Medical Marijuana Program

165 Capitol Avenue, Room 145, Hartford, CT 06106-1630 • (860) 713-6066
E-mail: dcp.mmp@ct.gov • **Website:** www.ct.gov/dcp/mmp

Petition to Add a Medical Condition, Medical Treatment or Disease to the List of Debilitating Conditions

INSTRUCTIONS: Please complete each section of this Petition and attach all supportive documents. All attachments must include a title referencing the Section letter to which it responds. Any Petition that is not fully or properly completed will not be submitted to the Board of Physicians.

Please Note: Any individually identifiable health information contained in a Petition shall be confidential and shall not be subject to disclosure under the Freedom of Information Act, as defined in section 1-200, Connecticut General Statutes.

Section A: Petitioner's Information

Name (First, Middle, Last): [redacted]			
Home Address (including Apartment or Suite #): [redacted]			
City: [redacted]		State: CT	Zip Code: [redacted]
Telephone Number: [redacted]	E-mail Address: [redacted]		

Section B: Medical Condition, Medical Treatment or Disease

Please specify the medical condition, medical treatment or disease that you are seeking to add to the list of debilitating medical conditions under the Act. Be as precise as possible in identifying the condition, treatment or disease.

Intractable Neuropathy Pain that is unresponsive to standard medical treatments.

Section C: Background

Provide information evidencing the extent to which the condition, treatment or disease is generally accepted by the medical community and other experts as a valid, existing medical condition, medical treatment or disease.

- Attach a comprehensive definition from a recognized medical source.
- Attach additional pages as needed.

Neuropathy: disease or dysfunction of one or more peripheral nerves, typically causing pain, numbness or weakness. The pain of neuropathy is constant or intermittent stabbing, electrical, pins and needles or burning.

Section D: Negative Effects of Current Treatment

If you claim a treatment, that has been prescribed for your condition causes you to suffer (i.e. severe or chronic pain, spasticity, etc.), provide information regarding the extent to which such treatment is generally accepted by the medical community and other experts as a valid treatment for your debilitating condition.

- Attach additional pages as necessary.
- If not applicable, please indicate N/A.

Standard medications only provide partial 30-40% reduction in pain, and often cause side effects such as drowsiness, sedation, GI side effects and a litany of other adverse effects that limit treatment.

Section E: Negative Effects of Condition or Treatment

Provide information regarding the extent to which the condition or the treatments thereof cause severe or chronic pain, severe nausea, spasticity or otherwise substantially limits one or more major life activities.

- Attach additional pages as necessary.

As noted before: Neuropathy causes debilitating pain, numbness, weakness, and imbalance that could lead to falls.

Standard medications can cause: nausea, constipation, drowsiness, hypersomnolence, mood changes and more.

Section F: Conventional Therapies

Provide information regarding the availability of conventional medical therapies, other than those that cause suffering, to alleviate suffering caused by the condition or the treatment thereof.

- Attach additional pages as necessary.

Medication categories used for neuropathy include: SNRIs, TCAs,Anti-convulsant medications, opiates, Lyrica,

Lidocaine cream/patch, compounding pharmacy creams (all have their own set of side effects).

Section G: General Evidence of Support for Medical Marijuana Treatment

Provide evidence, generally accepted among the medical community and other experts, that supports a finding that the use of marijuana alleviates suffering caused by the condition or the treatment thereof.

- Attach additional pages as necessary.

See attached letter. (Appendix A)

Section H: Scientific Evidence of Support for Medical Marijuana Treatment

Provide any information or studies regarding any beneficial or adverse effects from the use of marijuana in patients with the condition, treatment or disease that is the subject of the petition.

- Supporting evidence needs to be from professionally recognized sources such as peer reviewed articles or professional journals.
- Attach complete copies of any article or reference, not abstracts.

See attached in appendix. (Appendix B)

Section I: Professional Recommendations for Medical Marijuana Treatment

Attach letters in support of your petition from physicians or other licensed health care professionals knowledgeable about the condition, treatment or disease at issue.

See attached appendix. (Appendix C)

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Section J: Submission of Petition

In the event you are unable to answer or provide the required documentation to any of the Sections above (excluding Section D); provide a detailed explanation indicating what you believe is "good cause" for not doing so.

- Attach additional pages as necessary.

N/A

I hereby certify that the above information is correct and complete.

My signature below attests that the information provided in this petition is true and that the attached documents are authentic. I formally request that the commissioner present my petition and all supporting evidence to the Board of P

Signature: [redacted]

Date Signed: 12/22/18

Appendix A (Section G)

Polyneuropathy, in its simplest of forms, is defined as damage to the peripheral nerves. The condition is associated with numbness, muscle weakness, pain, and paresthesia, which can be incredibly disabling for those who are afflicted. Current therapeutic strategies have elicited adverse side effects and at best, have marginally controlled symptoms, which is why it is crucial to look into other alternatives for this chronic condition.

There is strong evidence that suggests that medical marijuana can benefit a variety of neuropathic patients. All studies examined had patients who experienced a clinically significant reduction in pain, which is defined as a 30% reduction or greater. The effectiveness of this treatment does not decrease based on administration, giving both patients and providers more flexibility in determining the best treatment option for them. For example, close to half of patients with HIV-induced neuropathy in two separate studies experienced a clinically significant reduction of pain while smoking medical cannabis.[1, 2] On the other hand, 50% of patients who were given CBD/THC oromucosal spray also experienced a significant reduction in pain, which shows that medical marijuana is effective regardless of the method of administration.[3] Additionally, patients did not request to increase their dosage over time, which is what usually occurs with other analgesic medications.

Currently, opioids are used to treat many neuropathy patients in Connecticut. This treatment not only runs the risk of being highly addictive but can also be counterintuitive, at times inducing hyperalgesia, which can increase a patient's sensitivity to painful stimuli. Medical marijuana can reduce opioid-induced hyperalgesia, as well as reduce underlying neuropathic pain to aid with this problem.[2]

Medical marijuana has a wide variety of medical applications and is currently being used to treat patients with facial neuropathy, trigeminal and post-herpetic neuralgia, cancer, multiple

sclerosis, among many other conditions in the state of Connecticut. Many of the indications that medical marijuana has already been approved for are associated with polyneuropathy. For example, common cancer treatments have shown to induce neuropathy in 30-40% of patients, with this statistic increasing to 75% with other medications.[4] Multiple sclerosis can also induce neuropathy, and Sativex has been proven to aid with this specifically, as well as other types of neuropathies in Canada.[5] Considering the fact that medical marijuana has already been approved for conditions that cause or are related to neuropathy, it seems only logical to approve it for polyneuropathy to aid a much larger range of people who suffer with the same condition. There are more than thirty-one states that utilize medical marijuana for the treatment of a variety of conditions. More importantly, states like New York, Montana, New Mexico, North Dakota, Arkansas, California, Oregon, as well as Washington State have neuropathy (or severe chronic pain) as an indication for medical marijuana.

With over one hundred different causes of neuropathy, there is a very large range of individuals who would benefit from an effective treatment. Having peripheral neuropathy added as an indication for medical marijuana in Connecticut is reasonable, especially since it has been approved in other states. There is currently no medication that is effective for neuropathy, making approving medical marijuana imperative. Doing so will greatly improve the quality of life for all those affected with this debilitating condition.

1. Ellis, et al. 2008. Smoked Medicinal Cannabis for Neuropathic Pain in HIV: A Randomized, Crossover Clinical Trial.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3066045/

2. Abrams DI, Jay CA, Shade SB, et al. Cannabis in painful HIV-associated sensory neuropathy: a randomized placebo-controlled trial. Neurology. 2007;68(7):515-521.

3. Hoggart, et al. 2014. A multicentre, open-label, follow-on study to assess the long-term maintenance of effect, tolerance and safety of THC/CBD oromucosal spray in the management of neuropathic pain.
https://link.springer.com/article/10.1007%2Fs00415-014-7502-9

4. Ward., et al. 2014. Cannabidiol inhibits paclitaxel-induced neuropathic pain through 5-HT1A receptors without diminishing nervous system function or chemotherapy efficacy.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3969077/

5. Barnes, MP. 2006. Sativex: clinical efficacy and tolerability in the treatment of symptoms of multiple sclerosis and neuropathic pain.
https://www.ncbi.nlm.nih.gov/pubmed/16553576/

Appendix B (Section H)

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Smoked Medicinal Cannabis for Neuropathic Pain in HIV: A Randomized, Crossover Clinical Trial

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Abstract

Despite management with opioids and other pain modifying therapies, neuropathic pain continues to reduce the quality of life and daily functioning in HIV-infected individuals. Cannabinoid receptors in the central and peripheral nervous systems have been shown to modulate pain perception. We conducted a clinical trial to assess the impact of smoked cannabis on neuropathic pain in HIV. This was a phase II, double-blind, placebo-controlled, crossover trial of analgesia with smoked cannabis in HIV-associated distal sensory predominant polyneuropathy (DSPN). Eligible subjects had neuropathic pain refractory to at least two previous analgesic classes; they continued on their prestudy analgesic regimens throughout the trial. Regulatory considerations dictated that subjects smoke under direct observation in a hospital setting. Treatments were placebo and active cannabis ranging in potency between 1 and 8% Δ-9-tetrahydrocannabinol, four times daily for 5 consecutive days during each of 2 treatment weeks, separated by a 2-week washout. The primary outcome was change in pain intensity as measured by the Descriptor Differential Scale (DDS) from a pretreatment baseline to the end of each treatment week. Secondary measures included assessments of mood and daily functioning. Of 127 volunteers screened, 34 eligible subjects enrolled and 28 completed both cannabis and placebo treatments. Among the completers, pain relief was greater with cannabis than placebo (median difference in DDS pain intensity change, 3.3 points, effect size = 0.60; p = 0.016). The proportions of subjects achieving at least 30% pain relief with cannabis versus placebo were 0.46 (95%CI 0.28, 0.65) and 0.18 (0.03, 0.32). Mood and daily functioning improved to a similar extent during both treatment periods. Although most side effects were mild and self-limited, two subjects experienced treatment-limiting toxicities. Smoked cannabis was generally well tolerated and effective when

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DISCLOSURE

Heather Bentley and Ben Gouaux are employees of the Center for Medicinal Cannabis Research at the University of California, San Diego, the study sponsor. Ms Bentley is Project Manager for the CMCR and assisted the investigator with regulatory issues, oversight/monitoring, and preparation of the manuscript. Mr. Gouaux is a Research Associate with the CMCR and assisted the investigator with regulatory issues, oversight/monitoring, data preparation and analysis, and preparation and submission of the article. The authors declare that over the past 3 years Dr. Atkinson has received compensation from Eli Lilly Pharmaceuticals. The authors declare that they have not received other financial support or compensation in the past 3 years or have any personal financial holdings that could be perceived as constituting a conflict of interest.

added to concomitant analgesic therapy in patients with medically refractory pain due to HIV DSPN.

Keywords

HIV; clinical; neuropathic pain; cannabis; polyneuropathy

INTRODUCTION

In 1999, a report of the United States Institute of Medicine (Watson *et al*, 2000) recommended further investigations of the possible benefits of cannabis (marijuana) as a medicinal agent for a variety of conditions, including neuropathic pain due to HIV distal sensory polyneuropathy (DSPN). The most abundant active ingredient in cannabis, tetrahydro-cannabinol (THC), and its synthetic derivatives, produce effective analgesia in most animal models of pain (Mao *et al*, 2000; Martin and Lichtman, 1998). The antinociceptive effects of THC are mediated through cannabinoid receptors (CB1, CB2) in the central and peripheral nervous systems (Calignano *et al*, 1998), which in turn interact with noradrenergic and κ-opioid systems in the spinal cord to modulate the perception of painful stimuli. The endogenous ligand of CB1, anandamide, itself is an effective antinociceptive agent (Calignano *et al*, 1998). In open-label clinical trials and one recent controlled trial (Abrams *et al*, 2007), medicinal cannabis has shown preliminary efficacy in relieving neuropathic pain.

Neuropathic pain in HIV is an important and persisting clinical problem, affecting 30% or more of HIV-infected individuals. Although combination antiretroviral (ARV) therapy has improved immunity and survival in HIV, it does not significantly benefit neuropathic pain. In fact, certain nucleoside-analogue HIV reverse transcriptase inhibitors, such as didanosine and stavudine, contribute to the frequent occurrence of painful DSPN, possibly through mitochondrial toxicity. Existing analgesic and adjunctive treatments are inadequate; neuropathic pain in DSPN persists in many cases despite attempts at management with opioids, nonsteroidal anti-inflammatory agents, and adjunctive pain modifying therapies, and patients suffer unfavorable side effects, reducing life quality and socioeconomic productivity.

Cannabis also may have adverse effects, including cognitive and motor dysfunction. Yet the extent to which these effects are treatment limiting has received little study. Given the paucity of rigorous scientific assessment of the potential medicinal value of cannabis, the State of California in 2001 commissioned research addressing this topic. As at that time alternative cannabis delivery systems had not been developed to provide the rapid tissue distribution afforded by smoking, the State specifically solicited research using smoked cannabis. We therefore conducted a clinical trial to ascertain a safe, clinically useful, and efficacious dosing range for smoked medicinal cannabis as a short-term analgesic in the treatment of refractory neuropathic pain in HIV DSPN. We evaluated the magnitude and clinical significance of side effects.

METHODS

Design

This was a phase II, single group, double-blind, placebo-controlled, crossover trial of smoked cannabis for the short-term treatment of neuropathic pain associated with HIV infection. Each subject participated in five study phases over 7 weeks as schematized in Figure 1: (1) a 1-week wash-in phase to obtain baseline measurements of pain and

neuropsychological (NP) functioning; (2) 5 days of smoked active or placebo cannabis; (3) 2 weeks wash-out to allow for drug clearance and to assess possible extended benefits or rebound worsening of pain after treatment is withdrawn; (4) 5 days smoked active or placebo cannabis; and (5) 2 weeks final wash-out.

Participants

Study participants were adults with documented HIV infection, neuropathic pain refractory to a least two previous analgesics, and an average score of 5 or higher on the pain intensity subscale of the Descriptor Differential Scale (DDS), described below. HIV DSPN was diagnosed by a board-certified clinical neurologist (RJE). The association of DSPN with HIV disease and ARV treatment was established according to the previously published research diagnostic criteria and included the presence of abnormal bilateral physical findings (reduced distal tendon reflexes, distal sensory loss) or electrophysiological abnormalities (distal leg sensory nerve conduction studies), plus symptoms of pain and paresthesias, acquired in the setting of HIV infection (AAN, 1991). Exclusion criteria were (1) current DSM-IV substance use disorders; (2) lifetime history of dependence on cannabis; (3) previous psychosis with or intolerance to cannabinoids; (4) concurrent use of approved cannabinoid medications (ie Marinol); (5) positive urine toxicology screen for cannabinoids during the wash-in week before initiating study treatment; and (6) serious medical conditions that might affect participant safety or the conduct of the trial. Individuals with a previous history of alcohol or other drug dependence were eligible provided that criteria for dependence had not been met within the last 12 months. Subjects were excluded if urine toxicology demonstrated ongoing use of nonprescribed, recreational drugs such as methamphetamine and cocaine.

Screening and baseline evaluations—Before administering study treatments, all subjects underwent comprehensive clinical and laboratory evaluations. Plasma HIV RNA (viral load; VL) was quantified by reverse transcriptase-polymerase chain reaction (Amplicor, Roche Diagnostic Systems, Indianapolis, IN) using the ultrasensitive assay (nominal lower limit of quantitation, 50 copies per ml). Blood CD4 + lymphocyte counts were measured by flow cytometry. Standard blood chemistry and hematology panels were performed. The overall severity of DSPN was characterized using the Total Neuropathy Score (TNS) (Cornblath *et al*, 1999). TNS is a validated measure, which combines information obtained from assessment of reported symptoms, physical signs, nerve conduction studies, and quantitative sensory testing. To evaluate potential cardiovascular, pulmonary, and other medical risks, we performed electrocardiogram (ECG) and chest radiography, and assessed past medical history, medication history, and conducted a focused general physical and neurological examination. Also performed were a drug use history, NP testing and an abridged Composite International Diagnostic Interview to assess for bipolar disorder, schizophrenia, recent drug or alcohol addiction, and other psychiatric exclusion criteria. Participants watched a video demonstrating the standardized smoking technique (Foltin *et al*, 1988), and each participant was observed practicing the smoking technique with a placebo cigarette.

Regulatory Issues and Study Medication

This trial was performed as an outpatient study at the General Clinical Research Center at the University of California, San Diego (UCSD) Medical Center. This study was approved and monitored by the UCSD Institutional Review Board, the Research Advisory Panel of California, the US Food and Drug Administration, the US Drug Enforcement Administration, the US Department of Health and Human Services, and the University of California Center for Medicinal Cannabis Research. Confidentiality of research participants

was protected by a federal Certificate of Confidentiality. All participants gave written informed consent to participate in this study.

All cannabis and placebo cigarettes were provided by the National Institute on Drug Abuse and were constructed of the same base material. Active strengths ranged from 1% to 8% Δ-9-THC concentration by weight. Placebo cigarettes were made from whole plant material with cannabinoids removed and were identical in appearance to active cigarettes. Cannabis was placed in an airtight container and stored in a locked, alarmed freezer at the UCSD Medical Center Investigational Drug Service Pharmacy. Cannabis was humidified at room temperature within a dessicator using a saturated sodium chloride solution for 12–24 h before use. Periodic assays for THC content were performed to confirm stability of material over time in storage. Nurses weighed material before and after smoking and returned all used and unused medication to the pharmacy Investigational Drug Service for appropriate disposal. Randomization was performed by a research pharmacist using a random number generator, and the key to study assignment was withheld from investigators until completion statistical analyses.

Cannabis Administration

On study days, participants smoked randomly assigned active or placebo cannabis under the observation of the study nurse who provided smoking cues ('inhale', 'hold', 'exhale') from an adjacent room. On day 1 of each intervention week, a dose escalation/titration protocol was employed to accommodate individual differences in sensitivity to the analgesic and adverse effects of cannabis (Figure 2). Over four smoking sessions, each participant titrated to the dose ('target dose') affording the best achievable pain relief without unacceptable adverse effects. Titration was started at 4% THC or placebo and adjusted incrementally downwards (to 2 or 1%) if side effects were intolerable, or upwards (to 6 or 8%) if pain relief was incomplete. The target dose was that providing the best analgesia whereas maintaining side effects, if any, at a tolerable level. Treatment was discontinued if side effects were intolerable despite adjusting to the minimum study dose (1%). The target dose was administered for the remaining 4 days, except that downward titration or dose withholding was available if adverse effects became intolerable.

To provide near-continuous drug effect for the duration of the 8-h study day, treatments were administered in four daily smoking sessions separated by intervals of 90–120 min. This interval was chosen based on previous studies demonstrating that the subjective 'high' after varying doses of cannabis declined to 50% of maximal effect after an average of 100 min (Harder and Rietbrock, 1997). Although the effect-time course for analgesia with cannabis may differ from the effect-time course for subjective 'highness', no formal studies of cannabis-related analgesia were available on which to base estimates of effect duration.

