CB1 is widely distributed in the peripheral and central nervous system, acting as a presynaptic modulator of neurotransmitter release. The main target for the effects of THC, CB1, occurs at many sites critical for nociception. CB2 is also activated by THC but in normal circumstances is found in immune cells only. However, in clinical pain the role of the CB2 receptor may be different because following tissue injury it is shown to be expressed in central nervous system microglia and dorsal root ganglion cells following tissue injury [28] CBD appears to have limited affinity for either cannabinoid receptor, but in higher doses may potentiate the effects of THC [32] and mediate non-cannabinoid effects by activating the TRPV1 receptor [8]. Combining the two in the same preparation is thought to lead not only to increased analgesic effect but may also result in antagonism of adverse effects [27].

## 2. Methods

### 2.1. Study design

This was a 5-week multi-centre (5 centres in UK, 1 in Belgium), randomised, double-blind, placebo-controlled parallel group study. Patients were screened to determine eligibility and completed baseline diary assessments of daily pain intensity and sleep disturbance scores in the 7–10 days prior to first treatment assignment. After eligibility was confirmed, patients were assigned to the next sequential randomisation number within each centre. The randomisation schedule had a 1:1 treatment allocation ratio with randomly permuted blocks stratified by centre and was generated using a computer based pseudo-random number algorithm. The randomi-

sation schedule was held by the sponsor with a copy in patient-specific sealed envelopes sent to the pharmacy in each centre. Once the patient's eligibility was confirmed, they were assigned to the next sequential randomisation number within each centre. The placebo medication was identical in composition, appearance, odour and taste with the study medication but without cannabis extract. That the smell and taste of the cannabinoid preparation might lead to unblinding was averted by disguising them with addition of peppermint oil to both preparations. All medication was provided in identical amber vials, packaged and labelled by the sponsor.

### 2.2. Study patients

Patients had to have a current history of unilateral peripheral neuropathic pain and allodynia. Further enrolment criteria are shown in Table 1. Concomitant analgesia was maintained at a stable dosage regimen for the duration of the study. The decision to recruit was based on the patient's history. No tests for drugs of abuse potential were carried out. Ethical approval was granted by the Local Ethics Committees of the participating centres. In one centre the approval was conditional on patients not driving during the trial.

### 2.3. Study medication and procedures

Initial dosing was under clinical supervision at the study site. A pre-dose 100 mm "Intoxication" (0 = no intoxication and 100 = extreme intoxication) Visual Analogue Scale (VAS) was obtained and vital signs were checked. A maximum of 8 sprays were administered over 2 h with Intoxication VAS and vital signs checked at regular intervals. If, following any dose, patients scored higher than 25 mm, or there were clinical concerns, e.g. the patients showing dysphoria or cardiovascular changes, subsequent doses were omitted [6,7].

After satisfactory completion of initial dosing, patients began home dose titration and were allowed a maximum dose of 8 sprays per 3-hour interval and a maximum of 48 sprays per 24 h. At the next visit (after 7–10 days) titration, compliance and adverse events were reviewed, and patients advised on how to optimise dosing for the rest of the study period. Those patients who satisfactorily completed the trial were offered the opportunity to participate in a common open-label extension study of sativex.

All used and unused study medication containers were returned at each visit to the research centre. Patients were withdrawn from the study if there were indications of misuse, including failure to record dosage accurately. Periodic telephone monitoring was undertaken at pre-arranged times during home dosing to check the patient's condition and to answer any queries. Throughout the study, allowable concomitant medications or treatments were continued to provide adequate background analgesia at a constant dose. Any medication, other than the study medication taken during the study, was recorded.

Patients kept a diary from the screening visit until end of treatment in which they recorded daily their pain and sleep scores (on the appropriate NRS), as well as adverse events and the number of sprays used.

Table 1  
Enrolment criteria

Inclusion criteria	Exclusion criteria
Unilateral peripheral neuropathic pain and allodynia	Cannabinoid use (cannabis, Marinol® (synthetic THC) or nabilone (synthetic cannabinoid analogue)) at least 7 days before randomisation. Subjects were required to abstain from use of cannabis during the study
Age 18 or over, male or female	Schizophrenia, psychosis, or other major psychiatric condition beyond depression with underlying condition
A history of at least 6 months duration of pain due to a clinically identifiable nerve lesion	Concomitant severe non-neuropathic pain or the presence of cancer related neuropathic pain or from diabetes mellitus
Demonstrate mechanical allodynia and impaired sensation within the territory of affected nerve(s) on clinical examination	Known history of alcohol or substance abuse
Patients with complex regional pain syndrome (CRPS) were eligible if they showed evidence of peripheral nerve lesion (diagnosed as CRPS type II)	Severe cardiovascular condition, poorly controlled hypertension, epilepsy, pregnancy, lactation, significant hepatic or renal impairment
A baseline severity score of at least 4 on the numerical rating scale for spontaneous pain for at least 4 of 7 days in the baseline week	Scheduled surgery or anaesthesia
A stable medication regimen of analgesics for at least 2 weeks prior to study entry	Terminal illness or subjects inappropriate for placebo therapies
Female patients of child bearing potential and male patients whose partner was of child bearing potential had to agree to use effective contraception	Known hypersensitivity to cannabinoids
Willing for his or her name to be notified to the UK Home Office	Participation within a trial in the last 12 weeks

#### 2.4. Testing for allodynia

Tests for allodynia were carried out at baseline and end of study. The investigator recorded the most painful area within the affected territory. Mechanical dynamic allodynia was assessed by stroking the skin over the affected area five times with a standardised brush, designed specifically for sensory testing (Senselab Brush-05, Somedic, Horby, Sweden) at  $\geq 5$  s intervals, and recording the pain severity on a 0–10 point scale. All strokes were of the same length, minimum 2 cm. Each dynamic allodynia score was calculated as the average of the five strokes.

Punctate allodynia was measured using an in-house built pressure algometer comprising a strain gauge connected to a metal filament with a diameter of 1 mm and blunt tip at baseline and end of study. The filament was manually directed against the skin at an angle of 90° and a steadily increasing pressure applied until the patient verbally indicated that they perceived pain (punctate pressure pain threshold). A contralateral mirror image site was used as control to identify any systemic effect from the trial drugs, as well as to introduce the method to the patient before performing the test on the allodynic site. This control site was checked for evidence of local injury, scar, rash or neurological deficit. During each session the normal contralateral side was tested first. Once the patient indicated that the sensation of pressure had turned into pain, the algometer was removed and the pressure reading (in grams) recorded. The same method was used for allodynic sites.

In addition, patients were asked to verbally rate the intensity of the pain elicited, choosing a number between 0 (no pain) and 10 (most intense pain imaginable). The investigators were aware of the previous punctate allodynia threshold and could use it as guidance. Because some investigators expressed concern at using a rigid threshold as a target for the second mea-

surement, it was agreed that they could exercise discretion in applying the force needed to reproduce approximately the same pain as at baseline. The patients' verbal pain score and pressure used were recorded. Each punctate pain provocation test was done only once during a single visit.

#### 2.5. Outcome measures

The primary outcome measure was a change from baseline on a numerical rating scale (NRS) of mean intensity of global neuropathic pain, where 0 = "No Pain" and 10 = "Worst Possible Pain". Secondary measures included the composite score calculated from the Neuropathic Pain Scale (NPS) [10], tests for mechanical allodynia, a four-step verbal rating scale for sleep disturbance (see below), the Pain Disability Index (PDI) [31], the Patient Global Impression of Change (PGIC) of both pain and allodynia, and the General Health Questionnaire (GHQ-12) [5]. Possible cognitive decline was assessed using the Brief Repeatable Battery of Neuropsychological tests (BRB-N) [7]. Information regarding the frequency of administration of the medication was recorded by the subjects in their diary. Adverse events were collected at each clinic visit, and haematology, clinical chemistry and ECG monitored at the beginning and end of the study.

#### 2.6. Statistical analysis

The sample size calculation was based on an expected SD of 1.8 for the pain intensity score, estimated from several studies on peripheral neuropathic pain. To detect a difference between treatment groups of 1.0 on a 0–10 (11-point) NRS with 80% power and a 5% level of significance, 52 evaluable subjects per group were required. A dropout rate of 15% was anticipated, bringing the total number of patients needed to 120.

The primary analysis for the primary and secondary end-points was performed on the intention-to-treat (ITT) population. The neuropathic pain intensity NRS score at baseline was defined as the mean of all diary entries from Day –7 to Day –1 and, for the end of treatment score, the mean of all diary entries during the last 7 days in the study, or the last 3 days in the event of withdrawal. The NRS scores were summarised by treatment group for baseline, each week and end of treatment. The change in NRS pain scores was compared between treatment groups using analysis of covariance, the model including treatment and trial centre as factors and baseline pain severity as a covariate. From this analysis the adjusted treatment means, treatment difference and 95% Confidence Interval (95% CI) for the treatment difference were calculated.

The total scores for all questionnaires (NPS, PDI, GHQ-12), as well as 0–10 NRS ratings of punctate and mechanical allodynia, were obtained at baseline and end of the 5-week trial. Sleep disturbance was measured by asking the subjects to indicate the number of times they woke in previous nights due to symptoms on a four category scale where 1 = none,

2 = once, 3 = twice, 4 = more than twice. The scores for this “Sleep Disturbance NRS” were obtained at baseline and weekly thereafter until the end of trial. Statistical comparisons were performed in the same way as the primary outcome measure. The PGIC was compared between treatments using Fisher’s Exact Test.