Outcome Measures

Outcome measures selected for this study were standardized, validated measures of multiple pain-associated constructs, including analgesia, improvement in function, and relief of pain-associated emotional distress. Details of these measures are provided below and the schedule of their administration is provided in Table 1.

Pain quality and impact. Descriptor Differential Scale—The principal evaluation of treatment efficacy was change in self-reported pain magnitude assessed by the DDS. The DDS is a ratio scale containing 24 words describing pain intensity and unpleasantness. Ratings are aggregated to provide a summary score on a 0- to 20-point scale. Participants rated their 'current' pain magnitude (at the time of assessment) relative to these descriptors. Pain intensity changes were compared from baseline to the end of each treatment week as

shown in Figure 1. The DDS demonstrates good internal consistency, reliability, objective correlation with experimentally induced pain (Gracely *et al*, 1978a,b), and sensitivity to analgesic effects on clinical pain syndromes (Gracely and Kwilosz, 1988). Participants also rated the quality and intensity of their pain experience on the McGill Pain Questionnaire (Chapman *et al*, 1985;Melzack, 1975). This included the Visual Analog Scale (VAS), a 10-cm line anchored at one end by the descriptor 'No Pain' and at the other by the words 'Worst Pain Imaginable.'

Additional clinical assessments—Table 1 specifies the schedule for additional clinical assessments. Disability, mood, and quality of life in study subjects were assessed using the Sickness Impact Profile (SIP; Gilson *et al*, 1975), the Profile of Mood States (POMS; McNair *et al*, 1992) and the Brief Symptom Inventory (BSI; Derogatis and Melisaratos, 1983). Treatment emergent effects of cannabis were assessed by clinician interview and self-report of physical and psychological symptoms as captured using a standardized inventory, the UKU Side Effect Rating Scale (Lingjaerde *et al*, 1987a,b). Also, a subjective Highness/ Sedation Scale adapted from Block *et al* (1998) was administered to assess the intensity of psychological effects commonly associated with the inhalation of cannabis. Subjects were asked to 'guess' the treatment to which they had been assigned using established procedures (Moscucci *et al*, 1987).

Safety assessements—Participants were monitored carefully before, during and after study treatments to detect clinically significant changes in blood pressure, heart rate, respiration, temperature, and HIV disease parameters including plasma VL and blood CD4 + lymphocyte counts. Additional evaluations included blood hematology and chemistry, urine dipstick toxicology for drugs of abuse, chest radiography, and ECG. Participants were instructed not to drive while on study and were provided with taxi transportation if unable to make other arrangements. Adverse drug effects were graded according to the Division of AIDS Table for Grading Severity of Adult Adverse Experiences (AACTG, 1992). For events rated Grade 2 or 1, study treatment was temporarily suspended until the event resolved. For events rated Grade 3 or 4, study treatment was permanently discontinued. In the event that treatment suspension was required more than once, the next lower dosing level was used for the remaining smoking sessions.

Concomitant nonstudy analgesics—As intractable pain was a criterion for study inclusion, subjects were permitted to continue taking concomitant analgesics such as opioids, nonsteroidal anti-inflammatory agents, and adjunctive pain medications. They were asked to maintain regular dosing during the study. However, to monitor compliance with these instructions, we recorded the average daily dose of these agents at each visit. For analytic purposes, these data were expressed as aspirin or morphine equivalents using standard conversions (AHCRP, 1992).

Statistical Analyses

Primary analyses—Baseline DDS values between the two arms were compared using the Wilcoxon's rank sum test. Prestudy power analyses indicated that a sample size of 30 individuals would yield an 80% chance ($\alpha = 0.05$) of detecting at least a 1.8 point difference between placebo-and active treatment-related changes in pain intensity as measured by DDS. The principal evaluation of treatment efficacy/tolerability in this study was the change in DDS pain intensity scores from baseline to the end of each treatment week (Figure 1) used completers only, as randomized. A conservative ITT analysis was also performed, using multiple imputation (MI) for the six subjects with incomplete data. For MI, the missing Δ values were imputed from the most unfavorable (highest) 50% of the observed

(completers) values. These comparisons used the *t*-test with the MI adjustment (Little and Rubin, 2002).

Secondary analyses were performed for study completers, except for the adverse event (AE) analysis, which included all randomized subjects. Change in average weekly VAS values between the placebo and active treatment weeks was analyzed using Wilcoxon's signed rank test (WSRT). The association between baseline pain and titrated dosing used the F-test of linear regression. The change in use of analgesics during the study was compared between placebo and active cannabis weeks using WSRT. The proportion of subjects guessing their treatment allocation was compared to a chance guess (50% correct guess) using the χ^2 onesample test for proportions.

The proportions of subjects with moderate or severe UKU symptoms possibly or probably attributable to study treatment were compared for the placebo and active cannabis weeks using the McNemar test, for each UKU side effect. Similarly, the proportions of subjects with clinically significant changes in heart rate, blood pressure, VL, and CD4 counts were compared between the two arms using the McNemar test. This test considers pairs of outcomes for the two treatment weeks and is appropriate for a crossover trial. The number of AEs (including the six dropouts) was compared between the two treatment weeks using WSRT.

RESULTS

Recruitment, Screening, and Completion of Assigned Treatments

Screening and subject disposition are summarized in the CONSORT diagram (Figure 3). Between February 2002 and November 2006, 127 subjects were screened, 34 met inclusion/exclusion criteria and 28 completed treatment with both active and placebo cannabis. Six randomized subjects failed to complete the study. As demonstrated in Table 2, completers did not differ significantly from the ITT population on demographics, medical variables, and cannabis experience. Two subjects were withdrawn for safety reasons. One cannabis-naive subject had an acute, cannabis-induced psychosis at the start of the second smoking week; unblinding revealed that he had received placebo during the first week and active cannabis during the second. A second subject developed an intractable, smoking-related cough during cannabis treatment; symptoms resolved spontaneously after smoking cessation. A third subject experienced intractable diarrhea deemed unlikely to be related to study treatments. A fourth elected to discontinue the protocol in order to fulfill an unanticipated personal commitment, and a fifth was lost to follow-up. The sixth was dropped because of a protocol-defined exclusion when urine toxicology was positive for methamphetamine.

Baseline Characteristics

Study participants were typically white (75%), high-school educated (mean 13.6, SD±2.0 years) men (100%) in their late 40s (48.8±6.8 years), who had been HIV infected for more than 5 years, and who were prescribed combination ARV therapy (93%) for advanced HIV disease. Most (72%) had been exposed to potentially neurotoxic dideoxynucleo-side reverse transcriptase inhibitors (d-drugs). Almost all (96%) had previous exposure to cannabis, generally remote (>1 year; 63%). The mean baseline TNS, reflecting symptoms, disability, neurological exam findings, and quantitative measures of peripheral nerve function, was 16 points (range, 9–34), corresponding to mild-to-moderately severe neuropathy as described previously (Cornblath *et al*, 1999). Of the 28 participants, 18 (64%) took opioid pain medications, 10 (36%) used concurrent NSAIDS, 8 (29%) used tricyclic antidepressants, and 18 (64%) used anticonvulsants. All participants continued to take concomitant analgesics and adjunctive pain-modifying medications throughout the trial.

Treatment Effects

The median (range) baseline pain as measured by DDS pain intensity scale was 11.1. (9.1, 13.7) points. During the placebo treatment week, 26 subjects (93%) titrated to a maximum nominal dose of 8% THC; the remaining two chose 6%. In comparison, during the cannabis treatment week, most subjects titrated to the 2% ($N = 9$) or 4% ($N = 10$) dose; the remainder titrated to 1% ($N = 1$), 6% ($N = 4$), and 8% ($N = 4$). Subjects with greater pain at baseline as measured by DDS chose higher nominal doses, although this association was statistically modest (linear regression $p = 0.052$, $R^2 = 0.14$).

Primary analysis—Pain reduction was significantly greater with cannabis compared to placebo (median difference in pain reduction = 3.3 DDS points; effect size = 0.60; $p = 0.016$, all completers included; Figure 4). The results were consistent for the ITT analysis ($p = 0.020$), and for the comparison based on the first week of treatment alone (median change in DDS pain = −4.1 and 0.1 for the cannabis and placebo arms, $p = 0.029$). There were no evident sequence effects: the degree of pain relief achieved with active cannabis did not differ significantly according to whether it was administered during the first or the second treatment week (mean reduction in DDS points, 4.1 *vs* 0.96; $p = 0.13$).

Additional analyses—The proportion of subjects achieving pain reduction of 30% or more was greater for the active cannabis than for the placebo cannabis week (0.46 (95%CI 0.28, 0.65) *vs* 0.18 (0.03, 0.32), $p = 0.043$). The number needed to treat (NNT) to achieve 30% pain reduction (active *vs* placebo cannabis) was 3.5 (95% CI 1.9, 20.8). In a secondary analysis of changes in reported pain as measured by the VAS, the median (range) change in pain scores from baseline was −17 (−58, 52) for cannabis as compared to −4 (−56, 28) for placebo ($p < 0.001$). As measured by the POMS, SIP, and BSI, there were similar improvements in total mood disturbance, physical disability, and quality of life for the cannabis and placebo treatments (data not shown).

Concomitant Analgesic Use

As intractable pain was a criterion for study inclusion, subjects were permitted to continue taking concomitant analgesics such as opioids, nonsteroidal anti-inflammatories and adjunctive pain medications. They were asked to maintain regular dosing during the study; however, to monitor compliance with these instructions, average daily doses of these agents were collected according to the schedule in Table 1. Concomitant opioids were used by 18 of the 28 subjects (64%). Changes from baseline in morphine equivalent doses were minimal and did not differ significantly for placebo (+ 5.8%) as compared to cannabis (+ 0.1%). Changes in DDS pain severity did not differ for those who did and did not use opioids (mean difference 0.21, 95%CI (−3.7, 4.1)). Of the 28 subjects 10 (36%) used nonopioid analgesics such as acetaminophen and NSAIDS. Changes in aspirin equivalents were minimal: 7.4% for placebo and 0.7% for active cannabis.

Preservation of Blinding

To assess preservation of the blind, subjects were asked to guess the treatment to which they were assigned at the end of dose titration (day 1) and at the end of each treatment week. After dose titration, subjects receiving placebo guessed no better than chance (5/13 (38%) incorrect *vs* 50% chance guessing), whereas those receiving cannabis rarely guessed incorrectly (1/15 (93%)). At the end of the first treatment week, subjects receiving placebo still guessed no better than chance (4/13 (31%) incorrect guesses). At the end of the first treatment week, DDS pain reduction was larger for the cannabis than placebo (median change = −4.08 *vs* 0.08, respectively). Most of the subjects crossing over to active cannabis

during their second treatment week correctly guessed their treatment assignment (12/13, 92%).

Treatment Safety and Adverse Events

Dose- and treatment-limiting AEs occurred in two subjects as described above. As assessed by the UKU and AE reports, the frequency of some nontreatment-limiting side effects was greater for cannabis than placebo. These included concentration difficulties, fatigue, sleepiness or sedation, increased duration of sleep, reduced salivation, and thirst. The combined UKU and DAIDS side effects frequency was greater with cannabis than placebo and there was a trend for moderate or severe AEs to be more frequent during active than during placebo administration. Changes in heart rate and blood pressure were asymptomatic and resolved spontaneously; none resulted in unblinding of the investigators. Increases in heart rate of 30 points or more within 30 min of a smoking session were more frequent with cannabis (13/28; 46%) than placebo (1/28; 4%). Blood pressure alterations and changes in VL and CD4 counts did not differ for cannabis and placebo.

DISCUSSION

In this randomized clinical trial, smoked cannabis at maximum tolerable dose (1–8% THC), significantly reduced neuropathic pain intensity in HIV-associated DSPN compared to placebo, when added to stable concomitant analgesics. Using verbal descriptors of pain magnitude from DDS, cannabis was associated with an average reduction of pain intensity from 'strong' to 'mild to moderate'. Also, cannabis was associated with a sizeable (46%) and significantly greater (*vs* 18% for placebo) proportion of patients who achieved what is generally considered clinically meaningful pain relief (eg ≥30% reduction in pain; Farrar *et al*, 2001). Mood disturbance, physical disability, and quality of life all improved significantly for subjects during study treatments, regardless of treatment order.

A recently published, influential review concluded that the potential medicinal benefits of cannabis, including analgesia for neuropathic pain, warranted further high quality research (Watson *et al*, 2000). We employed methodological criteria generally regarded as essential for establishing the validity of treatment outcome research in chronic pain syndromes, including rigorous specification of neurologic diagnosis, randomization and placebo control, assessment of study blinding, tracking of cointerventions, and an individualized dosing strategy designed to optimize outcomes (Deyo, 1983). The study sample is arguably representative of clinic populations of painful HIV DSPN, given the duration and stage of HIV disease, use of concurrent analgesics, as well as history of exposure to ARV agents known to be associated with painful DSPN.

This study's findings are consistent with and extend other recent research supporting the short-term efficacy of cannabis for neuropathic pain. Thus one recent, inpatient randomized clinical trial of painful DSPN noted that inhaled cannabis, in doses comparable to those in the present report, significantly reduced pain intensity (34%) compared to placebo (17%; Abrams *et al*, 2007). Our findings extend the efficacy of cannabis to individuals with intractable pain, as our cohort had substantially greater number of subjects taking concomitant analgesics (100%) than did Abrams *et al* (22%). Most of our subjects took concomitant opioid therapy and almost all took at least one other concurrent pain-modifying medication. This afforded us the opportunity to evaluate potential pharmacodynamic interactions, such as synergy with opioids, as suggested by previous investigators. We observed no interaction (positive or negative synergism) between opioids and cannabis. Two other placebo-controlled studies of neuropathic pain associated with multiple sclerosis indicated that both sublingual Δ-9-THC alone or with cannabidiol (Rog *et al*, 2005), and oral synthetic Δ-9-THC (Svendsen *et al*, 2004) significantly outperformed placebo. As regards

the pain benefits of cannabis compared to other available therapies for painful DSPN, as assessed by NNT: our results (NNT = 3.5) are equivalent to those achieved by Abrams *et al* (2007) (NNT = 3.6), are in the range of the leading anticonvulsants (lamotrigine, NNT = 5.4; gabapentin, NNT = 3.8) (Simpson *et al*, 2003; Backonja, 2002) and are superior to null results obtained for amitriptyline (Kieburtz *et al*, 1998; Shlay *et al*, 1998) and mexiletine (Kieburtz *et al*, 1998).

Blinding in this study was performed using conventional measures, which included randomization of subjects to treatment assignments known only to the study pharmacist. We expected that because the prominent psychoactive effects of cannabis would distinguish it from placebo—as is true for other potent analgesic agents such as opioids—some subjects would correctly 'guess' their treatment assignment. To evaluate preservation of the blind, we asked each subject to report his or her impression of what treatment they received at several time points during the study as previously described. Blinding was considered to be preserved when the accuracy of treatment guesses was no different from random guessing (50%). Correct guessing was related to two factors: first, whether the subject received placebo or cannabis first; and second, when during the study they were asked to make their guess. Thus among subjects randomized to receive placebo first, guessing was no better than chance through the end of the first treatment week, whereas among subjects randomized to receive cannabis first, the majority correctly guessed their treatment assignment at all time points. Furthermore, by the second treatment week, when all subjects had been given the opportunity to compare the cannabis placebo and treatments, even those randomized to receive placebo first correctly guessed their treatment assignment. These findings raise the possibility that some of the DDS pain reduction was placebo driven. To assess whether correct treatment guessing influenced treatment responses, we performed secondary analyses showing that in the placebo group during the first treatment week, when guessing was no better than chance, cannabis still provided pain relief superior to that of placebo. This finding suggests that although placebo effects were present, treatment effects were independent.

Several other potential limitations were addressed. Attrition, approximately 18%, was somewhat higher than projected, but was within the range of other trials of HIV-associated and other painful neuropathic syndromes (Kieburtz *et al*, 1998; Max *et al*, 1992; Shlay *et al*, 1998; Simpson *et al*, 2003). However, an ITT sensitivity analysis demonstrated that the superiority of cannabis was robust to reasonable assumptions about the treatment responses of the dropouts. We included subjects with DSPN related either to HIV itself or to nucleoside ARV drug exposure; a more homogeneous sample may have had a different outcome. Finally, durability of analgesia, which is of paramount concern in chronic pain syndromes, could not be assessed in this short-term study. Because DDS is a relatively complex instrument for capturing pain reports, its validity and reliability might be limited by confusion and sedation during cannabis treatment. We therefore considered a simpler pain assessment tool, VAS, which is less susceptible to confounding by neurocognitive side effects. Similar to DDS, VAS also showed superior analgesia with cannabis.

The therapeutic application of cannabis depends on palatability and safety concerns as well as efficacy. Smoking is not an optimal delivery system. Long-term use of smoked cannabis is associated with symptoms suggestive of obstructive lung disease, and although short-term use is not (Tetrault *et al*, 2007), many individuals cannot tolerate smoking. Alternative administration routes for cannabinoids, including vaporization and mucosal sprays, are currently approved for clinical use in Great Britain and Canada and are under evaluation in the United States. Cannabis has potent psychotropic effects including 'paradoxical' effects (eg depersonalization, hallucination, suspiciousness) in an important minority of individuals (Hall and Solowij, 1998). A recent meta-analysis suggested an increased risk of psychotic

illness in individuals who had ever used cannabis (Moore *et al*, 2007), although it was acknowledged that vulnerability to psychotic disorder and use of cannabis may be confounded.

Our findings suggest that cannabinoid therapy may be an effective option for pain relief in patients with medically intractable pain due to HIV-associated DSPN. As with all analgesics, dose limiting side effects should be carefully monitored, particularly during the initial trials of therapy.

Acknowledgments

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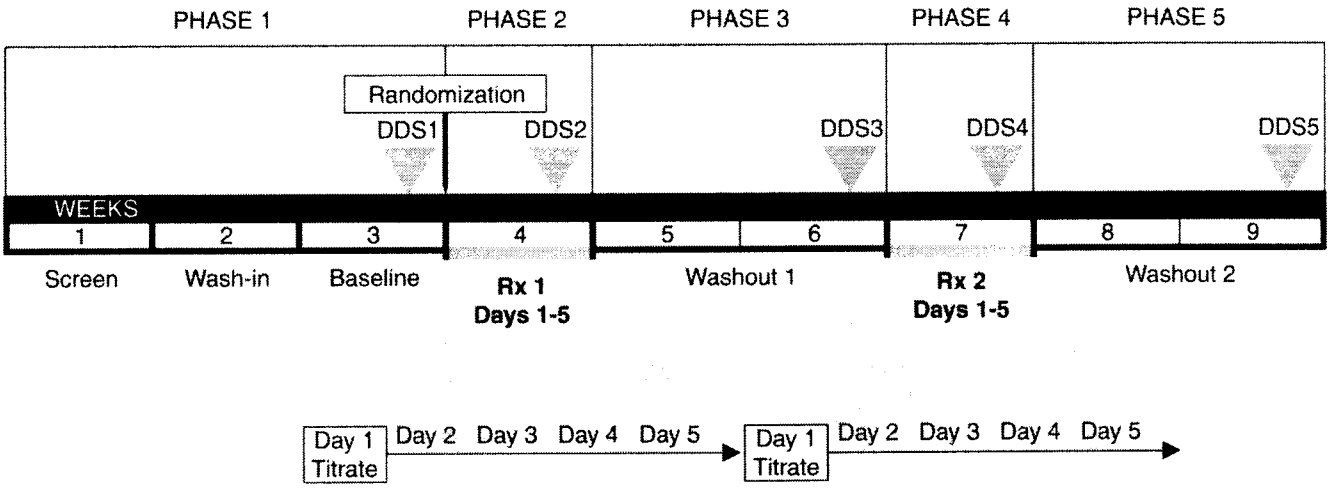

Figure 1.