### 3. Results

A total of 141 patients were assessed for eligibility, 16 (11%) of whom failed to meet the eligibility criteria. Sixty-three subjects were randomised to sativex and 62 to placebo (Fig. 1). At all participating centres, the randomisation led to a complete balance between treatment allocations. Baseline demographic details for both groups are shown in Table 2. The treatment groups were well matched for age, duration of neuropathic pain, distribution of diagnostic pain subgroups, height, weight and for history of previous cannabis use. The diagnosis was based on existing clinical, imaging and neurophysiological

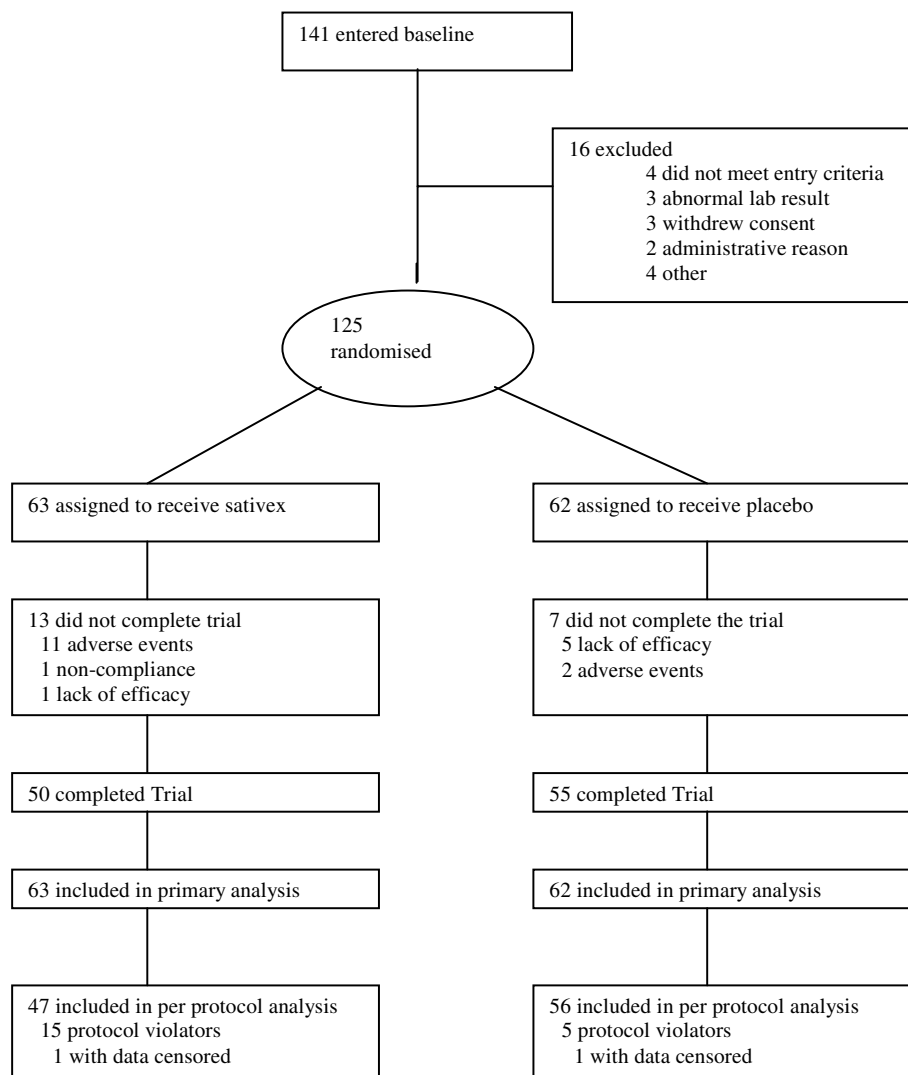


Fig. 1. Study flow.

Table 2  
Patient characteristics

	Sativex ( <i>N</i> = 63)	Placebo ( <i>N</i> = 62)
Age, yr mean (SD)	52.4 (15.8)	54.3 (15.2)
Women, <i>N</i> (%)	35 (55.6)	39 (62.9)
White, <i>N</i> (%)	61 (97)	60 (97)
Weight, kg mean (SD)		
Men	79.9 (16.7)	86.8 (16.7)
Women	72.0 (18.2)	72.7 (17.3)
Duration of pain, yr mean (SD)	6.4 (5.7)	6.2 (6.4)
Underlying diagnosis		
Subjects (%)		
Postherpetic neuralgia	10 (16)	7 (11)
Peripheral neuropathy	13 (21)	12 (19)
Upper limb	2	1
Lower limb	5	4
Face/neck/trunk	6	7
Focal nerve lesion	26 (41)	28 (45)
Upper limb	8	7
Lower Limb	10	11
Face/neck/trunk	8	10
Radiculopathy	7 (11)	6 (10)
CRPS type II	7 (11)	8 (13)
Other	0 (0)	1 (2)
Prior cannabis use <i>N</i> (%)	13 (21)	12 (19)
Concomitant medication		
Subjects <i>N</i> (%)		
Antiepileptic	21 (33)	21 (34)
Tricyclic	16 (25)	21 (34)
Opioid	40 (63)	46 (74)
Strong <sup>a</sup>	7 (11)	8 (13)
Weak <sup>b</sup>	33 (52)	38 (61)
Analgesic, non-opioid	10 (16)	6 (10)
Anti-inflammatory	10 (16)	15 (24)
Pain NRS, mean (SD)	7.3 (1.4)	7.2 (1.5)
NPS composite score, mean (SD)	61.1 (13.0)	62.4 (13.7)
Dynamic allodynia NRS, mean (SD)	5.4 (2.7)	5.0 (3.4)
Punctate allodynia NRS, mean (SD)	7.3 (1.8)	7.4 (2.1)
Punctate allodynia, pressure g, mean (SD)	68.8 (47.7)	83.0 (77.4)
Pain Disability Index (PDI) mean (SD)	40.9 (14.7)	42.1 (13.4)
Sleep disturbance NRS, mean (SD)	3.0 (0.8)	3.0 (0.9)
GHQ-12, mean (SD)	17.2 (7.3)	17.6 (6.5)

<sup>a</sup> Morphine, methadone, oxycodone, pethidine.