Study Schema. After screening, eligible subjects were randomized to receive cannabis or placebo first (treatment week 1; Rx 1), followed by the alternative treatment (treatment week 2; Rx 2). The principal measure of pain, the Descriptor Differential Scale (DDS), was measured at five time points (DDS1–5; arrowheads). The primary outcome was the difference in DDS change from baseline (DDS1) to the end of each treatment (active or placebo) week (DDS2/4). Remaining DDS assessments (3, 5) were used in secondary analyses. During each day of the 5-day treatment week, subjects smoked cannabis or placebo cigarettes four times daily. On day 1 of each week, cannabis dose was titrated to efficacy and tolerability as described in the text. On the remaining days (2–4), subjects smoked the maximum tolerated dose achieved on day 1.

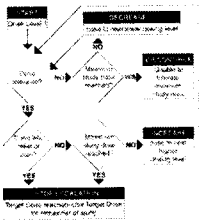

Figure 2.
Dose escalation schedule for day 1 of the study treatment weeks. See text for details. The objective of the dose escalation was to find, for each study subject, a dose of smoked cannabis that optimized pain relief, while minimizing unwanted adverse effects.

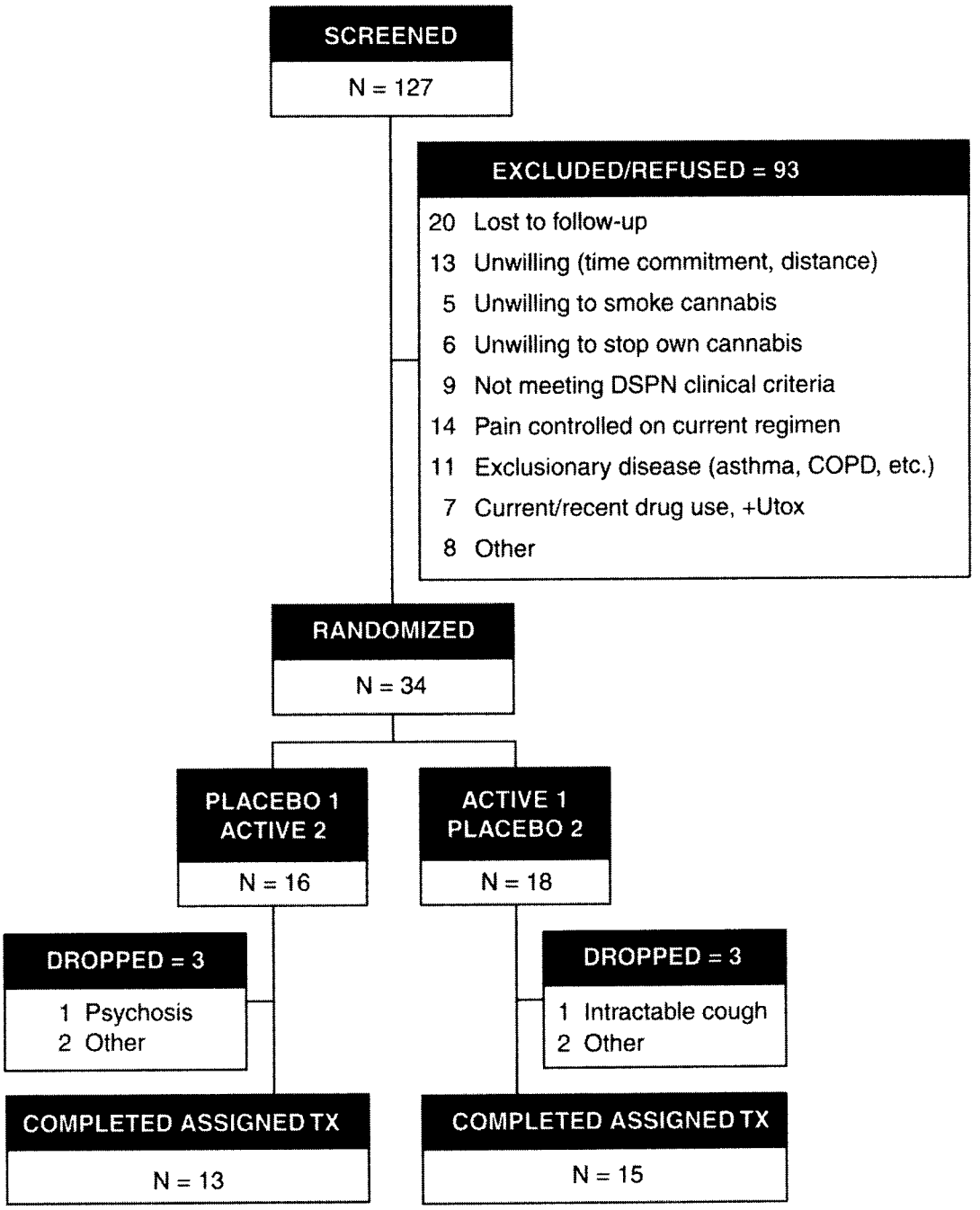

Figure 3.
CONSORT Flow Diagram. Disposition of subjects screened, randomized, and completing both treatment periods. Placebo 1, subjects randomized to receive placebo cannabis during the first treatment week; Active 1, subjects randomized to receive active cannabis during the first treatment week. DSPN, distal sensory polyneuropathy; + Utox, positive urine toxicology for substances of abuse, including cannabis.

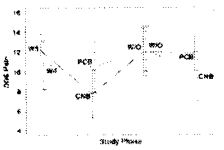

Figure 4.

Plot of treatment effect. DDS pain severity scores (mean, 95% CI) for participants in the cannabis (CNB) and placebo (PCB) arms before study treatment (W/I), during each of the 2 treatment weeks (1, 2) and during the Washout (W/O) between treatment weeks. Cannabis was superior to placebo in this crossover trial whether subjects were treated with cannabis during the first or second treatment week. The median difference in DDS pain severity change was 3.3 points ($p = 0.016$, WRT).

Table 1

Schedule of Clinical Assessments According to Study Phase

	Screen	Baseline	Rx 1	Washout	Rx 2	Washout
DDS pain	√	√[a]	√[a]	√	√[a]	√
VAS pain	√	√	√√√√√	√	√√√√√	√
Daily pain medication record						
NP testing, disability, mood and quality of life measures						
Treatment safety measures						
Chest radiograph	√					√
Blood chemistry, hematology, plasma HIV RNA		√		√		√
CD4 lymphocytes		√				√
Urine toxicology	√	√				
Blood THC quantitation[a]			√√√√√		√√√√√	
Treatment guessing (preservation of blind)			√√√		√√√	

Abbreviations: Rx, Treatment Week; DDS, Descriptor Differential Scale; VAS, Visual Analog Scale.

[a]Evaluations used in calculating the measure of primary outcome.

√√√√√ indicates daily evaluations during each treatment week.

Table 2

Baseline characteristics of all randomized subjects and completers

	All Randomized (*N* = 34)	Completed treatment (*N* = 28)
Male sex—*N* (%)	33 (97)	28 (100)
Age in years—mean (SD)	49.1 (6.9)	48.8 (6.8)
Education in years—mean (SD)	13.9 (2.3)	13.6 (2.0)
White race—*N* (%)	24 (71)	21 (75)
Hispanic ethnicity—*N* (%)	4 (12)	2 (7)
On combination ART—*N* (%)	32 (94)	26 (93)
Prior d-drug exposure—*N* (%)	21 (72)	18 (72)
Previous cannabis experience—*N* (%)	31 (91)	27 (96)
Concomitant pain-modifying agents *		
Non-narcotic analgesics—*N* (%)	12 (35)	10 (36)
Antidepressants—*N* (%)	8 (24)	8 (29)
Anticonvulsants—*N* (%)	21 (62)	18 (64)
Opioids—*N* (%)	22 (65)	18 (64)
Any pain-modifier—*N* (%)	31 (91)	25 (89)

Abbreviations: ART, antiretroviral therapy; d-drug, neurotoxic dideoxynucleoside antiretrovirals (d4T, ddI, ddC; information not available for 5 and 3 patients, respectively).

* Information not provided by one subject.

Appendix B (Section H)

Expert Opinion on Pharmacotherapy

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Sativex®: clinical efficacy and tolerability in the treatment of symptoms of multiple sclerosis and neuropathic pain

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Expert Opinion

Sativex®: clinical efficacy and tolerability in the treatment of symptoms of multiple sclerosis and neuropathic pain

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Sativex® is one of the first cannabis-based medicines to undergo conventional clinical development and to be approved as a prescription medicine. It is an oromucosal spray that allows flexible, individualised dosing. Patients self titrate their overall dose and pattern of dosing according to their response to and tolerance of the medicine. This usually results in the administration of ~ 8 – 12 sprays/day. Each spray delivers tetrahydrocannabinol 2.7 mg and cannabidiol 2.5 mg, giving an approximate average dose of tetrahydrocannabinol 22 – 32 mg/day and cannabidiol 20 – 30 mg/day. Development has concentrated on the treatment of symptoms of multiple sclerosis, notably spasticity and neuropathic pain, as well as the treatment of neuropathic pain of other aetiologies. Positive results in placebo-controlled trials of the use of Sativex as an add-on therapy in these indications demonstrate that Sativex is efficacious and well tolerated in the treatment of these symptoms. Sativex has been approved for use in neuropathic pain due to multiple sclerosis in Canada. If ongoing studies replicate the results already observed, further approvals for the treatment of spasticity in multiple sclerosis and for neuropathic pain are likely.

Keywords: cannabis, multiple sclerosis, neuropathic pain, Sativex®, spasticity

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1. Introduction

This paper discusses the efficacy and tolerability of the cannabis-based medicine, Sativex®. It is not intended to be a review of cannabis in general, but seeks only to consider the potential role of Sativex in the management of multiple sclerosis (MS) and neuropathic pain.

1.1 Multiple sclerosis

MS is an intractable neurological condition of unknown aetiology. There has been wide debate regarding the cause of MS, and the general consensus is that the disease is caused by a combination of genetic predisposition and an unknown environmental trigger. In recent years, a number of disease-modifying drugs have been licensed. There is evidence that these drugs slow down disease progression and reduce the frequency of relapses [1]. However, despite this advance, the disease is still characterised by slow progression, and there remains a need for further and better medication with regard to control or alleviation of a wide variety of disabling symptoms.

There is a well-known geographical variation in the prevalence of MS – being more common in northern latitudes and relatively unknown in the tropics. The prevalence is, at least in northern Europe, ~ 120/100,000 population and, thus, there are considerable numbers of people with a wide range of disabling and

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distressing symptoms. The most common symptoms include spasticity (increasing muscle tone resulting in stiffness and impaired movement), muscle spasms (involuntary, and often painful, muscle contractions), tremor, poor bladder and bowel control, neuropathic pain, dysarthria (slurred speech) and a variety of cognitive and intellectual problems, including memory disturbance [2]. The ability to control these symptoms varies considerably, and existing medication is limited in efficacy and carries a considerable range of undesirable side effects. There is no doubt that better symptomatic treatment is needed for many of the symptoms associated with MS.

1.2 Neuropathic pain

Neuropathic pain, defined as pain initiated or caused by a primary lesion or dysfunction in the nervous system, is present in up to 1% of the population. It is often accompanied by symptoms such as sensory deficits and positive sensory phenomena, such as dysaesthesia, allodynia, hyperalgesia and paraesthesia, and may be associated with mood changes, sleep disturbance and fatigue. Neuropathic pain is one of the most difficult types of pain to treat. Treatment of neuropathic pain with tricyclic antidepressants, serotonin and noradrenaline uptake inhibitors and anticonvulsants is of limited efficacy, and is often associated with undesirable adverse events [3]. There is a need for further efficacious neuralgic analgesic agents that are associated with less troublesome side effect profiles.

From the early studies outlined below, Sativex would seem to be useful for both spasticity and neuropathic pain. It is well tolerated and, overall, seems to have a useful, and potentially important, place in the management of these two distressing symptoms.

2. Pharmacology

2.1 Cannabinoid receptors

Although the history of human cannabis use goes back > 5000 years, the endogenous cannabinoid system was discovered little more than a decade ago. Two distinct cannabinoid receptors CB_1 and CB_2, have been characterised by the use of specific agonists and antagonists and each has been cloned. In addition, two endogenous ligands, arachidonoyl ethanolamide (anandamide) and 2-arachidonoyl glycerol, have been investigated, although a recent review article [4] reported that three other endogenous ligands for cannabinoid receptors have been discovered, but have not been fully investigated. It is likely that other subtypes of cannabinoid receptors also exist and the decision of Howlett *et al.* [4] not, at this time, to name cannabinoid receptors in terms of endogenous ligands, is likely to prove to be wise.

Both the CB_1 and CB_2 receptors are coupled through the $G_{i/o}$ protein, negatively to adenylyl cyclase and positively to mitogen-activated protein kinase [4,5]. The CB_1 receptor is also coupled through a G protein to certain types of calcium and potassium channel. CB_1 receptors are present in the CNS and also in some peripheral tissues, including immune cells, reproductive tissues, gastrointestinal tissues, sympathetic ganglia, heart, lung, urinary bladder and adrenal gland. Central and peripheral neuronal CB_1 receptors are found mainly at nerve terminals, and one function of these receptors is to inhibit neurotransmitter release. CB_2 receptors are present primarily on peripheral and central immune cells. Their roles are proving more difficult to establish, but seem to include the modulation of cytokine release. Therefore, whilst the CB_1 receptor has a neuromodulatory role, the CB_2 receptor seems to be immunomodulatory.

Within the CNS, the distribution of CB_1 receptors is heterogeneous, accounting for several well-documented pharmacological properties of CB_1 receptor agonists. For example, the cerebral cortex, hippocampus, lateral caudate-putamen, substantia nigra pars reticulata, globus pallidus, entopeduncular nucleus and the molecular layer of the cerebellum are all populated with particularly high concentrations of CB_1 receptors, consistent with the well-documented motor and psychoactive effects of cannabis. In addition, CB_1 receptors are found on pain pathways in the brain and spinal cord [6] and also outside the CNS at the peripheral terminals of primary afferent neurons, and it is these CB_1 receptors that are thought to mediate the pain-relieving effects of cannabis.

2.2 Sativex

Sativex is a cannabis-based medicinal product containing a defined quantity of specific cannabinoids [7]. It contains tetrahydrocannabinol (THC) and cannabidiol (CBD) extracts of *Cannabis sativa L.* equivalent to THC 27 mg/ml and CBD 25 mg/ml. Tetranabinex® (THC Botanical Drug Substance [BDS]) contains THC ≥ 60% w/w. Nabidiolex® (CBD BDS) contains ≥ CBD 55% w/w. Each BDS contains other cannabinoids and components typically found in plant extracts, such as alkanes, triglycerides, waxes, nitrogenous compounds, amino acids, sugars, aldehydes, alcohols and ketones, flavonoids, glycosides, vitamins, pigments and terpenes [8,9].

GW Pharmaceuticals have developed chemovars of *Cannabis sativa* that produce either principally tetrahydrocannabinolic acid (THCA) plus THC (as > 90% of the total cannabinoid present) or cannabidiolic acid (CBDA) and CBD (as > 85% of the total cannabinoid present) [10]. THCA and CBDA decarboxylate naturally to THC and CBD, a process that can be accelerated by heating. On reaching maturity the plants are harvested and, following decarboxylation, the dried plant material is extracted and partially purified to yield the finished extract – the BDS. The finished dosage form contains a blend of THC BDS and CBD BDS, along with the pharmaceutical excipients ethanol, propylene glycol and peppermint oil.

Use of illegal cannabis by people with MS or pain is well established [11] and has been widely publicised in the lay press. As a result of this anecdotal evidence and some pioneering early clinical research, there is encouraging support for the safety and

efficacy of cannabis in a range of medical conditions [12]. However, cannabis obtained illegally is variable in cannabinoid content and contains numerous impurities [13]. In addition, the most commonly used pulmonary route of administration of illegal cannabis is likely to be associated with unwanted morbidity [14]. Therefore, the potential exists for a modern cannabis-based medicine, which could produce considerable beneficial effects in certain patient groups [15]. In order for cannabis-based medicine to be made available as a therapeutic medicine, it is necessary to demonstrate that it is safe and has useful therapeutic properties.

Sativex was developed to address this need. Plant extracts have potential advantages over single synthetic cannabinoids, as other plant components are known to have therapeutic or synergistic activity. McPartland and Russo [8] reviewed the literature concerning the medical uses of cannabis and THC. They concluded '*that there is good evidence to show that secondary compounds in cannabis may enhance the beneficial effects of THC. Other cannabinoid and non-cannabinoid compounds in herbal cannabis or its extracts may reduce THC-induced anxiety, cholinergic deficits and immunosuppression. Cannabis terpenoids and flavonoids may also increase cerebral blood flow, enhance cortical activity, kill respiratory pathogens and provide anti-inflammatory activity*' [8].

The principal pharmacological effects of THC include analgesia, muscle relaxation, antiemesis and appetite stimulation, and it has psychoactive effects [16]. CBD has analgesic, anticonvulsant, muscle relaxant, anxiolytic, neuroprotective, antioxidant and antipsychotic activity [17].

The therapeutic dose of THC is highly variable between patients, and, therefore, it is important that the patient can accurately control their dose to get an adequate therapeutic response whilst avoiding intolerable side effects. The oromucosal route of administration allows self-titration by delivering small variable doses and is a convenient and accessible route of delivery that enables patients to take medication frequently throughout the day while maintaining a normal lifestyle.

The pharmacokinetic parameters of Sativex following a single dose administration of Sativex to healthy volunteers is given in **Table 1**.

The metabolism of THC and CBD has not been studied for Sativex, as this has been previously well described [18-20]. THC is very rapidly metabolised by human liver enzymes. The human hepatic CYP2C9 isozyme catalyses the formation of 11-OH-THC, the primary metabolite, which is further metabolised by the liver to other compounds, including 11-nor-carboxy-E^9-THC (THC-COOH), the most abundant metabolite in human plasma and urine. The CYP3A subfamily catalyse the formation of other hydroxylated minor metabolites. After 72 h from intravenous administration, the urinary excretion of THC metabolites in both sexes was 13 – 17%, and 25 – 30% in faeces, of the total dose. After oral administration, the faecal excretion was 48 – 53%. The major metabolite was found to be 11-OH-E^9-THC, which is mainly excreted unchanged in faeces, and as acidic conjugates in urine. Demographic, body type and drug history variables had little effect on the excretion pattern [21]. It is worth noting that the metabolites accumulate in lipid stores and are released slowly over some weeks.