<sup>b</sup> Tramadol, codeine, dihydrocodeine, dextropropoxyphene.

data. Aetiologies varied from post-infectious to traumatic, vascular and idiopathic. In nearly one-half of patients the cause was posttraumatic and involved a single nerve or nerve branch (focal nerve lesion) while in one-fifth the lesion was at cervical, brachial or lumbosacral plexus level or involved several nerves (peripheral neuropathy); in this group the original cause was either inflammation or diffuse trauma and remained frequently unknown. The locations of focal nerve lesions and periph-

eral neuropathics were similar across the two groups (Table 2). The background use of concomitant analgesic medication was high in both groups. The most frequently reported medication was opioids, being taken by 74% of the placebo group and 63% of the sativex group. Other frequently used background medications were tricyclic antidepressants, antiepileptic drugs, and NSAIDs (Table 2).

Thirteen sativex patients (21%) failed to complete the study; 11 withdrew because of side effects, 1 due to patient non-compliance and one due to lack of efficacy. Seven patients (11%) on placebo failed to complete the study, 2 because of adverse effects and 5 because of lack of effect. All randomised patients were included in the ITT analysis. For the per-protocol (PP) analysis, there were 47 patients on sativex and 56 on placebo. Protocol violations were due to failure to meet the stringent time window set for the final visits (12 patients on sativex, 2 on placebo), use of prohibited medication (6 on sativex, two of whom also failed to meet the final visit time window, and 2 on placebo) or violation of inclusion/exclusion criteria (0 on sativex, 2 on placebo). One patient in each group had their data censored because of use of prohibited medication after Day 26.

### 3.1. Primary outcome measure

At baseline, the mean intensity of reported pain scores (SD) on NRS was in the severe range with no difference between the sativex and placebo groups 7.3 (1.4) and 7.2 (1.5), respectively (Table 2). At the end of treatment, the sativex group demonstrated an adjusted mean change in NRS score of  $-1.48$  points (a 22% reduction) while the change for the placebo group was  $-0.52$  points (an 8% reduction) (Fig. 2). The estimated treatment

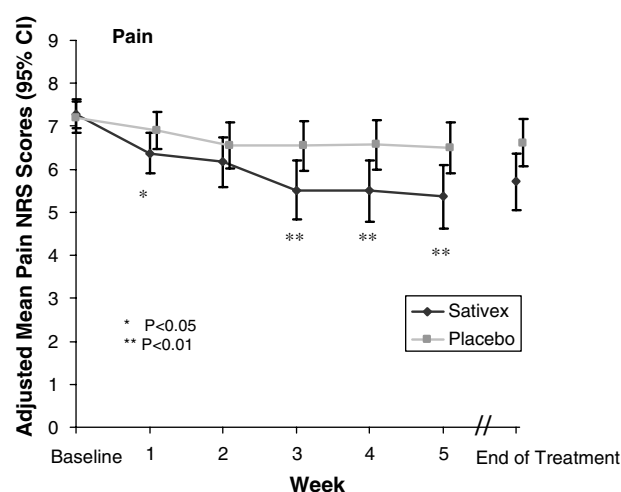


Fig. 2. Reduction of global neuropathic pain NRS scores in the two groups during the trial. First-week: home-titration; subsequent four weeks: maintenance therapy. Weekly mean pain scores were obtained from pain diaries. End-point scores were obtained from diary entries during the last 7 days, or last 3 days in case of withdrawal, for the ITT analysis. Error bars represent 95% confidence intervals.



difference of  $-0.96$  points was statistically significant in favour of sativex ( $p = 0.004$ ; 95% CI:  $-1.59, -0.32$ ). The improvement in pain over placebo was evident from the second week after self-titration and was maintained until the end of the study (Fig. 2). On sativex, 26% of patients had at least a 30% reduction in pain score and 20% of patients had at least a 50% reduction in pain score, compared with 15% and 8% of patients on placebo; the NNT (50%) and NNT (30%) calculated from these figures were 8.5 and 8.6, respectively. Analysis of the PP population also showed a significant treatment difference of  $-1.42$  points in favour of sativex ( $p < 0.001$ ; 95% CI:  $-2.10, -0.74$ ).