CBD is extensively metabolised, and > 33 metabolites have been identified in urine. The major metabolic route is hydroxylation and oxidation at C-7, followed by further hydroxylation in the pentyl and propenyl groups. The major oxidised metabolite is CBD-7-oic acid containing a hydroxyethyl side chain [22]. Studies examining the interaction of cannabis and THC with other pharmacological agents have not been extensive. However, *in vitro* studies indicate that THC and, to a greater extent CBD, may both inhibit hepatic microsomal CYP activity, specifically CYP2C19 and CYP3A4 isozymes (**Table 2**). However, studies undertaken by GW Pharma have indicated a low probability of clinically important interaction at normal clinical doses of Sativex.

CBD was generally more inhibitory than THC, with the exception of CYP2C9, and, in particular, could be considered a relatively potent inhibitor of CYP2C19 and CYP3A4 (inhibitory concentration of 50% [IC_{50}] ≤ 10 μM). Furthermore, there was an increase in inhibition of CYP2C9 and CYP2D6 by the 1:1 (% [v/v]) mixture compared with the single extracts. It was concluded that THC was a relatively weak inhibitor of CYP3A4 and a weak inhibitor of CYP1A2, CYP2C9 and CYP2C19, but not an inhibitor of CYP2D6.

CBD is an inhibitor of CYP2C19 and CYP3A4 activity and a relatively weak inhibitor of CYP1A2, CYP2C9 and CYP2D6.

Based purely upon the IC_{50}, values it is possible to conclude that CBD might contribute to, or participate in, CYP-derived inhibitory drug–drug interactions *in vivo*.

However, comparison of the IC_{50} and C_{max} values after dosing with Sativex show large differences in concentrations. The lowest IC_{50} value *in vitro* (~ 1.9 μg/ml) is significantly greater than mean C_{max} following dosing with Sativex 10 mg in clinical studies (< 7 ng/ml for THC and lower for CBD). It is also considerably greater than the highest C_{max} (THC, 24 ng/ml) following Sativex (Study GWPK0215, GW Pharmaceuticals, unpublished data) or the highest C_{max} (CBD, 16.97 ng/ml; THC, 33.63 ng/ml) recorded during an assessment of plasma concentrations during chronic stable dosing with Sativex in a long-term study (GWMS0001 extension study, GW Pharmaceuticals, unpublished data).

Therefore, based upon plasma concentrations, it would seem that the probability of clinically important interaction at normal clinical doses of Sativex is small.

3. Clinical efficacy

Sativex has been investigated in seven placebo-controlled studies. These trials have been carried out in people with MS and other neurological conditions resulting in pain and/or other symptoms including spasticity, spasm, tremor and bladder problems. In all trials, Sativex or placebo was administered as an add-on treatment to existing medications and, at their

Table 1. Pharmacokinetic parameters of Sativex following single-dose administration to healthy volunteers.

Mean pharmacokinetic parameters	t_{max} (min)	C_{max} (ng/ml)	$t_{½}$ (min)	AUC_{0-t} (min•ng/ml)	$AUC_{0-\infty}$ (min•ng/ml)
CBD	253	3.33	108.72	680.61	718.46
THC	263	4.90	84.23	894.80	918.81
11-Hydroxy THC	230	4.49	130.11	1423.20	1463.67

$AUC_{0-\infty}$: Area under concentation-time curve from 0 to infinity; AUC_{0-t}: Area under data points; CBD: Cannabidiol; THC: Tetrahydrocannabinol.

Table 2. Inhibitory concentrations of cannabidiol, tetrahydrocannabinol and a 1:1 mixture (% [v/v]) on CYP activity *in vitro*.

Extract	CYP1A2	CYP2C9	CYP2C19	CYP2D6	CYP3A4
THC (μM)	40	44	34	100	26
THC (ng/ml)	12578.80	13836.68	10691.98	31447.00	8176.22
CBD (μM)	14	72	9	84	7
CBD (ng/ml)	4402.58	22641.84	2830.23	26415.48	2201.29
THC/CBD (μM)	12	20	7	38	6
THC/CBD (ng/ml)	3773.64	6289.40	2201.29	11949.86	1886.82

CBD: Cannabidiol; THC: Tetrahydrocannabinol.

conclusion, all patients were given the option to continue into long-term, open-label extension studies. Although patients were allowed to take up to 48 actuations (sprays)/day, the median number of actuations following a 1 – 2 week titration period, varied between 10 and 15 in all studies. This equates to THC 27 – 41 mg/day and CBD 25 – 38 mg/day.

3.1 Relief of neuropathic pain in multiple sclerosis

The principle evidence for the use of Sativex in the relief of neuropathic pain due to MS is derived from two studies performed by GW Pharmaceuticals.

The first study included 66 randomised patients with a clinical diagnosis of MS and central neuropathic pain. The patients entered a 7- to 10-day baseline period, followed by a 4-week randomised, parallel group comparison of Sativex with placebo. Dosing was self-titrated up to symptom resolution or maximum tolerated dose. The primary efficacy measure was the severity of pain as measured by the 11-point numerical rating scale (NRS), and the difference between Sativex and placebo was evaluated by analysis of covariance with baseline severity as a covariate.

In this study, the primary efficacy measure was statistically significant in favour of Sativex, with an estimated treatment difference of 1.25 NRS units in favour of the drug over placebo (95% CI, -2.11 to -0.39; p = 0.005).

The main secondary efficacy measure, the neuropathic pain scale (NPS), was also statistically significant in favour of Sativex over placebo, with an estimated treatment difference of 6.59 in favour of the drug (p = 0.044).

The actual level of pain relief achieved with Sativex, using the primary efficacy end point of the NRS score, represented a 41% improvement over baseline and almost a 20% improvement over placebo. These improvements were observed in patients who were already maintained on a stable regimen of their existing analgesic medication, and thus improvements were over and above the best possible pain relief that the patients had previously been able to obtain with currently available therapies. Benefits of this magnitude against a background of the best available analgesic medication are clinically significant.

A responder analysis was conducted to assess the number of patients experiencing substantial improvements in their level of neuropathic pain. This analysis separates the groups according to the number of patients experiencing various levels of pain relief. The analysis also allows for the calculation of the numbers of patients requiring treatment before each level of pain relief is experienced. The results of this analysis are presented in **Table 3**. This table shows that many more patients treated with Sativex achieved a 1-, 2- or 3-point improvement in pain score than patients treated with placebo. Statistical analysis yields statistically significant outcomes in favour of Sativex at all three thresholds tested.

The second GW study (GWPS0105, GW Pharmaceuticals, unpublished data) was a multi-centre, randomised, double-blind, placebo-controlled parallel group comparison of the effects of Sativex over 3 weeks in patients with chronic refractory pain due to MS or other defects of neurological function. The primary objective of the study was to compare Sativex with placebo in the relief of chronic refractory pain of

neurological origin. A total of 70 patients were randomised into the study, of whom 43 (61%) had MS.

The primary outcome measure for this study was the pain score using the 11-point NRS (the same measure as was used in Study GWMS0107). In this study, analgesic escape medication was allowed and recorded daily. Use of escape medication could confound the interpretation of the primary efficacy variable (the extent of pain relief recorded by the patient). However, assessment of pain relief, based on the level of use of escape medication (one of the secondary variables in the study), is informative.

During the double-blind phase of this study, patients on Sativex used escape medication on a median of 4.8% of the study days, whereas patients randomised to placebo took escape medication on a median of 45% of the study days. This difference was statistically significant ($p = 0.006$). It is noteworthy that even though the patients treated with Sativex were taking escape medication on significantly fewer days than patients randomised to placebo, nonetheless, they still reported a greater degree of pain relief.

3.2 Relief of spasticity due to multiple sclerosis

The principle evidence for the use of Sativex in relieving spasticity due to MS comes from two studies performed by GW Pharmaceuticals (GW Pharmacueticals, unpublished data).

The first was a double-blind, placebo-controlled trial that examined the effect of Sativex in any of five patient-defined primary symptoms of MS (pain, spasticity, spasm, bladder symptoms and tremor) [23]. All symptoms were assessed using a 100 mm visual analogue scale (VAS).

In the subgroup of patients who considered spasticity to be their primary symptom of MS ($n = 39$), the adjusted mean difference in VAS score between Sativex and placebo groups after 6 weeks (the end of the double-blind period) was 22.8 mm. This result was highly statistically significant ($p = 0.001$). Several comparisons were made in this study. However, the spasticity result remained statistically significant despite an adjustment for multiplicity of comparisons (Bonferroni correction for 11 tests; $p = 0.011$).

The second study (GWMS0106, GW Pharmaceuticals, unpublished data) was a more comprehensive 6-week parallel group, randomised, double-blind, multi-centre study of the use of Sativex compared with placebo in the alleviation of spasticity in MS patients.

Patients with stable MS for ≥ 3 months, on a stable regimen of concomitant medication and whose spasticity was not adequately relieved by current therapy, were eligible for inclusion.

The inclusion criteria specified significant spasticity in at least two muscle groups, defined as a score ≥ 2 on the Ashworth Scale, and it was originally intended that this scale would also serve as the primary end point. However, during the progress of the trial, but before the blinding was broken, further studies were produced that indicated that the Ashworth scale was a poor measure of treatment effect in spasticity [24]. There is now little doubt that the Ashworth scale is not a good measure of spasticity and this has been confirmed by the author's group [25,26]. The company changed the primary end point to the difference from baseline to end-of-study on a NRS for spasticity. This was assessed by taking the mean of 7 days of diary entries made by the patient. At the end of treatment, a statistically significant difference of 0.52 (95% CI, -1.029 to -0.004; $p = 0.048$) was observed. Other secondary end points were also statistically significant. Although the Ashworth scale showed a trend to improvement in the Sativex group, such change was not statistically significant.

3.3 Relief of neuropathic pain of multiple aetiology

GW Pharmaceuticals performed a further study (GWNP0101, GW Pharmaceuticals, data on file) in neuropathic pain of peripheral original and mechanical allodynia. This study was a 5-week, double-blind, randomised, placebo-controlled, parallel design trial involving 125 patients with chronic (> 6 months) pain. As in the other Sativex studies in pain, the patients were allowed to remain on their stable analgesic regime.

Treatment with Sativex resulted in an observed mean decrease on the 11-point NRS of 1.57 points (21.6%) compared with 0.59 points (8.2%) for the placebo group, representing an estimated treatment difference of 0.98 (95% CI, 0.32 – 1.59; $p = 0.004$).

For the secondary efficacy measures of NPS composite score ($p = 0.007$), sleep NRS ($p = 0.001$), dynamic allodynia ($p = 0.042$), static allodynia ($p = 0.021$), Pain Disability Index ($p = 0.003$) and Patient's Global Impression of Change ($p = 0.001$), Sativex was also was superior to placebo.

3.4 Improvement in sleep quality in multiple sclerosis and neuropathic pain of multiple aetiologies

Sleep quality is a major problem for many MS patients. The most relevant data on the use of Sativex to improve sleep parameters comes from the MS studies outlined above. In GWMS0107, sleep disturbance due to pain resulting from MS was investigated using a NRS scale. The results showed a treatment difference of 1.39 boxes in favour of Sativex over placebo. This result was statistically significant ($p = 0.003$). This study has now been published in the peer-reviewed literature [27].

Study GWMS0001 comprised a 6-week, randomised, double-blind phase in which patients received either Sativex or placebo (Part 1 of the study), followed by a 4-week, open-label assessment of Sativex (Part 2). In each part of the study sleep was evaluated using a questionnaire that evaluated quality of sleep, quantity of sleep and feeling on waking.

In Part 1, assessment of the sleep quality subscore of the sleep questionnaire was statistically significant in favour of Sativex ($p = 0.047$). Data for quantity of sleep and feeling on waking were not statistically significant, although the Sativex group fared better than the placebo group in each case. Comparisons of sleep questionnaire subscores recorded at the end of Part 2 were statistically significant compared with those of

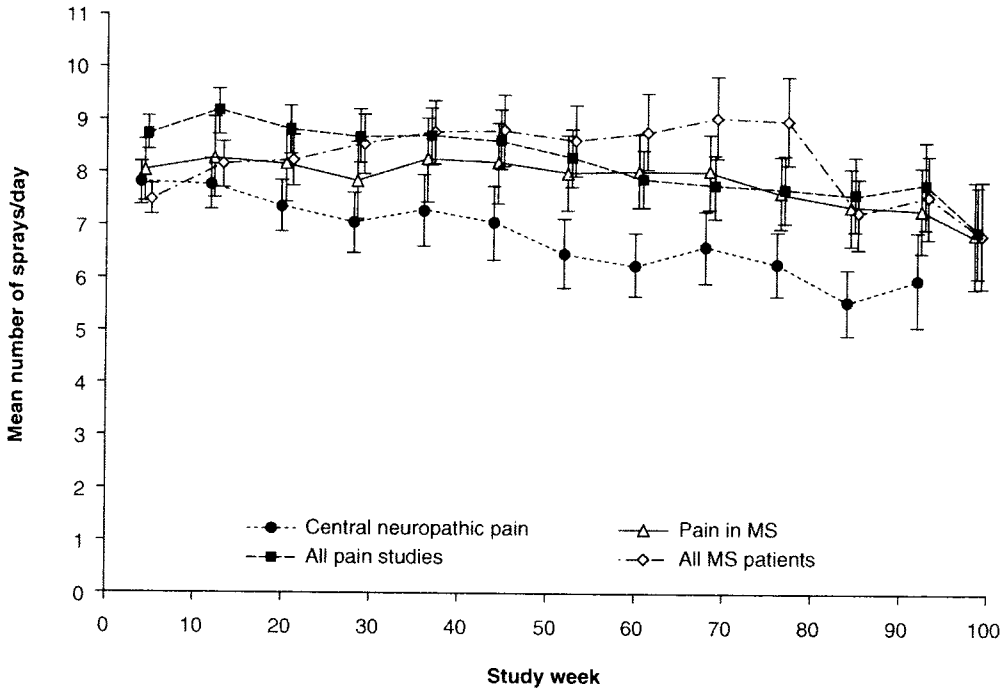

Figure 1. Mean daily number of sprays over time in long-term extension studies of Sativex in both pain and multiple sclerosis.
MS: Multiple sclerosis.

placebo-treated patients in Part 1 (these patients switched to Sativex for Part 2) ($p = 0.004$ for sleep quality; $p = 0.05$ for quantity of sleep; and $p = 0.003$ for feeling on waking).

Therefore, four of the six analyses of sleep parameters in the two studies exclusively involving MS patients showed a statistically significant benefit for Sativex with the remaining two parameters showing a favourable trend.

The effect of Sativex on sleep was also investigated in the pain studies outlined above. In all cases, the effect on sleep was significantly superior to placebo although the effect was assessed on different scales.

In a sleep laboratory study, there was no evidence that either THC or CBD significantly altered sleep architecture [28]. Therefore, it seems likely that the beneficial effect on sleep observed in clinical studies is more explicable in terms of nocturnal symptom relief rather than a primary hypnotic effect.

4. Long-term treatment

An extension study to investigate long-term therapy with Sativex (GWEXT0102, GW Pharmaceuticals, unpublished data) has been conducted. The results of this study have confirmed that the reduction of pain and spasticity scores seen in the acute studies is maintained over ≥ 6 months. In addition, the number of withdrawals from the long-term study due to lack of efficacy was very low. However, although this is useful early evidence that the effect of Sativex is maintained in the longer term, more studies are clearly required in order to document the longer-term effects and sustainability in more detail.

The extension studies also demonstrated an absence of the development of tolerance to Sativex as the level of dosing was maintained. **Figure 1** illustrates this point.

This figure demonstrates the number of actuations/day of Sativex; there is no increase over time. Analysis of concomitant medication in these studies also demonstrated that there was no increased use of other pain relieving medication over the follow-up period. Once again, this is useful early information regarding the long-term efficacy of Sativex, but further studies are clearly required.

5. Safety

Table 3 illustrates reported adverse events that have a possible causal relationship to Sativex occurring at a level > 3% in any of the studies by GW Pharmaceuticals.

Adverse events that could be associated with the route of administration of the medicine have been reported. Application-site-type reactions consist mainly of mild-to-moderate stinging at the time of application. However, ulceration and oral leukoplakia have rarely been observed. In view of this, subjects who observe discomfort at the site of application of the medicine have been advised to vary the site of application within the mouth and not to continue spraying onto sore or

Table 3. Undesirable effects occurring at ≥ 3% in acute and/or extension studies.

	Extension studies: all subjects (n = 644)		Acute studies: sativex (n = 353)		Acute studies: placebo (n = 289)	
	n	%	n	%	n	%
Diarrhoea	60	9.3	13	3.7	5	1.7
Dry mouth	49	7.6	35	9.9	9	3.1
Glossodynia*	31	4.8	5	1.4	4	1.4
Mouth ulceration*	30	4.7	6	1.7	1	0.3
Nausea	77	12.0	36	10.2	19	6.6
Oral discomfort*	12	1.9	12	3.4	14	4.8
Oral mucosal disorder*	22	3.4	1	0.3	1	0.3
Oral pain*	46	7.1	18	5.1	20	6.9
Tooth discolouration*	25	3.9	1	0.3	1	0.3
Vomiting	36	5.6	9	2.5	4	1.4
General disorders and administration site conditions						
Application site pain*	29	4.5	17	4.8	15	5.2
Fatigue	57	8.9	43	12.2	15	5.2
Feeling drunk	25	3.9	19	5.4	2	0.7
Lethargy	22	3.4	8	2.3	2	0.7
Weakness	22	3.4	8	2.3	2	0.7
Nervous system disorders						
Balance impaired	24	3.7	8	2.3	2	0.7
Disturbance in attention	23	3.6	17	4.8	0	0.0
Dizziness	158	24.5	127	36	35	12.1
Dysgeusia*	49	7.6	13	3.7	5	1.7
Memory impairment	22	3.4	3	0.8	0	0.0
Somnolence	48	7.5	24	6.8	7	2.4
Psychiatric disorders						
Disorientation	14	2.2	13	3.7	1	0.3
Euphoric mood	23	3.6	15	4.2	3	1.0

*Possible application site reactions.

inflamed mucus membrane. Regular inspection of the oral mucosa has also been advised in long-term administration. If lesions or persistent soreness are observed then medication should be interrupted until the problem has resolved.

There have been two serious reports of oral leukoplakia. In both cases, the diagnosis was made on clinical grounds, with smear cytology results that were consistent with leukoplakia. Only one subject underwent a formal biopsy, which reported no sign of leukoplakia. One other case of leukoplakia has been reported and is currently under investigation.

Oral leukoplakia is seen in the general population and the incidence is increased in cigarette smokers, and further increased in female smokers. It is also seen in chewing tobacco and smoke-free tobacco users. Oral leukoplakia has been seen in cannabis users. However, this has only been documented in cannabis smokers, who are also tobacco users.

Certain adverse events reported are recognised as CNS effects associated with the use of Sativex. In general, these events would be expected to resolve rapidly if doses are withheld and can usually be avoided or minimised thereafter by careful reduction of dosing.

Small increases in pulse rate and small decreases in blood pressure and postural hypotension have been observed following initial dose introduction so caution during initial dose titration is essential. Fainting episodes have been observed with use of Sativex.

Psychiatric symptoms such as anxiety, confusion or disorientation, illusions or hallucinations, changes in mood, and paranoid ideas have been reported during treatment with Sativex. These are likely to be the result of intoxication type reaction and are generally mild-to-moderate in severity and well tolerated. They can be expected to remit on reduction or interruption of Sativex medication.

The recent study by Rog *et al.* [27] showed some minor cognitive side effects particularly with regard to memory.

6. Expert opinion and conclusions

Cannabis has been used historically for many decades, but in more recent years has been designated as an illegal substance in most countries. This is a pity, as the historical, and largely anecdotal, evidence has long indicated the efficacy of cannabis, particularly for the relief of pain and muscle spasms. The illegality of the compound has clearly prevented the development of proper trials and the development of an efficacious and safe product. It is encouraging that Canadian authorities have now licensed one form of cannabis (Sativex) for use in neuropathic pain. So far the UK licensing authorities have refused a licence on the grounds that further evidence is needed with regard to efficacy, although the authorities were satisfied on safety grounds. The UK authorities were particularly anxious that the company had used a patient reported outcome measure in their spasticity studies and the so-called objective measure (Ashworth scale) did not achieve statistical significance. This is a surprising conclusion given that there is no reliable and valid objective measure of spasticity and the experience of spasticity, and more particularly pain, has by their very nature to be subjective. The studies performed by GW Pharmaceuticals in neuropathic pain and spasticity in MS have been encouragingly positive with regard to the assessment of symptoms on subjective reported scales – mainly Numerical Rating Scales. Obviously the overall evidence of the efficacy of Sativex is based on a few studies conducted by a single company and further confirmatory evidence is obviously needed in the coming years. However, these early studies have involved significant numbers of patients and the results have been positive with regard to relief of spasticity and relief of pain. In particular, the drug has been found to be safe and well tolerated, both in the short- and long-term. Current therapeutic possibilities with regard to the management of neuropathic pain and spasticity are strictly limited. A range of neuralgic analgesic medication exists, and clinicians also have a range of oral medication for the relief of spasticity. However, all of these drugs have a significant range of side effects that often limit and reduce tolerability, particularly in those people who already have a significant range of disabling symptoms. For example, oral medication for spasticity, includes baclofen, dantrolene sodium and tizanidine. Although all of these agents have definite antispastic effects, the dosage required often induces troublesome muscle weakness and fatigability, which further disables an individual who often has these symptoms as part of the underlying disease process. Local injection techniques are available, particularly the use of botulinum toxin for the management of spasticity. However, botulinum toxin is not uniformly available and often only used in specialist centres. It is also expensive and thus, its use is limited, particularly in the developing world.

Therefore, in both neuropathic pain and spasticity there is a clear need for an efficacious agent that is well tolerated, with a minimal range of side effects. These early studies demonstrate that Sativex may fulfil this role. The studies have demonstrated its safety, efficacy and tolerability. It represents a potentially significant advance in the management of these troublesome symptoms.

Conflict of interest

The author acknowledges the assistance of GW Pharmaceuticals with regard to access to clinical trial data. Many of the GW Pharmaceuticals studies have not yet been published in the peer-reviewed literature. Further details are available from the company at GW Pharmaceuticals PLC, Alexander House, Forehill, Ely, Cambridgeshire, CB7 4ZA, UK.

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Appendix B (Section H)

HIGH LIGHT

Cannabis in painful HIV-associated sensory neuropathy

A randomized placebo-controlled trial

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Abstract—*Objective:* To determine the effect of smoked cannabis on the neuropathic pain of HIV-associated sensory neuropathy and an experimental pain model. *Methods:* Prospective randomized placebo-controlled trial conducted in the inpatient General Clinical Research Center between May 2003 and May 2005 involving adults with painful HIV-associated sensory neuropathy. Patients were randomly assigned to smoke either cannabis (3.56% tetrahydrocannabinol) or identical placebo cigarettes with the cannabinoids extracted three times daily for 5 days. Primary outcome measures included ratings of chronic pain and the percentage achieving >30% reduction in pain intensity. Acute analgesic and anti-hyperalgesic effects of smoked cannabis were assessed using a cutaneous heat stimulation procedure and the heat/capsaicin sensitization model. *Results:* Fifty patients completed the entire trial. Smoked cannabis reduced daily pain by 34% (median reduction; IQR = −71, −16) vs 17% (IQR = −29, 8) with placebo ($p = 0.03$). Greater than 30% reduction in pain was reported by 52% in the cannabis group and by 24% in the placebo group ($p = 0.04$). The first cannabis cigarette reduced chronic pain by a median of 72% vs 15% with placebo ($p < 0.001$). Cannabis reduced experimentally induced hyperalgesia to both brush and von Frey hair stimuli ($p \leq 0.05$) but appeared to have little effect on the painfulness of noxious heat stimulation. No serious adverse events were reported. *Conclusion:* Smoked cannabis was well tolerated and effectively relieved chronic neuropathic pain from HIV-associated sensory neuropathy. The findings are comparable to oral drugs used for chronic neuropathic pain.

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HIV-associated sensory neuropathy (HIV-SN) is the most common peripheral nerve disorder complicating HIV-1 (HIV) infection.[1-3] The dominant symptom in HIV-SN is pain, most often described as "aching," "painful numbness," or "burning." Hyperalgesia and allodynia are common, while weakness is rare and usually confined to the intrinsic foot muscles.

Anticonvulsant drugs have been shown to be effective, specifically lamotrigine and gabapentin, but some patients fail to respond or cannot tolerate these agents.[4,5] Adverse drug-drug interactions with antiretrovirals limit the utility of other antiepileptic drugs used for neuropathic pain, such as carbamazepine.[6] Peptide T, mexiletine, acupuncture, and capsaicin cream were no more effective than placebo in relieving pain from HIV-SN.[7-11] Similarly, tricyclic antidepressants also were no more beneficial than placebo in relieving pain in controlled trials for HIV-SN.[9,10]

Extensive preclinical research has demonstrated analgesic effects of exogenous cannabinoids as well as an endogenous cannabinoid system involved in pain and analgesia.[12,13] The need for a greater variety of effective therapeutic options has led to heightened interest in evaluating smoked cannabis as a treatment for chronic neuropathic pain. Incorporating an experimental pain model into the assessment of smoked cannabis in patients with chronic pain from HIV-SN provides a standardized reference point for each patient's subjective ratings of ongoing chronic pain. The Long Thermal Stimulation procedure tests for acute analgesia by measuring the painfulness of a 1-minute heat stimulus.[14] The heat/capsaicin sensitization model tests for anti-hyperalgesic effects.[15] By simultaneously evaluating acute experimentally induced pain and hyperalgesia and ongoing neuropathic pain, we sought to determine the effect of smoked cannabis on the neuropathic pain of HIV-SN, and to determine if cannabinoids have a more general analgesic and anti-hyperalgesic effect.

Methods. *Study patients.* Patients were adults with HIV infection and symptomatic HIV-SN with an average daily pain score of

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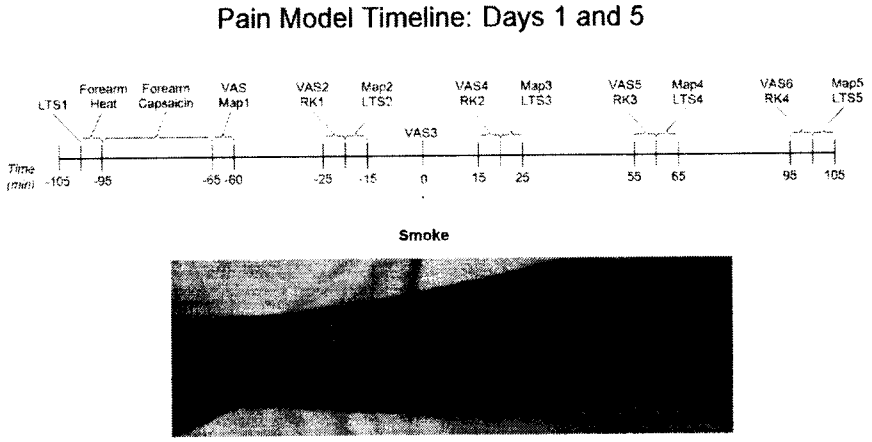

Figure 1. Timeline of procedures associated with first and last smoking sessions (day 1 and day 5) and illustration of marking of borders of hyperalgesia on the forearm surrounding the stimulated area. Procedures: LTS = long thermal stimulation—upper arm (45 °C for 1 minute); forearm heat: 45 °C for 5 minutes; forearm capsaicin: 0.075% for 30 minutes; VAS = Visual Analog Scale—Rating of current neuropathic pain; map = map area of secondary hyperalgesia (brush and von Frey); RK = rekindling—forearm (40 °C for 5 minutes).

at least 30 mm on the 100 mm visual analog scale during the outpatient pre-intervention phase. Patients were in stable health, were without current substance abuse (including tobacco), and followed a stable medication regimen for pain and HIV for at least 8 weeks prior to enrollment. Painful HIV-SN was confirmed by symptoms of symmetric distal pain or dysesthesias in the lower extremities for at least 2 weeks, combined with absent or depressed ankle reflexes or sensory loss of vibration, pin, temperature, or touch on examination by the study neurologist (C.A.J.). A family history of polyneuropathy, neuropathy due to causes other than HIV or dideoxynucleosides, and use of isoniazid, dapsone, or metronidazole within 8 weeks prior to enrollment were exclusionary. HIV neuropathy was defined as onset of symptoms without concomitant dideoxynucleoside antiretroviral therapy and nucleoside neuropathy as symptom onset during dideoxynucleoside treatment. Subjects with HIV neuropathy whose symptoms worsened on dideoxynucleoside agents were considered to have both HIV and nucleoside neuropathy.

All patients were required to have prior experience smoking cannabis (defined as six or more times in their lifetime), so that they would know how to inhale and what neuropsychologic effects to expect. Current users were asked to discontinue any cannabis use prior to study admission.

The study was approved by the Institutional Review Board at the University of California San Francisco, the Research Advisory Panel of California, the Drug Enforcement Administration, the Food and Drug Administration, and the National Institute on Drug Abuse. Written informed consent was obtained from all patients. The trial was monitored by an independent Data Safety Monitoring Board (DSMB) established by the University of California Center for Medicinal Cannabis Research.

Study medication. The National Institute on Drug Abuse provided identically appearing pre-rolled cannabis and placebo cigarettes weighing on average 0.9 g. Active cannabis cigarettes contained 3.56% delta-9-tetrahydrocannabinol (delta-9-THC), and identical-appearing placebo cannabis cigarettes from which the active components had been extracted contained 0% delta-9-THC. The cigarettes were kept in a locked and alarmed freezer until they were dispensed to a locked freezer in the San Francisco General Hospital General Clinical Research Center where the inpatient study was conducted. The frozen cigarettes were rehydrated overnight in a humidifier. Patients were housed in a room with a fan ventilating to the outside. Research staff monitored patients during smoking sessions, weighed the cannabis cigarettes immediately before and after they were administered to patients, and returned all leftover material to the pharmacy. To maximize standardization of inhaled doses, patients followed a uniform puff procedure.[16]

Study timeline and procedures. The study had four phases: a 7-day outpatient pre-intervention phase (study days −9 to −3) to establish eligibility; a 2-day inpatient lead-in phase (study days −2 and −1) in which patients were acclimated to the inpatient General Clinical Research Center setting and baseline measurements were obtained; a 5-day inpatient intervention phase (study days 1 to 5); and a 7-day outpatient post-intervention phase (study days 6 to 12) during which patients continued to record pain ratings each day.

Randomization (1:1) to cannabis or placebo cigarettes was computer-generated by the study statistician and managed by an independent research pharmacist. Treatment was double-blind. After hospital admission on day −2, patients were not allowed to leave the hospital or receive visitors. Patients smoked their first cigarette at 2 PM on day 1, and their last cigarette at 2 PM on day 5. Pain model procedures and repeated ratings of chronic pain were incorporated into the first and last smoking session, as shown in figure 1. On the intervening study days, patients smoked, as tolerated, one cigarette three times daily (8:00 AM, 2:00 PM, 8:00 PM). Preadmission analgesics were continued throughout the study.

Primary outcome measure: Daily diary pain VAS. Beginning with the outpatient pre-intervention phase and extending through the post-intervention phase, patients completed a diary at 8 AM each morning to rate their chronic neuropathic pain during the preceding 24 hours on a 100 mm visual analog scale (VAS) labeled "no pain" at 0 mm and "worst pain imaginable" at 100 mm.

Secondary outcome measures: Day 1 and day 5 smoking sessions. Ratings of chronic neuropathic pain VAS. To assess the immediate effect of smoked cannabis on chronic neuropathic pain, patients rated their current pain at 40-minute intervals three times before and three times after smoking the first and last cigarette on a 100-mm VAS (figure 1). In the pilot study, we observed rapid increases in plasma levels of delta-9 THC after 2 minutes (mean = 96.8 ng/mL; 95% CI = 48.7, 145.0) with rapid declines after 1 hour (mean = 6.2 ng/mL; 95% CI = 3.3, 9.2). This study was designed so these measures were collected within the time of peak plasma levels.

LTS procedure. The long thermal stimulation procedure (LTS) was used to assess acute analgesic effects. Skin on the non-dominant shoulder was heated using a computer-controlled Peltier device with a 15.7-cm^2 surface area thermode (TSA 2001, Medoc, Israel).[17,18] The probe is held against the skin at a holding temperature of 32 °C and then heated to 45 °C at a linear rate. On reaching 45 °C, pain is then rated continuously using an electronic visual analog scale with a 100-mm linear track for 1 minute before thermode removal. The LTS procedure was performed twice before and three times after smoking.

Heat/capsaicin sensitization model. The heat/capsaicin sensitization model was used to assess anti-hyperalgesic effects by inducing neuronal sensitization sufficient to produce an area of cutaneous secondary hyperalgesia that can be mapped and quantified.[14,15,17,19] Heat/capsaicin sensitization was induced on a 22.8 cm^2 stimulation site on the forearm by using the thermode to heat the skin to 45 °C for 5 minutes followed by treating the stimulation site with topical capsaicin cream (0.075%, Capzaisin HP, Chattem Inc.; Chattanooga, TN) for 30 minutes. Cutaneous hyperalgesia was maintained by heating the stimulation site to 40 °C for 5 minutes (rekindling procedure) at 40-minute intervals. After each rekindling, areas of secondary hyperalgesia were quantified with a 1-inch foam brush and with a 26-g von Frey hair (a mildly noxious pin-like sensation) by stimulating along linear rostral–caudal and lateral–medial paths around the stimulation site in 5-mm steps at 1-second intervals. Starting well outside the hyperalgesic area and continuing toward the treated skin area, the skin was marked where patients reported a definite change in

sensation (such as burning, tenderness, or more intense pricking). The distances from the center of the stimulation site were then measured and surface area calculated. The first (baseline) rekindling was performed before smoking and rekindling was repeated three times after smoking.

Safety, side effects, and mood ratings. On study days −1, 2, and 5, patients completed the Profile of Mood States to assess total mood disturbance and subscales of tension-anxiety, depression-dejection, anger-hostility, vigor-activity, fatigue-inertia, and confusion-bewilderment.[20] Side effects of anxiety, sedation, disorientation, paranoia, confusion, dizziness, and nausea were patient-rated on a 0 to 3 scale (none, mild, moderate, severe) at 9:00 AM, 3:00 PM, and 9:00 PM during the entire hospital stay. Adverse events were graded using the NIH Division of AIDS table for grading severity of adult adverse experiences.[21]

Statistical analysis. Study sample size was based on an open-label pilot trial in 16 patients with HIV-SN of very similar design.[22] The mean reduction in pain was 30.1% (95% CI: −61.2, 1.0). Ten pilot patients (62%) had a greater than 30% decrease in their daily pain, the prespecified criterion of clinically meaningful pain relief.[23] Applying the same variances to a randomized, placebo-controlled trial and conservatively estimating that 50% of cannabis patients and 13% of placebo patients would meet the 30% pain reduction criterion yields a sample size of 48 patients with an alpha of 0.05 and a beta of 0.20.

Statistical analyses were conducted on a modified intent-to-treat (ITT) sample. All patients who remained in the study at each time point were included in the analyses. The primary outcome was the proportion of patients in the cannabis and placebo groups who experienced at least a 30% reduction in daily diary pain level from baseline (average of the two daily diary pain levels rated at 8 AM on study day −1 and study day 1) to end-of-treatment (average of study days 4 and 5). p Values were obtained using χ^2 test for 2 by 2 tables.

The co-primary outcome variable was the percent change in pain from baseline. Percent change in each group was not normally distributed; therefore, the nonparametric Mann-Whitney test was used to compare percent change in pain across study groups. Pain reduction was also modeled as a function of group and time using a repeated measures model (generalized estimating equations). All available patient information, including information on patients who later withdrew from the study, was included in this model. The data were fitted using time squared to allow for non-linearity in the relationship between group and time. To adjust for potentially confounding patient characteristics, we controlled for age, gender, pre-study ongoing use of cannabis (yes or no), cause of neuropathy, and baseline daily pain.

Secondary outcome variables collected while smoking the first cigarette on day 1 and the last cigarette on day 5 consisted of percent change (relative to pre-smoking baseline for that session) in 100 mm VAS ratings of chronic neuropathic pain, painfulness of the LTS procedure, and areas of secondary hyperalgesia produced by the heat/capsaicin sensitization model to brush and von Frey hair stimuli. For each of these repeated measures, the area under the curve (AUC) for percent change in pain or area of sensitization was computed relative to pre-smoking baseline values (or the average of the pre-smoking values if multiple measurements were available). The total AUC was standardized as average percent change per hour by dividing each AUC by 60. Differences in AUC were compared using Mann-Whitney tests as these data were not normally distributed.

Additional secondary outcome analyses of the percent change in total mood disturbance and percent change in the six subscales of the Profile of Mood States was analyzed using independent t tests or Mann-Whitney tests if the data were not normally distributed. Side effect ratings were compared using repeated measures models (generalized estimating equations), using a negative binomial distribution to allow for rare events and over-dispersed data and adjusted for differences in mean recorded side effects across study days and time of day of measurement.

Role of the funding source. The University of California Center for Medicinal Cannabis Research provided assistance with obtaining necessary regulatory approvals, data quality monitoring, and establishing the study's Data Safety Monitoring Board.