### 3.2. Secondary outcome measures

All questionnaire-based measures of pain and pain-related co-morbidity improved significantly more in patients randomised to sativex than placebo (Table 3). NPS composite score in the sativex group decreased significantly more than in the placebo group. Sleep disturbance also decreased early on and improvement was maintained until the end of the study (Fig. 3). Of the seven functional areas assessed in the PDI, only sexual activity failed to show a substantial improvement on sativex (Table 3).

### 3.3. Allodynia

#### 3.3.1. Dynamic mechanical allodynia

All patients recruited into the study showed dynamic allodynia. There was no difference in detected mean (SD) allodynia pain scores between the two groups at baseline (5.4 (2.7) vs. 5.0 (3.4)). At the end of treatment, the mean reduction of dynamic allodynia was 20% in the sativex group, and 5% in the placebo group, with an estimated mean treatment difference of  $-0.82$  ( $p = 0.042$ ; 95% CI:  $-1.6, -0.03$ ) in favour of sativex. NNT for 30% reduction in the allodynia score was 9.2 and for 50% reduction 7.5.

#### 3.3.2. Punctate allodynia

At baseline, all randomised patients except one on sativex showed punctate allodynia with clearly reduced thresholds in the affected area vs. contralateral control

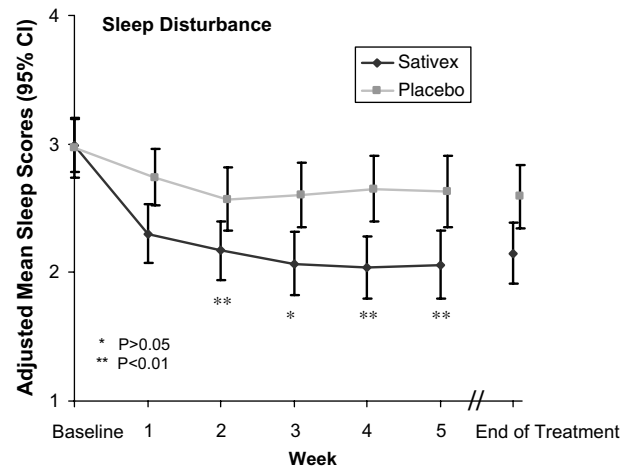


Fig. 3. Reduction in sleep disturbance scores in the two groups during the trial. For details, see text, and legend for Fig. 2.

(mean (SD) difference between the contralateral site and allodynic site: 127 (78) g). The severity of the allodynia within the affected area was comparable between both sativex and placebo groups for pressure needed to elicit pain (68.8 (47.7) g vs. 83.0 (77.4) g) and for the level of pain generated by the stimulus itself (7.3 (1.7) vs. 7.4 (2.1)). At the end of study, there was no evidence of a change in the punctate pain threshold at the contralateral control site, irrespective of whether the patients were on sativex or placebo (treatment difference 11.1 g in favour of placebo;  $p = 0.3$ ). At the allodynic site, the placebo group reported unchanged punctate pain pressure thresholds at end of study (83.0 (77.4) g vs. 85.8 (68.9) g) with no change in pain levels (7.4 (2.1) and 7.2 (2.2)). In the sativex group, the threshold levels increased from 68.8 (47.7) g to 86.2 (73.2) g but not significantly compared to the placebo group ( $p = 0.14$ ). Despite this increase of applied punctate pressure there was a notable decrease in the allodynia pain scores (baseline: 7.3 (1.7) vs. end of treatment: 6.2 (2.6)). The estimated treatment difference of  $-0.87$  was in favour of sativex ( $p = 0.021$ ; 95% CI:  $-1.62, -0.13$ ), giving an NNT (30%) of 5.9 and NNT (50%) of 13.4.

Inspection of punctate allodynia data revealed that in some cases the pressure applied with the algometer to the allodynic site had changed considerably between

Table 3  
Summary of the results of the secondary efficacy end-points (ITT analysis)

Secondary outcomes	Sativex	Placebo	Estimated mean difference (95% CI) <sup>a</sup>	p-Value
NPS composite score	-10.07	-2.04	-8.03 (-13.83, -2.23)	0.007
Sleep disturbance NRS	-0.79	-0.36	-0.43 (-0.67, -0.19)	0.001
Pain Disability Index (PDI)	-5.61	0.24	-5.85 (-9.62, -2.09)	0.003
Dynamic allodynia NRS	-1.18	-0.37	-0.82 (-1.60, -0.03)	0.042
Punctate allodynia NRS	-1.09	-0.21	-0.87 (-1.62, -0.13)	0.021
GHQ-12	-3.09	-2.34	-0.75 (-2.84, 1.35)	0.483
PGIC (all neuropathic pain)	51.61	19.35	32.26 (16.40, 48.12)	<0.001
PGIC (pain at allodynic site)	46.77	17.74	29.03 (13.79, 44.67)	0.001

<sup>a</sup> All treatment comparisons in favour of sativex.

pre-treatment and post-treatment. When a sensitivity analysis was carried out in patients in whom the investigators applied a similar degree of force (<5% greater) to the allodynic area on the second testing occasion (44 patients on sativex and 45 on placebo), there was a significantly larger reduction of allodynia pain in the sativex group than the placebo group leading to a treatment difference of  $-0.94$  ( $p = 0.046$ ; 95% CI:  $-1.85, -0.02$ ) in line with the ITT analysis.

When all subjects were analysed together, there was a strong correlation between the intensity of punctate allodynia, dynamic allodynia and spontaneous pain at baseline and end of study, with similar strong correlations between the three parameters for change in scores (punctate allodynia vs. dynamic allodynia,  $r = 0.526$ ,  $p < 0.001$ ; punctate allodynia vs. pain  $r = 0.369$ ;  $p < 0.001$ ; dynamic allodynia vs. pain,  $r = 0.436$ ,  $p < 0.001$ ). Inspection of sativex and placebo groups separately showed that similar significant correlations were present, except for change in dynamic allodynia in the placebo group ( $r = 0.065$ ,  $p = 0.61$ ).

Results of the secondary efficacy end-points are summarised in Table 3. Thirty-two (51.6%) patients taking sativex compared to 12 (19.3%) taking placebo considered their primary condition to be very much, much or minimally improved ( $p < 0.001$ , Fisher's exact test). The odds ratio for achieving a better response on sativex than placebo, calculated from a logistic regression of the data, was 3.55 (95% CI:  $-7.61, -1.72$ ) in favour of sativex. There was no difference between groups in the GHQ-12 score.

### 3.4. Dosing pattern

The mean (SD) number of sprays taken during the first week of dose titration for sativex and placebo was 7.3 (3.5) and 10.9 (3.9), respectively. From the second week onwards, the dose frequency remained stable in

both treatment groups, with no tendency to increasing dose over the duration of the study. The number of sprays used daily in the placebo group was higher than in the sativex group (Table 4). Over the study period, patients randomised to sativex used a mean (SD) of 10.9 (6.8) sprays daily compared with 19.0 (8.3) by patients on placebo.

### 3.5. Adverse events and withdrawals

Fifty-seven (91%) patients in the sativex group experienced at least one adverse event (AE) during the course of the study compared with 48 (77%) patients in the placebo group. The most frequent AEs were central nervous system related or gastrointestinal. Most were observed at onset of treatment, and in the majority described as mild. However, 6 (10%) patients on sativex reported several gastrointestinal AEs (nausea, vomiting diarrhoea, constipation) with none on placebo reporting the same. Severe symptoms suggesting involvement of the nervous system were reported with sativex in 7 (11%) and placebo 5 (8%) cases. All reported gastrointestinal AEs combined irrespective of their severity were more common in the sativex group (31/63 (49%) than in the placebo group (20/62 (32%),  $p = 0.003$ , Fisher's exact test), whereas the nervous system AEs (33/63 vs. 23/62,  $p > 0.10$ ) were not. One case of severe psychiatric AE was recorded on both groups (with sativex, emotional stress associated with paranoid thinking and with placebo, confusion) and 6 further mild-to-moderate ones in the sativex group as opposed to 3 in the placebo group; these were mainly mood related. AEs seen in 3 or more subjects are shown in Table 5 for all AEs and for those considered possibly related to treatment.

In the sativex group, 11 (18%) patients withdrew due to an AE compared with 2 (3%) in the placebo group. There was one transient ischaemic attack in the sativex group rated as a serious adverse event (SAE) and

Table 4  
Summary of exposure to study medicine (number of sprays per day based on patient diary entries)

		Sativex ( $N = 63$ )	Number of patients remaining	Placebo ( $N = 62$ )	Number of patients remaining
Week 1	Mean (SD)	7.31 (3.54)	62	10.94 (3.90)	62
	Median (range)	6.64 (1.3–14.7)		11.14 (3.0–21.3)	
Week 2	Mean (SD)	12.46 (8.07)	58	20.08 (9.79)	61
	Median (range)	10.86 (1.6–42.7)		19.71 (2.3–47.9)	
Week 3	Mean (SD)	13.32 (8.30)	55	21.10 (10.79)	60
	Median (range)	11.43 (1.7–37.4)		20.07 (1.7–48.0)	
Week 4	Mean (SD)	12.86 (8.63)	53	22.23 (11.51)	57
	Median (range)	10.86 (2.0–39.0)		20.43 (1.7–48.1)	
Week 5	Mean (SD)	13.63 (8.65)	48	22.26 (11.68)	54
	Median (range)	12.64 (1.1–37.7)		19.93 (2.9–50.6)	
Overall	Mean (SD)	10.89 (6.81)		19.02 (8.32)	
	Median (range)	9.81 (1.3–31.4)		17.91 (2.4–41.5)	

Table 5

Treatment emergent adverse events (AEs) experienced by 3 or more subjects (~ 5%) receiving sativex compared with placebo and the % of subject who withdrew due to these AEs