Results. *Study patients.* A total of 223 patients were assessed for eligibility between May 2003 and May 2005 (figure 2) and 55 individuals were enrolled. Of these, 27 were randomized to cannabis cigarettes and 28 were randomized to placebo cigarettes. One patient withdrew during the inpatient intervention phase prior to smoking the first cigarette, and four additional patients withdrew prior to completion of the inpatient phase, leaving 25 patients in each group who completed the entire study. All smoking sessions were observed by research staff and completed per protocol.

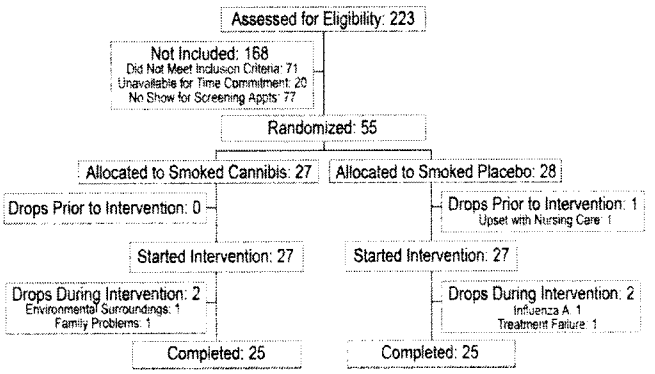

Figure 2. Flow of participants through the trial.

Thirty randomized patients completed the experimental pain model portion of the study (14 cannabis, 16 placebo). Of the 25 patients who did not fully participate in this portion of the study, 17 could not tolerate the painful stimulation when tested during the outpatient pre-intervention phase, one developed a blister, one discontinued prior to study day 1, and six did not meet eligibility criteria for the pain model portion (extensive tattooing in one and heat pain detection threshold above 47 °C in five).

The patients randomized to cannabis and placebo cigarettes were similar with regard to demographic and baseline characteristics (table 1). Patients were predominantly men with 14 years of HIV infection and 7 years of peripheral neuropathy. Neuropathy was believed to be secondary to antiretroviral medications in the majority of patients in both groups. Over half of patients in each group used concomitant medications for pain, with about one quarter of each group using more than one type of concomitant medication. The most frequently used concomitant medication was gabapentin (15 patients) followed by opioids (14 patients).

Primary outcome measure. Median daily pain ratings for the two groups throughout the entire study are shown in figure 3. Baseline (average of day −1 and day 1) daily diary pain ratings were similar (cannabis median 52, interquartile range [IQR] = 38, 71; placebo median 57, IQR = 40, 74). Among those who completed the study, 13 of 25 patients randomized to cannabis cigarettes had >30% reduction in pain from baseline to end of treatment vs 6 of 25 patients receiving placebo cigarettes (52% vs 24%; difference 28%, 95% CI 2% to 54%, $p = 0.04$). The median reduction in chronic neuropathic pain on the daily diary VAS was 34% (IQR = −71, −16) in the cannabis group and 17% in the placebo group (IQR = −29, 8; difference = 18%; $p = 0.03$, Mann-Whitney test). In the multivariable repeated measures model, which analyzed available data from all randomized patients, the estimated group difference was slightly larger than the observed dif-

Table 1 *Patient characteristics*

	Cannabis (n = 27)	Placebo (n = 28)
Sex, n (%)*		
Male	22 (81)	26 (93)
Female	5 (19)	2 (7)
Age, y, mean ± SD	50 ± 6	47 ± 7
Race/ethnicity, n (%)		
White	14 (52)	11 (39)
African American	9 (33)	12 (43)
Latino	3 (11)	5 (18)
Asian/Pacific Islander	1 (4)	0
Duration of HIV, y, mean ± SD	15 ± 4	14 ± 5
On HAART, n (%)	18 (67)	24 (86)
CD4+ T lymphocyte (cells/mm^3), median (IQR)	355 (250, 536)	444 (311, 523)
Viral load, n (%)		
<400	19 (70)	17 (61)
≥400	8 (30)	11 (39)
Duration of neuropathy, y, median (IQR)	7 (3, 9)	7 (3, 9)
Cause of neuropathy, n (%)		
HIV	10 (37)	7 (25)
Nucleosides	12 (44)	14 (50)
Both	5 (19)	7 (25)
Intensity of pain at baseline (0–100), mean ± SD	53 ± 20	54 ± 23
Current cannabis use, n (%)		
Yes	21 (78)	19 (68)
No	6 (22)	9 (32)
Concomitant medications, n (%)	15 (56)	16 (57)
Types of concomitant medications, n (%)†		
Gabapentin	7 (26)	7 (25)
Opioid	5 (19)	8 (29)
Other medication	9 (33)	10 (36)
Multiple concomitant medications, n (%)	6 (22)	7 (25)

* Male to female transgender for 1 cannabis and 2 placebo patients.
† Multiple responses possible.

ference among those who completed the study (26%; 95% CI = 0, 51; $p = 0.05$).

Secondary outcome measures. Smoking the first cannabis cigarette reduced chronic pain ratings (AUC) by a median of 72% vs a reduction of 15% with placebo cigarettes ($p < 0.001$, Mann-Whitney test; figure 4A). On day 5 just prior to smoking the last cigarette, median ratings of current chronic pain intensity were lower in the cannabis group (15; IQR = 7, 34) than in the placebo group (29; IQR = 20, 60; $p = 0.006$, Mann-Whitney test). Smoking the last cigarette further reduced chronic pain ratings 51% in the cannabis group vs 5% in the placebo group ($p < 0.001$, Mann-Whitney test).

In the 30 patients who underwent the pain model portion of the study, LTS (a measure of acute analgesia to noxious heat stimuli) did not appear to be substantially reduced by smoking the first cigarette on day 1 in either group (figure 4B, median = −22% for cannabis and −5% for placebo; $p = 0.31$). Areas of experimental heat/capsaicin secondary hyperalgesia on the forearm were similar in the two groups prior to smoking the first cigarette. Active cannabis reduced the area to both brush and von Frey hair stimuli compared to placebo (median = −34% vs −11%; $p = 0.05$ and −52% vs + 3%; $p = 0.05$; figure 4, C and D). Smoking the last cigarette on day 5 did not alter the painfulness of the LTS procedure or reduce the areas of secondary hyperalgesia in either group.

Safety and mood effects of cannabis. No patient withdrew from the study because of adverse events. One episode of grade 3 dizziness related to study medication occurred in the cannabis group. One case of transient grade 3 anxiety possibly related to study medication was reported in each group. Both patients received a one-time dose of lorazepam. No other patients required psychotropic medications for treatment of dysphoric effects. No episodes of hypertension, hypotension, or tachycardia requiring medical intervention occurred.

Mean recorded side effects were low in both study groups. However, side effects ratings were higher in patients in the cannabis group, as shown in table 2, for anx-

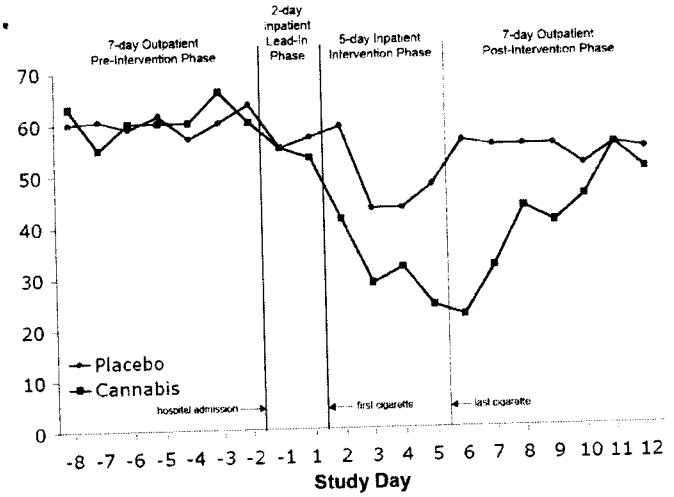

Figure 3. Time course of the intensity of chronic neuropathic pain as rated on the daily diary VAS at 8 AM for the previous 24-hour period. Each point represents the group median. Study admission was at noon on study day −2, the first cigarette was smoked at 2 PM on study day 1, and the last cigarette was smoked at 2 PM on study day 5.

iety ($p = 0.04$), sedation ($p < 0.001$), disorientation ($p < 0.001$), confusion ($p < 0.001$), and dizziness ($p < 0.001$). Although these differences were significant, the values for both groups hovered closer to zero than one and do not represent any serious safety concerns in this short-term study. The Profile of Mood States indicated a reduction in total mood disturbance during the 5 days of smoking (median −33% cannabis vs −29% placebo; $p = 0.28$). Although all subscale scores declined in both groups, the only difference was a larger decrease in depression-dejection in the placebo group (median −63% cannabis vs −76% placebo; $p = 0.05$, Mann-Whitney test).

Discussion. Over a 5-day inpatient intervention period, smoking cannabis cigarettes three times a day reduced HIV-SN pain by 34%, significantly more than the 17% reduction with placebo cigarettes. A >30% reduction in pain has been validated as a clinically significant level of improvement.[23] In the current study, half (52%) of those randomized to cannabis experienced at least a 30% reduction in pain, while a quarter (24%) of those randomized to placebo experienced a similar reduction in pain.

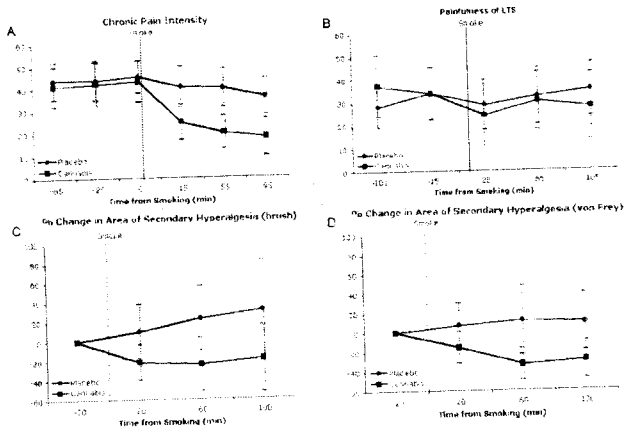

Figure 4. First smoking session: time course during the first 95 minutes after smoking of intensity of chronic pain as measured on the visual analog scale (A; cannabis n = 25, placebo n = 25), painfulness of LTS (B; cannabis n = 14, placebo n = 16), and areas of secondary hyperalgesia to brush and von Frey hair stimulation (C and D; cannabis n = 14, placebo n = 16). Mean ± 95% CI.

***Table 2** Mean side effect scores by study group*

	Adjusted estimates	
	Cannabis, mean (95% CI)	Placebo, mean (95% CI)
Anxiety*	0.25 (0.14, 0.44)	0.10 (0.05, 0.22)
Sedation†	0.54 (0.36, 0.81)	0.08 (0.04, 0.17)
Disorientation†	0.16 (0.07, 0.34)	0.01 (0.00, 0.04)
Paranoia	0.13 (0.03, 0.45)	0.04 (0.01, 0.14)
Confusion†	0.17 (0.07, 0.39)	0.01 (0.00, 0.06)
Dizziness†	0.15 (0.07, 0.31)	0.02 (0.01, 0.05)
Nausea	0.11 (0.04, 0.30)	0.03 (0.01, 0.14)

Side effects were rated three times daily on a 0 to 3 scale (0 = none, 1 = mild, 2 = moderate, 3 = severe).

* p, 0.05; † $p < 0.001$.

In this randomized, placebo-controlled study, the number needed to treat (NNT) on the primary outcome measure of >30% pain reduction among all completing patients was 3.6 (1/[52%−24%]). Trials vary in their primary outcome measure, so comparing NNT figures only approximates relative potency. The NNT for lamotrigine was 5.4 for HIV-related painful DSP.[4,24] Although one group of investigators reported success with gabapentin, their data analysis does not allow calculation of an NNT.[5] The NNT in the present study is comparable to that reported in trials of gabapentin for other types of chronic neuropathic pain. In a large study of gabapentin for postherpetic neuralgia the NNT was 3.4 and for diabetic neuropathy the NNT was 4.0.[25,26] A recent meta-analysis of 107 controlled trials for neuropathic pain showed that only tricyclic antidepressants and higher potency opioids consistently achieved NNT values lower than 3.7.[24] However, for HIV-SN, tricyclic antidepressants were not effective.[9,10] Opioids have not been systematically evaluated for painful HIV-SN, but studies show efficacy across a broad spectrum of neuropathic pain disorders.[27,28]

In addition to patient-reported changes in ongoing chronic pain, smoked cannabis attenuated the cutaneous hyperalgesia associated with central neuronal sensitization produced by a standardized experimental pain model. Although one cannot entirely exclude pain relief due to relaxation, a high, or unblinding, the mood effects recorded argue against such an explanation. Only one of the six Profile of Mood States subscales (depression-dejection) showed a significant group difference, and actually favored placebo. Moreover, ratings of side effects in the cannabis group

were low. The rigorous experimental pain model outcome measures are novel to each patient and not strongly associated with expectations of relief of chronic pain. Areas of secondary hyperalgesia are mapped by an investigator while the patient looks away, and thus may be less subjective than pain intensity ratings on a VAS scale. Therefore, the present study provides evidence that cannabis has analgesic effects on acute central neuronal sensitization produced by the experimental pain model as well as on the neuronal mechanisms associated with painful HIV-SN.

The results reported here in neuropathic pain patients exposed to an experimental pain model are consistent with preclinical pain model studies with cannabinoids. Systemic cannabinoids are effective in animal models of acute mechanical and thermal pain, inflammation and hyperalgesia, and nerve injury.[29-35] In healthy human volunteers, smoked cannabis increased pressure pain tolerance thresholds.[36] The present study in chronic pain patients also shows an effect on experimental hyperalgesia. Although smoked cannabis did not appear to suppress the painfulness of the LTS procedure (analogous to the hot plate or tail flick test in animals), this may reflect the relatively low concentration of delta-9-THC in the study cigarettes.

The clinical literature on cannabinoids for pain conditions other than HIV-SN is limited and essentially restricted to isolated delta-9-THC preparations. Fifteen and 20 mg of delta-9-THC produced significant analgesia in cancer patients with pain, as well as antiemesis and appetite stimulation, but some patients reported unwanted side effects such as sedation and depersonalization at the 20 mg dose level.[37,38] In a follow-up study, 10 mg of delta-9-THC produced analgesic effects comparable to 60 mg of codeine, and 20 mg of delta-9-THC was equivalent to 120 mg of codeine. Two recent placebo-controlled studies of cannabinoids for central neuropathic pain associated with multiple sclerosis produced results similar to the present study. In a crossover trial of synthetic delta-9-THC up to 10 mg/day, an NNT of 3.5 was reported.[39] A trial of a sublingual spray containing delta-9-THC alone or combined with cannabidiol showed a 41% pain reduction with active drug vs a 22% reduction with placebo.[40]

The Institute of Medicine report on cannabis and medicine concluded that cannabinoids likely have a natural role in pain modulation, control of movement, and memory.[41] The Institute of Medicine report, along with other recent reviews, suggest that if cannabis compounds can be shown to have therapeutic value then the margin of safety is acceptable.[42,43] An acceptable safety margin has been shown in the present study as well as in a previous study of cannabinoids in patients with HIV-1 infection.[44]

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Appendix B (Section H)

ORIGINAL COMMUNICATION

A multicentre, open-label, follow-on study to assess the long-term maintenance of effect, tolerance and safety of THC/CBD oromucosal spray in the management of neuropathic pain

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Abstract Peripheral neuropathic pain (PNP) poses a significant clinical challenge. The long-term efficacy of delta-9-tetrahydrocannabinol (THC)/cannabidiol (CBD) oromucosal spray was investigated in this 38-week open-label extension study. In total, 380 patients with PNP associated with diabetes or allodynia entered this study from two parent randomised, controlled trials. Patients received THC/CBD spray for a further 38 weeks in addition to their current analgesic therapy. Neuropathic pain severity was the primary efficacy measure using a pain 0–10 numerical rating scale (NRS). Additional efficacy, safety and tolerability outcomes were also investigated. In total, 234 patients completed the study (62 %). The pain NRS showed a decrease in score over time in patients from a mean of 6.9 points (baseline in the parent studies) to a mean of 4.2 points (end of open-label follow-up). The proportion of patients who reported at least a clinically relevant 30 % improvement in pain continued to increase with time (up to 9 months); at least half of all patients reported a 30 % improvement at all time points. Improvements were observed for all secondary efficacy outcomes, including sleep quality 0–10 NRS scores, neuropathic pain scale scores, subject global impression of change and EQ-5D questionnaire scores. THC/CBD spray was well tolerated for the study duration and patients did not seek to increase their dose with time, with no new safety concerns arising from long-term use. In this previously difficult to manage patient population, THC/CBD spray was beneficial for the majority of patients with PNP associated with diabetes or allodynia.

Keywords Cannabidiol · Cannabinoid · Delta-9-tetrahydrocannabinol · Neuropathic pain · THC/CBD spray

Introduction

Neuropathic pain is a chronic, debilitating condition with an estimated prevalence of over 1 % in the general US population [1]. It can be triggered by a variety of conditions, but the mechanisms of developing neuropathic pain are specific to the damage and/or dysfunction of the nervous system and are not necessarily related to the underlying disease. It has therefore been suggested that the optimal approach to neuropathic pain

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management should be based on the mechanism(s) underlying the pain, rather than the disease which triggers the neuropathic events [2, 3]. However, many patients achieve only partial pain relief despite management with analgesic agents. Thus, there is still a clear unmet need for this group of patients.

The endocannabinoid system modulator, Δ^9-tetrahydrocannabinol (THC)/cannabidiol (CBD) oromucosal spray (Sativex®), is formulated from plant extracts prepared from genetically distinct chemotypes of *Cannabis sativa* L. These cannabis plants contain cannabinoids, which act primarily via specific cannabinoid receptors designated CB_1 and CB_2 [4]. CB_1 receptors are predominantly found in the central nervous system, while CB_2 receptors are located primarily in the periphery, including the immune system [4].

The two most relevant cannabinoids in this product are THC and CBD, contained in the spray at an approximate 1:1 ratio with smaller amounts of other cannabinoids, flavonoids and terpenes [5]. It has been recently licenced for use in various European countries for the relief of spasticity in multiple sclerosis (MS) [6], as well as outside the European Union. THC/CBD spray is also licenced for use in Canada for the management of central neuropathic pain (CNP) in MS.

THC and CBD have analgesic effects in numerous animal models of pain [7–10]. Previous clinical studies using synthetic THC or a synthetic metabolite of THC demonstrated effects in patients with CNP [11] and peripheral neuropathic pain (PNP) associated with allodynia [12], respectively. In a randomised controlled trial (RCT), THC/CBD spray showed analgesic effects in CNP associated with MS [13, 14], as well as in pain following brachial plexus avulsion [15]. A further study concluded that THC/CBD spray provided a clinically relevant improvement in PNP associated with allodynia [16].

Two parent RCTs preceded the current study [17, 18]. Both showed the ability of THC/CBD spray to alleviate pain in patients with PNP associated with diabetes mellitus or allodynia (i.e., different underlying pathologies). However, there was a need to investigate the long-term efficacy, safety and tolerability of THC/CBD spray in this indication. This 9-month open-label, follow-on study was therefore designed and performed in accordance with the guidance notes for the clinical development of new medicinal products in neuropathic pain, compiled by Committee for Medicinal Products for Human Use (CHMP) [19].

Methods

Study design

The study comprised 38 weeks of open-label THC/CBD spray treatment, following the original clinical trials treatment period, at 66 study sites (38 centres in the United Kingdom, 15 in the Czech Republic, 8 in Romania, four in Belgium and one in Canada). Patients with allodynia or PNP associated with diabetes who had received THC/CBD spray or placebo in one of two parent RCTs were invited to take part in the study. At this study extension baseline visit (visit 1 of 6), the following information was recorded: eligibility, informed consent, medical history, physical examination, 12-lead electrocardiogram (ECG), pain 0–10 numerical rating scale (NRS) and adverse events (AEs). Further study visits took place at weeks 2, 14, 26 and 38, with an end of study visit 28 days following study completion or withdrawal. At each subsequent study visit, the following information was recorded: concomitant medications, vital signs, AEs, oral examination, intoxication 0–10 NRS, neuropathic pain scale (NPS) score and sleep quality 0–10 NRS score. Patients also completed a daily dosing diary and a weekly symptom diary recording the severity of their neuropathic pain using a pain 0–10 NRS. At week 38 the following further information was recorded: subject global impression of change (SGIC) and EQ-5D lifestyle questionnaires, clinical laboratory sampling and a pregnancy test for female patients.

Inclusion and exclusion criteria

Main inclusion criteria

Eligible patients had participated in, completed and complied with all the study requirements of one of the above-mentioned parent RCTs [17, 18] and had completed the parent study within the last 7 days. Eligible patients showed tolerability to the study medication (THC/CBD spray or placebo) in the parent RCTs and were expected to gain clinical benefit from receiving THC/CBD in the opinion of the investigator. Furthermore, they had to be willing to comply with the study protocol procedures and agree for the responsible authorities (i.e., primary care physician or hospital consultant) to be notified of their participation in the study.

Exclusion criteria

The exclusion criteria of the previous RCTs were re-checked. These included exclusion of patients with a concurrent history of severe psychiatric, convulsive, renal, hepatic or cardiovascular disorders, or those with a history of alcohol or substance abuse. Those with a known or suspected hypersensitivity to cannabis or cannabinoid-based medications were excluded. Females of child-bearing age, or males with partners of child-bearing age were also excluded, unless willing to ensure that adequate contraception was used for the study duration and for 3 months

thereafter. Pregnant or lactating females were excluded, as were patients who had received any investigational medicinal product within 12 weeks of study commencement (with the exception of THC/CBD spray taken during the preceding RCTs). Patients with any physical abnormalities or a disease (in the opinion of the investigator) which could compromise their safety during the study were excluded, as were those who had been previously randomised into this open-label extension study, as well as those intending to donate blood during the study (for safety reasons).

Treatment and dosing

A pump action oromucosal spray was used to deliver study medication. Each 100 µL actuation of THC/CBD spray delivered 2.7 mg of THC and 2.5 mg of CBD to the oral mucosa. Patients were restricted to a maximum of eight sprays per 3 h period and 24 actuations every 24 h. A 2-week titration period to allow for dosing optimisation began at study visit 2 (on day 14). During the baseline period patients self-titrated, titrating upwards by up to 50 % of the previous day's dose to reach their optimal dose depending on efficacy, tolerability and maximum permitted dose.

Concomitant medication

Due to the long-term nature of the study, investigators were allowed to prescribe medications or other managements to provide adequate supportive care if the patient's condition required, provided the inclusion and exclusion criteria were not compromised. Sites were advised to proceed with caution when co-administering any drugs exhibiting significant metabolites, inhibitors or activators of cytochrome P450 3A isoenzymes, due to the potential interaction with cannabis-based medicines.

Prohibited medication

Patients were required to abstain from using any herbal cannabis or cannabinoids other than THC/CBD spray for the entire study duration.

Study endpoints

Primary efficacy endpoints

The primary efficacy endpoint was the change in pain severity, defined as the change from the parent RCT baseline to the end of open-label treatment in pain 0–10 point NRS scores. The pain 0–10 NRS was recorded by patients weekly on a selected nominated day in their diary books. The question posed differed slightly depending on which parent RCT the patient had participated in. Patients with allodynia were asked: "On a scale of '0–10' please indicate the average level of your nerve pain over the last 7 days", while patients with diabetic neuropathy were asked: "On a scale of '0–10' please indicate the average level of your nerve pain due to diabetes over the last 7 days". The anchors for both questions were: 0 = 'no pain' and 10 = 'worst possible pain'. Patients were instructed to relate 'no pain' to the time prior to the onset of their neuropathic pain. The proportion of responders with an equal to or greater than 30 or 50 % improvement in the level of pain experienced was a co-primary endpoint of this study.

Secondary efficacy endpoints

Other efficacy endpoints were THC/CBD spray daily dose, NPS score, sleep quality 0–10 NRS score, intoxication 0–10 NRS score and SGIC and quality of life EQ-5D health questionnaire outcomes.

NPS

The NPS (neuropathic pain scale PDF [17, 20]) was collected at the pre-treatment baseline and the final visit of the parent RCTs and at each of the open-label extension study visits (end of weeks 2, 14, 26 and 38). The main variable for analysis was NPS score at each visit, which was summarised by parent RCTs and overall, using descriptive statistics at each time point. Summaries of the changes from the pre-treatment baseline of the parent RCTs were produced.

Sleep quality 0–10 NRS

The sleep quality 0–10 NRS score was collected at the pre-treatment baseline and the final visit of the parent RCTs and at each of the open-label extension study visits (end of weeks 2, 14, 26 and 38). Patients were asked, "On a scale of '0–10', please indicate how your pain disrupted your sleep last night?" with the anchors: 0 = 'did not disrupt sleep' and 10 = 'completely disrupted (unable to sleep at all)'. The main variable for analysis was the sleep quality 0–10 NRS score at each visit, which was summarised by parent RCTs and overall, using descriptive statistics at each time point.

Intoxication 0–10 NRS

The intoxication 0–10 NRS score was collected at the pre-treatment baseline and the final visit of the parent RCTs and at each of the open-label extension study visits (end of

weeks 2, 14, 26 and 38). Patients were asked how intoxicated they felt, with the anchors: 0 = 'no intoxication' and 10 = 'extreme intoxication'. The main variable for analysis was the intoxication 0–10 NRS score at each visit, which was summarised by parent RCTs and overall, using descriptive statistics at each time point.

SGIC

The SGIC was collected at the end of open-label study (completion or withdrawal) only. A 7-point Likert-type scale was used to evaluate the patients perception of their nerve pain with the anchors: 'very much improved', 'much improved', 'slightly improved', 'no change', 'slightly worse', 'much worse' or 'very much worse'.

Eq-5D

The EQ-5D questionnaire (see [17]) was completed at pre-treatment baseline and at the final visit of the parent RCTs, as well as at the end of open-label extension study (completion or withdrawal). The weighted health state index was calculated for each assessment without imputation to account for missing values (i.e. if one or more individual items were missing then the whole index was missing). Both weighted health state index and self-rated health status were summarised by parent RCTs and overall at the three time points using descriptive summary statistics. Summaries of the changes from the pre-treatment baseline of the parent RCTs were produced.

In addition, the five EQ-5D descriptive system questions (mobility, activity, self-care, pain, anxiety) were summarised by parent RCTs and overall as shift tables from the pre-treatment baseline of the parent RCTs to end of the open-label extension study (completion or withdrawal).

Safety endpoints

The safety endpoints of the study included the incidence of AEs, laboratory parameters, vital signs and ECG results.

Statistical methods

There was no formal sample size for the study. Patients who had participated in the two parent RCTs to investigate neuropathic pain were considered for enrolment into the current study. As the study was non-comparative, no formal hypothesis testing was performed. The statistics are descriptive only.

Amendments during the trial

During the course of the study, one amendment affecting the open-label extension study was implemented and approved by the Multi Centre Research Ethics Committee, Ethical Committees and competent authorities. The amendment relaxed an entry criterion related to glycosylated haemoglobin, sinus bradycardia and creatinine clearance to allow some patients that had safely completed the parent RCTs to enter the extension study. Following the growing tolerability and safety evidence on Sativex, the blood glucose test was removed from the list of biochemistry tests to be performed. There were also minor corrections to the study medication-dosing regimen on the first 2 days of dosing, which was inconsistent with the parent studies, and other instructions given to the patients.

Results

This open-label extension study took place between 18 October 2005 and 15 June 2007. A full summary breakdown of all patients enrolled is shown in Fig. 1. In the parent RCT, which looked at PNP associated with allodynia, 246 patients were randomised and 173 (70 %) completed the study [17]. In the parent RCT, which involved PNP associated with diabetes, 298 patients were randomised and 230 (77 %) completed the study [18]. 21 patients in the allodynia RCT and 15 patients in the diabetes RCT, who terminated study treatment prematurely but completed all study procedures, were also eligible for the open-label extension study. This was a total of 439 completers within the two studies. There were 57 patients (13 %) who were eligible, but elected not to continue into the open-label extension. While the reasons for this were not captured during the study, the vast majority was simply down to the patient's choice. This left a total of 382 patients who were screened for the open-label extension study, of these 166 patients had previously been taking THC/CBD spray (mean daily doses: allodynia RCT = 8.9 sprays per day; diabetic neuropathy RCT = 9.5 sprays per day) and 216 had been taking placebo (mean daily doses: allodynia RCT = 14.2 sprays per day; diabetic neuropathy RCT = 13.8 sprays per day). Study population demographics are presented in Table 1. The overall mean duration of PNP in these patients at enrolment was 5.4 years and was similar between the patients from both the parent RCTs. THC/CBD was used for 94 % of days in the open-label extension study; the median use was 249 days. From month 1 to month 9, the median daily dose of THC/CBD spray was 6.0–8.0 actuations.

Study withdrawals occurred throughout the open-label extension study with no notable difference in the time to withdrawal for either previous treatment group. However, 27 % of patients who had received placebo in the parent RCTs withdrew from the extension study due to AEs compared with 11 % who had received THC/CBD spray.

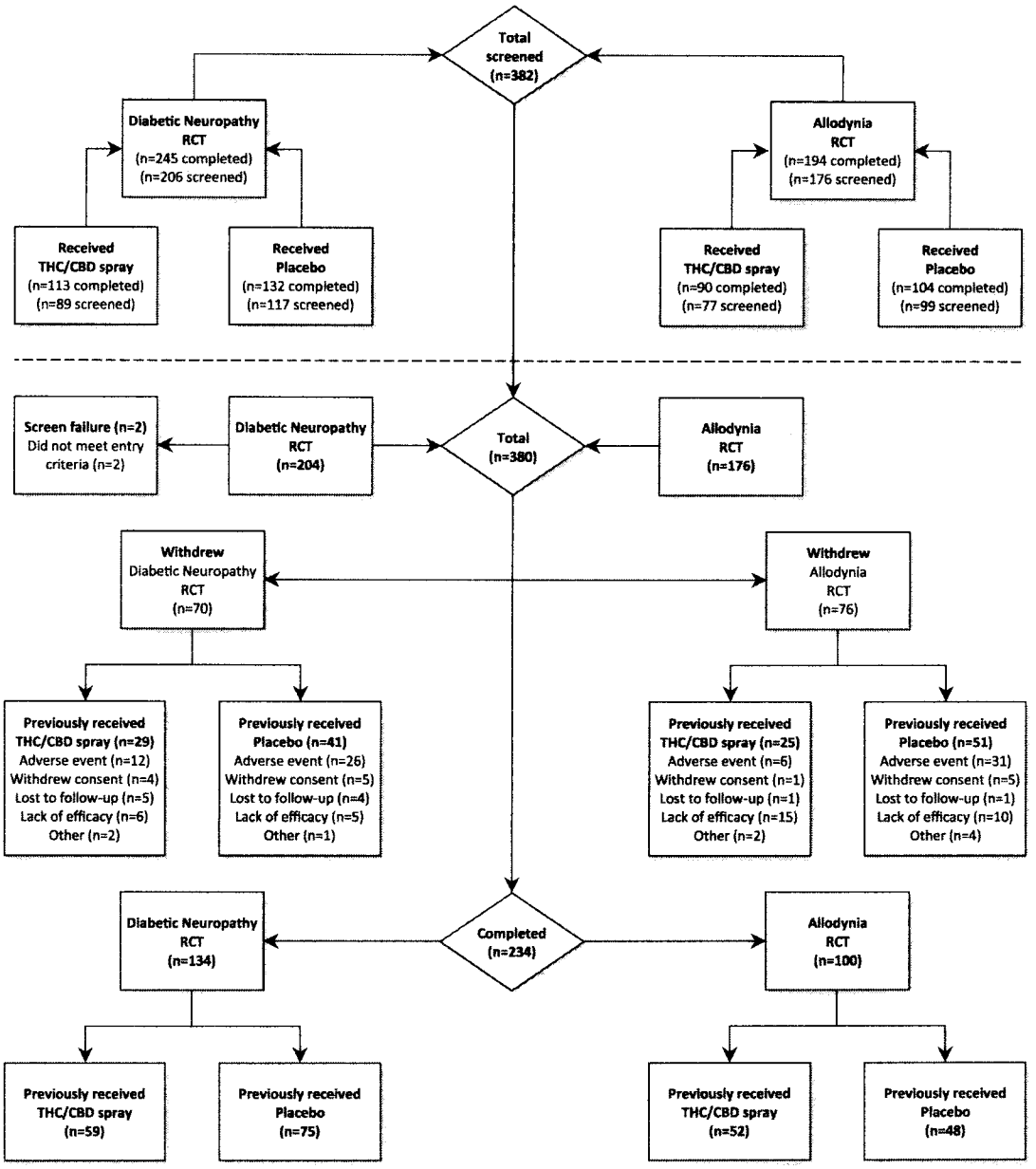

Fig. 1 Disposition of patients

13 % of patients who had received THC/CBD spray in the parent RCTs withdrew from the extension study due to a lack of efficacy compared with 7 % who had received placebo.

Concomitant medication

Concomitant analgesic medication was used by 84 % of patients, many of whom were receiving polypharmacy for pain management. A summary of concomitant medications used during the study is presented in Table 2. The most common analgesics taken at baseline were anticonvulsants, tricyclic anti-depressants, opioids and non-steroidal anti-inflammatory drugs (NSAIDs). The most commonly used non-analgesic concomitant medications were HMG-CoA reductase inhibitors (38 %), ACE inhibitors (35 %), biguanides (29 %) and platelet aggregation inhibitors (25 %).

Eighty-nine percent of patients had a history of previously trying and failing at least one analgesic for their PNP; the two most common being anticonvulsants and NSAIDs.

Table 1 Demographics, baseline characteristics and underlying reason for peripheral neuropathic pain (PNP) by parent randomised control trial (RCT)

Patient demographics and baseline characteristics by parent RCT			
Demographic/characteristic	No. of patients (%)		
	Diabetic neuropathy RCT (n = 204)	Allodynia RCT (n = 176)	Combined (n = 380)
Gender			
Male	122 (60)	78 (44)	200 (53)
Female	82 (40)	98 (56)	180 (47)
Ethnic origin			
White/Caucasian	200 (98)	174 (99)	374 (98)
Black/African American	1 (<0.5)	1 (1)	2 (1)
Hispanic/Latino	1 (<0.5)	0	1 (<0.5)
Asian	2 (1)	0	2 (1)
Others[a]	0	1 (1)	1 (<0.5)
Previous cannabis use (at any time, prior to parent RCTs)	21 (10)	17 (10)	38 (10)
Demographic/characteristic	Mean (SD)		
	Diabetic neuropathy RCT (n = 204)	Allodynia RCT (n = 176)	Combined (n = 380)
Age (years)	59.1 (10.04)	56.3 (13.88)	57.8 (12.03)
Body mass index (kg/m^2)	31.7 (6.95)	27.7 (5.85)	29.9 (6.76)
Duration of any underlying condition causing peripheral neuropathic pain (PNP) (years)	12.29 (8.83)	6.54 (6.82)	9.63 (8.46)
Duration of PNP due to underlying condition (years)	4.99 (4.27)	5.77 (6.27)	5.35 (5.30)
Type of underlying condition causing PNP by parent RCT	No. of patients (%)		
Condition	Diabetic neuropathy RCT (n = 204)	Allodynia RCT (n = 176)	Combined (n = 380)
Focal nerve lesion	–	69 (39)	69 (18)
Peripheral neuropathy	–	46 (26)	46 (12)
Post-herpetic neuralgia	–	40 (23)	40 (11)
Complex regional pain syndrome type 2	–	25 (14)	25 (7)
Diabetes mellitus	204 (100)	–	204 (54)

[a] The patient of "other" ethnic origin was of Chinese/English mixed race

Efficacy results

Pain 0–10 NRS

All patients showed an improvement in pain 0–10 NRS score over the initial weeks of treatment and there was subsequent maintenance of analgesia over time (Fig. 2). The parent RCT data are shown in Table 3. The baseline for the combined parent studies was a mean of 6.9 points that had decreased to 5.5 points by the end of the parent RCTs. This improvement continued with time in the current study. At month 9 that was the end of open-label treatment, the mean pain 0–10 NRS score had reduced further to 4.2 points in the remaining patients (Fig. 2). Moreover, this improvement was observed over a stable background of concomitant analgesic therapy throughout the 9 months of assessment (Table 2). The mean pain score of patients who had previously received placebo during the parent RCTs decreased by 1.4 points over the 9 months of this extension study when they received THC/CBD spray (Table 3).