Adverse event	Number (%) of patients experiencing AEs		Number (%) of patients who withdrew due to AE	
	Sativex (N = 63)	Placebo (N = 62)	Sativex (N = 63)	Placebo (N = 62)
Dizziness	18 (28.6)	9 (14.5)	2 (3.2)	0
Nausea	14 (22.2)	7 (11.3)	1 (1.6)	0
Fatigue	13 (20.6)	5 (8.1)	0	0
Dry mouth	11 (17.5)	3 (4.8)	0	0
Vomiting	8 (12.7)	3 (4.8)	2 (3.2)	0
Feeling drunk	6 (9.5)	1 (1.6)	1 (1.6)	0
Headache	6 (9.5)	9 (14.5)	0	0
Diarrhoea	4 (6.3)	0	2 (3.2)	0
Nasopharyngitis	4 (6.3)	2 (3.2)	0	0
Anorexia	4 (6.3)	0	1 (1.6)	0
Somnolence	4 (6.3)	1 (1.6)	0	1 (1.6)
Abdominal pain upper	3 (4.8)	1 (1.6)	0	0
Disturbance in attention	3 (4.8)	0	0	0
Memory impairment	3 (4.8)	0	0	0

considered unrelated to study treatment. Oral discomfort, other than dryness of mouth, occurred in 8 (13%) patients taking sativex and 11 (18%) taking placebo and was usually reported as mild. One patient on sativex had transient mucosal ulcerations but leukoplakia was not observed. No significant haematological or biochemical abnormalities were encountered in laboratory parameters.

The Brief Repeatable Battery of Neuropsychological Tests (BRB-N) was given to 85 patients (43 randomised to sativex and 42 to placebo). No difference was seen between groups assessed for cognitive function with this method at the beginning and end of treatment (Table 6).

Intoxication scores (SD) remained low throughout the study, peaking after the self-titration week at 8.0 (15.4) for sativex and 3.0 (7.9) for placebo on a 0–100 scale, respectively. Five patients on sativex and 2 patients on placebo scored more than 40/100 during the maintenance period.

### 3.6. Long-term use of sativex

At the end of their 5-week trial period, each patient was offered the chance to enter an open-label extension study. Of the 125 subjects eligible, a total 89 (71%) of the patients accepted the offer. They subsequently underwent re-titration of sativex from zero, in a way identical

to that used in the randomisation phase. Patients were reviewed initially at 4 weeks thereafter every 8 weeks.

The duration of participation in the extension trial ranged from 1 to 871 days. By study closure, 56 (63%) patients had been withdrawn; 18 patients due to adverse effects, 16 due to lack of efficacy, 15 due to withdrawal of consent, 7 for other reasons. The mean (SD) duration of the participation of withdrawn patients was 135 (147) days. An LOCF analysis involving 76 patients carried out at 52 weeks demonstrated a mean decrease of pain NRS from the baseline of 7.3 (1.4) to 5.9 (2.4), i.e., similar to that seen in the randomised trial. The daily number of sprays did not increase appreciably during this period (N (SD) 10.2 (6.0) at the end of the re-titration vs. 12.2 (7.6) at 52 weeks). Two episodes of serious adverse effects were reported (urticaria with eyelid oedema and an event of somnolence, dysarthria and weakness) both leading to withdrawal of the patient in question from the study.

## 4. Discussion

This study demonstrates that sativex is effective in the relief of peripheral neuropathic pain when given in addition to existing medication. Greater than 30% improvement in pain intensity, generally considered as clinically meaningful [9], was reported by 26% of subjects receiving sativex, compared with 15% of patients taking

Table 6

Psychomotor function during the trial shown as adjusted mean change from baseline in the BRB-N for each treatment group

Test	Sativex	N	Placebo	N	Difference	p-Value
Selective reminding	0.55	43	0.52	42	0.02	0.92
10/36 Spatial recall	0.85	43	0.31	42	0.53	0.21
Symbol digit modalities	1.48	43	3.63	42	−2.15	0.16
Paced serial addition	7.67	33	6.38	34	1.28	0.66
Word list generation	2.35	42	2.44	42	−0.08	0.96

No difference between groups (positive difference denotes better function on sativex and negative on placebo).



placebo. At recruitment, all our patients were either non-responders to several conventional neuropathic analgesics, or were in severe pain despite taking appropriate therapy. Considering the refractory nature of their pain, and that patients remained on their existing analgesia, the improvement of the ongoing pain in those on the active drug is encouraging. Further evidence for the efficacy of sativex comes from improvement in mechanical dynamic and punctate allodynia pain, sleep and disability demonstrated in this study. Reduction in systematically measured mechanical allodynia is not commonly reported in controlled trials on neuropathic pain [17] and usually only seen in single dose studies or following other than oral administration, and failure is common. [3,21,23,29,34–36]. Because to date there are no reliable data converting reduction in allodynia scores to clinically meaningful improvement, the NNT values presented should be interpreted with caution.

In comparison with pain relief reported from other cannabis-related clinical trials, sativex in our group of patients demonstrated a greater difference over placebo (0.96, 95% CI –1.59, –0.32) than in patients with plexus avulsion (treatment difference –0.58, 95% CI –0.98, –0.18) but somewhat less than in patients with central pain due to MS (–1.25; 95% CI –2.11, 0.39) [6,26]. The treatment difference reported for dronabinol in MS patients deprived of concomitant analgesic medication was 0.6 (95% CI –1.8, 0) while that for smoked cannabis in painful HIV neuropathy was approximately the same as in the present study (as extrapolated from the reported median 18% treatment difference in pain relief from mean baseline scores of 53 and 54/100) [1,30]. Differences in patient populations, numbers of withdrawals, concomitant medications, trial designs and trial durations probably explain a great deal of these varying results. Interestingly, the two other cannabinoid trials in which evoked pain was assessed, albeit in a limited fashion, also report some benefit in line with the present study [1,30].

Our reason for maintaining existing analgesia was based on both ethical and clinical considerations. A number of treatments that have shown efficacy in peripheral neuropathic pain are in widespread use in accordance with existing guidelines [2]. Depriving a patient from such therapies during a placebo-controlled trial could not be ethically justified. Clinical practice is also moving toward combination therapies due to the realisation that in chronic neuropathic pain multiple mechanisms are the norm [12,39].

The lack of GHQ-12 to show any change during the present study is in line with virtually all other cannabinoid trials in which the psychosocial domain was explored, irrespective of the measure used (GHQ-30, [40]; GHQ-28, [33]; SF-36, [30]; GHQ-12, [6]; HADS, [26]; POMS, [1]). GHQ-12 is a well-validated measure of anxiety, depression and social dysfunction [37] and

shows adequate sensitivity to change in longitudinal studies in manifest depression [11]. The role of the endocannabinoid system in the regulation of anxiety and mood disorders still remains unclear, and both CB1 agonists and antagonists have been shown to possess either anxiolytic or anxiogenic effects as well as variable effects on mood [38]. It is possible that GHQ-12 cannot detect modest changes in a population such as ours scoring just above the mean of the general population [24]. Alternatively, the above paradoxical effects of THC, or the ability of CBD to block some of the psychomimetic effects of THC, may explain the lack of change in this measure.

The self-titration schedule used in this study was chosen for several reasons. Previous studies [6,26] indicated that individual subjects have a variable threshold to the known pharmacodynamic effects of sativex. A self-titration regimen permitted individual patients to optimise their dose on the basis of their own efficacy and tolerability response. Both experimental and human volunteer studies suggest that tolerance to some of the side effects of cannabis occurs within days of its repeated administration [14,18,22]. A self-titration regimen allows for this to occur, further optimising the therapeutic response. There appears to be substantial between-patient variability in the pharmacokinetics of THC and other cannabinoids [13,14] and in such circumstances the implementation of a fixed-dose regimen is likely to yield suboptimal results.

The mean number of sprays taken daily by the sativex group remained stable during the course of the study despite patients having the freedom to determine their own dosing, indicating that tolerance did not develop at least over the 4-week stable treatment period of this study. The dose titration regimen used was usually successful in providing the optimal therapeutic level for individual patients. This conclusion is endorsed by the observation that those patients who took part in the open-label extension study did not increase the number of daily sprays during the first 52 weeks of open-label treatment while apparently maintaining the initial analgesic effect.

While the therapeutic effects of cannabis have often been attributed to THC, the second major constituent of the trial medication, CBD has been shown to have effects which may be additive to those of THC in pain relief in animal models, and also to have the potential to ameliorate some of the psychoactive effects of THC [27]. This interaction between the two components may permit subjects to tolerate mean daily doses of more than 27 mg THC. This dose is in excess of those used in other controlled studies of THC, and may account for the observed efficacy [14].

The adverse events reported by the patients were mostly gastrointestinal, central nervous system related or topical. While reported gastrointestinal AEs were more common in the sativex group, central nervous sys-

tem AEs were not; and, importantly, objective measurement of psychomotor performance did not vary across the two groups. In general, the number of patients who withdrew is similar to those reported in well-known large trials of other drugs used in neuropathic pain [4,25]. That PCIG scores favoured sativex over placebo suggests that subjective pain relief, reduced disability and improved sleep overrode the negative impact of AEs.

There was no formal assessment of whether unblinding might have taken place. The psychotropic effects of cannabis are well known to the public, and 20% of the participants in the present trial had previous exposure to cannabis. A post-hoc analysis found that previous use of cannabis was not predictive of the change in mean pain scores. Classical psychotropic effects of cannabis were reported by relatively few patients. The intoxication scores were marginally higher in the sativex group, and psychometric tests (BRB-N) remained unchanged during the trial. It is therefore unlikely that a significant number of those on sativex would have correctly guessed they were on active medication unless they deliberately overdosed. From returned trial medication it was concluded that such practice did not take place. Patients taking placebo may have concluded that they were taking inactive substance, given that they used a relatively high number of sprays. However, the majority of patients took less than the highest allowable dosage. Also, only 5 (8%) of the placebo group withdrew for lack of efficacy, suggesting that no significant unblinding took place.

We conclude that the results from this study indicate that sativex has a positive broad spectrum therapeutic effect in neuropathic pain, when used in addition to existing analgesic medication. The emergence of a highly standardised, uniform preparation of THC:CBD should allow for further studies which better define the role for cannabinoids in the treatment of neuropathic pain syndromes.

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