Table 2 Summary of concomitant analgesic and non-analgesic medications taken by ≥5 % of all patients during the study and by parent randomised controlled trial (RCT)

Number of analgesic medications taken by parent RCT			
Analgesics taken	No. of patients (%)		
	Diabetic neuropathy RCT (n = 204)	Allodynia RCT (n = 176)	Combined (n = 380)
0	47 (23)	12 (7)	59 (16)
≥1	157 (77)	164 (93)	321 (84)
≥2	117 (57)	122 (69)	239 (63)
≥3	66 (32)	84 (48)	150 (39)
≥4	41 (20)	53 (30)	94 (25)

Analgesic medications taken at the start and end of the study		
Analgesic type	No. of patients (total %)	
	Study onset	End of study
Anticonvulsants[a]	167 (44)	173 (46)
Tricyclic anti-depressants[b]	133 (35)	131 (34)
Non-steroidal anti-inflammatories[c]	118 (31)	118 (31)
Other opioids[d]	118 (31)	123 (32)
Other analgesics[e]	88 (23)	97 (26)
Strong opioids[f]	56 (15)	57 (15)

Non-analgesic medications taken during the study by parent RCT			
Non-analgesics	No. of patients (%)		
	Diabetic neuropathy RCT (n = 204)	Allodynia RCT (n = 176)	Combined (n = 380)
HMG CoA reductase inhibitors	120 (59)	25 (14)	145 (38)
ACE inhibitors	111 (54)	23 (13)	134 (35)
Biguanides	108 (53)	4 (2)	112 (29)
Platelet aggregation inhibitors (excl. Heparin)	79 (39)	16 (9)	95 (25)
Fast-acting insulins and analogues	84 (41)	1 (1)	85 (22)
Proton pump inhibitors	46 (23)	38 (22)	84 (22)
Selective beta (β) blocking agents	55 (27)	20 (11)	75 (20)
Sulfonamides	54 (26)	10 (6)	64 (17)
Dihydropyridine derivatives	47 (23)	14 (8)	61 (16)
Sulfonamides, urea derivatives	56 (27)	3 (2)	59 (16)
Angiotensin II antagonists, plain	36 (18)	11 (6)	47 (12)
Thiazides, plain	30 (15)	11 (6)	41 (11)
Intermediate-acting insulins and analogues	40 (20)	0	40 (11)
Long-acting insulins and analogues	40 (20)	0	40 (11)
Glucocorticoids	17 (8)	18 (10)	35 (9)
Thyroid hormones	15 (7)	17 (10)	32 (8)
Intermediate-acting insulins and analogues (combined with fast-acting)	31 (15)	0	31 (8)
Selective β-2 adrenoreceptor agonists	15 (7)	16 (9)	31 (8)
Organic nitrates	24 (12)	6 (3)	30 (8)
Alpha-adrenoreceptor antagonists	15 (7)	8 (5)	23 (6)
Fibrates	20 (10)	3 (2)	23 (6)
Osmotically acting laxatives	9 (4)	13 (7)	22 (6)
Penicillins with extended spectrums	13 (6)	8 (5)	21 (6)
Heparin group	17 (8)	3 (2)	20 (5)
Propulsives	13 (6)	6 (3)	19 (5)

Examples of analgesics included in each class [a] Gabapentin, [b] Amitriptyline, [c] Diclofenac, [d] Codeine, [e] Paracetamol and [f] Morphine

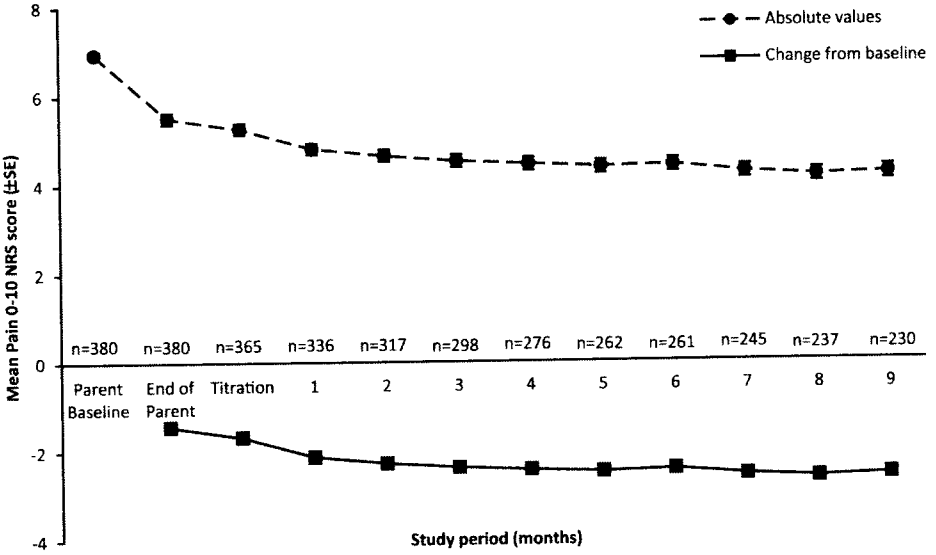

Fig. 2 Patient diary pain 0–10 NRS scores by time (combined patients)

Table 3 Pain 0–10 numerical rating scale scores and new responders at the 30 % improvement level by previous treatment in parent randomised controlled trial (RCT)

Diary pain 0–10 numerical rating scale scores by time and previous treatment in parent RCT												
Study period	Diabetic neuropathy				Allodynia				Combined			
	THC/CBD spray		Placebo		THC/CBD spray		Placebo		THC/CBD spray		Placebo	
	n	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)
Baseline parent RCT	88	6.66 (1.69)	116	6.68 (1.57)	77	7.31 (1.60)	99	7.19 (1.42)	165	6.96 (1.67)	215	6.92 (1.52)
Last week of parent RCT	88	4.65 (2.74)	116	5.11 (2.52)	77	5.87 (2.31)	99	6.43 (1.98)	165	5.22 (2.61)	215	5.72 (2.38)
Current study month 1	81	4.12 (2.44)	104	4.32 (2.30)	69	5.16 (2.26)	82	5.81 (1.96)	150	4.60 (2.41)	186	4.98 (2.27)
Current study month 9	58	3.33 (2.05)	73	3.45 (2.15)	50	5.01 (2.34)	49	5.61 (2.21)	108	4.11 (2.34)	122	4.32 (2.41)

New responders at the 30 % level by previous treatment in parent RCT			
Treatment in parent RCT	No. of patients (%)		
	Diabetic neuropathy (n = 204)	Allodynia (n = 176)	Combined (n = 380)
THC/CBD spray	24 (12)	17 (10)	41 (11)
Placebo	37 (18)	29 (16)	66 (17)

Pain improvement at the 30 and 50 % responder level

A meta-analysis of patients with various painful conditions suggested an approximate 30 % improvement in pain as being clinically significant [21]. The proportion of patients who reported at least a 30 % improvement in pain compared to parent RCT baselines increased with time in this study, with at least half of all patients reporting an improvement in pain at all time points (Fig. 3). Additionally, the number of patients who demonstrated a 50 % improvement increased with time, with a minimum of 30 % of patients at the 50 % improvement level at all time points (Fig. 3). A total of 107 patients (28 % of total) were new responders at the 30 % level of improvement. Of these, 46 (12 % of total) were from the allodynia RCT and 61 (16 % of total) were from the diabetic neuropathy RCT. More than half of these patients (66 patients; 17 % of total) had previously received placebo in the parent RCTs (Table 3).

Secondary efficacy measures

An improvement in the specific NPS scores from the end of the parent RCTs was sustained for the duration of the study and continued to decrease with time until week 26 (Fig. 4). This improvement was seen across all patient groups

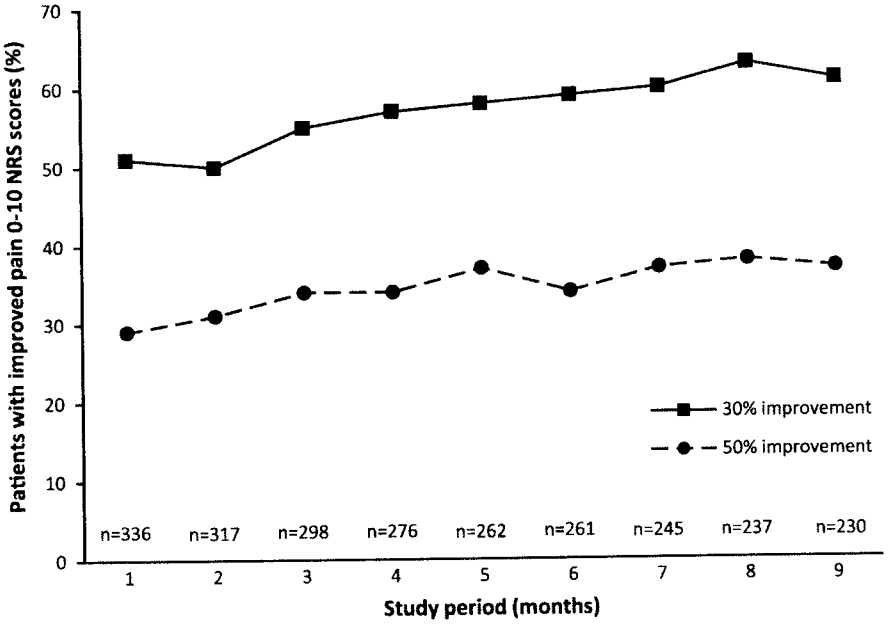

Fig. 3 Pain 0–10 NRS responders at 30 and 50 % improvement by time (combined patients)

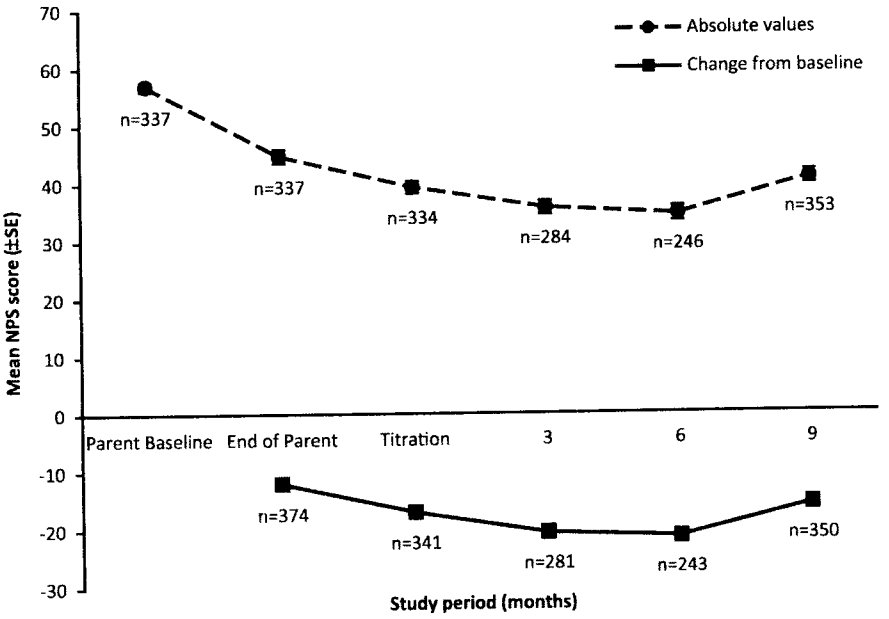

Fig. 4 NPS scores by time (combined patients)

regardless of the type of pain, with a maximum response occurring between 14 and 26 weeks (Fig. 4). The mean NPS total score increased at week 38 (end of treatment) resulting from increased attendance at this visit (94 % attendance at week 38 versus 65 % at week 26). This score therefore gives a better estimate of efficacy and remained an improvement from the end of the parent RCTs.

The summary of responses to treatment at the end of the study in the SGIC analysis is illustrated in Fig. 5. 70 % of patients reported an improvement in nerve pain and only 8 % reported deterioration. 22 % of patients reported no change. Sleep quality 0–10 NRS scores and EQ-5D health questionnaire outcomes, which had improved during the parent RCTs, were maintained for the entire duration of the current study.

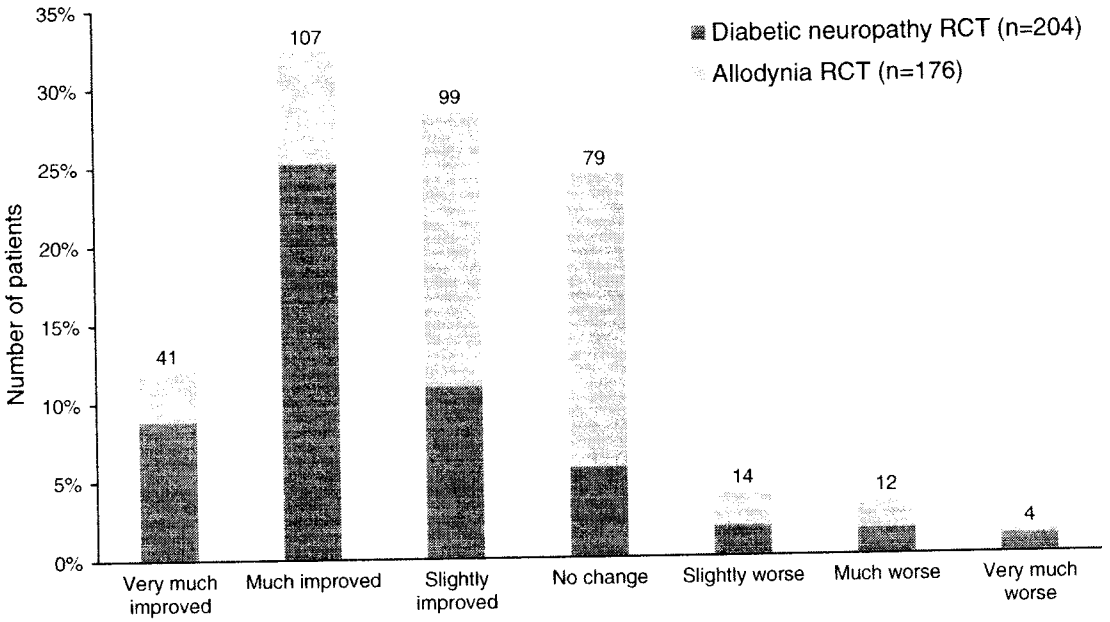

Fig. 5 Subject global impression of change. Total patient numbers for each category are shown above each column

Safety and tolerability

Adverse events

A summary of the most common all-cause and treatment-related AEs with an incidence of 5 % or greater is presented in Table 4. The most common all-cause AEs reported by system organ class (SOC) were nervous system disorders (44 %), gastrointestinal disorders (36 %), general disorders and administration site conditions (24 %), infections and infestations (23 %) and psychiatric disorders (21 %) (Table 4). The only psychiatric disorder with an incidence of 5 % or greater by preferred term was disorientation, experienced by 19 (5 %) of patients.

The most common treatment-related AEs were dizziness (19 %), nausea (9 %), dry mouth (8 %), dysgeusia (7 %), fatigue (7 %), somnolence (7 %) and feeling drunk (6 %). The majority (74 %) of treatment-emergent AEs resolved without sequelae by the end of the study. AEs which were most commonly reported to be continuing at the end of the study were fatigue, dizziness and insomnia.

There were no significant differences in the incidence of AEs reported in relation to the patients' mean daily dose. 77 % in the lower mean dose category (<6.8 actuations per day) reported at least one AE and 78 % in the higher dose category (>6.8 actuations per day) reported at least one AE.

Serious adverse events and deaths

A total of 40 patients (11 %) experienced serious adverse events (SAEs) during the study, with four patients (1 %) experiencing a treatment-related SAE. The prevalent all-cause SAEs reported were in the SOCs of nervous system disorders in ten patients (3 %), infections and infestations in seven patients (2 %), gastrointestinal disorders and general disorders and administration site conditions in five patients (1 %) and cardiac disorders in four patients (1 %). The only SAEs that were considered to be treatment related were in the SOCs of nervous system disorders and psychiatric disorders, with two patients experiencing amnesia, one event of paranoia, and one suicide attempt.

Two deaths were reported during the course of the study. One was from acute pancreatitis and the other from disseminated cancer. Both events were considered to be unrelated to the study medication.

Treatment cessation due to adverse events

Twenty-three percent of patients permanently ceased study medication due to AEs; 7 % due to severe AEs and 18 % due to AEs that were considered to be treatment-related. The majority of these events occurred within the first 7 days of treatment, and were within the SOCs of nervous system disorders and gastrointestinal disorders. Psychiatric AEs that resulted in cessation of study treatment totalled 21 events (5 % of total), 16 of which occurred in patients who had received placebo during the parent RCTs and five in patients who had received THC/CBD spray. Of the 42 patients (11 % of total) who ceased study medication due to nervous system AEs, 28 had previously received placebo in the parent RCT, while 14 had received THC/CBD spray. From the withdrawals due to AEs in the gastrointestinal

Table 4 Most common adverse events (AEs) by primary system organ class and preferred term for patients with at least one AE with an incidence of 5 % or greater by causality

System organ class (SOC)	No. (%) of patients	
Preferred term	All causality	Treatment related
Total patients with at least one adverse event	295 (78)	224 (59)
Nervous system disorders	168 (44)	140 (37)
Dizziness	79 (21)	74 (19)
Dysgeusia	29 (8)	28 (7)
Somnolence	28 (7)	27 (7)
Headache	23 (6)	11 (3)
Gastrointestinal disorders	135 (36)	97 (26)
Nausea	42 (11)	35 (9)
Dry mouth	30 (8)	29 (8)
Vomiting	25 (7)	11 (3)
General disorders and administration site conditions	92 (24)	69 (18)
Fatigue	31 (8)	27 (7)
Feeling drunk	21 (6)	21 (6)
Infections and infestations	89 (23)	9 (2)
Psychiatric disorders	79 (21)	55 (14)
Disorientation	19 (5)	18 (5)
Musculoskeletal and connective tissue disorders	47 (12)	4 (1)
Respiratory, thoracic and mediastinal disorders	43 (11)	16 (4)
Metabolism and nutrition disorders	38 (10)	15 (4)
Injury, poisoning and procedural complications	29 (8)	8 (2)
Vascular disorders	22 (6)	0

disorders SOC (7 % of total), 20 patients had previously received placebo in the parent RCTs and 8 had previously received THC/CBD spray.

Laboratory data and vital signs

The laboratory parameters (biochemistry, haematology and urinalysis) showed no notable trends from baseline and no long-term effects on vital signs were evident.

Intoxication 0–10 NRS

The mean (±SD) baseline intoxication score for the combined parent studies was 0.9 (±2.0) points, which increased to 1.2 (±1.9) points by the end of the parent RCTs. The mean score peaked at 1.9 (±2.3) points following the 2-week titration period and stabilised at 1.5–1.7 (±2.1–2.3) points from 14 weeks onwards. After 9 months of treatment the mean intoxication score was 1.5 (±2.3) points, an increase from baseline of 0.6 (±2.6) points.

Discussion

This study has provided further data to support sustained long-term benefit, safety and tolerability of continued THC/CBD spray use in the management of PNP. Improvements in PNP scores were observed after 4 weeks of treatment with THC/CBD spray and maintained over the 9 months of the study, without an associated increase in daily dose of THC/CBD spray and with no evidence of tolerance developing.

Neuropathic pain is one of the most difficult types of pain to treat [19] and less than half of treated patients receive meaningful benefit with existing drugs, including tricyclic and related anti-depressants, antiepileptic agents and opioids [22]. The population enrolled in this study were diagnosed with neuropathic pain, either secondary to diabetes mellitus or associated with allodynia. They had completed a double-blind RCT of THC/CBD spray for either indication [17, 18]. The majority of patients eligible for this study were already established on a stable dose of regular analgesia (many receiving multiple analgesic medications), but were still experiencing moderate to severe PNP at the onset of the parent RCTs [17, 18].

The population of patients evaluated in this study represented an especially challenging group. The mean duration of PNP was in excess of 5 years and they were largely resistant to existing analgesics. The vast majority reported having tried and failed analgesic therapy in the past. Only a small proportion of patients withdrew from the study due to lack of efficacy and that the majority completed 9 months of treatment with THC/CBD spray with no increase in the number of concomitant analgesic medications suggests that this therapy is effective.

The primary efficacy measure of pain was the 0–10 NRS score that showed an improvement within the first 4 weeks of treatment, especially and not surprisingly in the patients previously exposed to placebo. This positive response was maintained with moderate continuing improvement over the 9-month treatment period being reported by more than half of the patients reaching the final visit. After 9 months of open-label THC/CBD spray treatment, the majority of patients remaining in this study reported a 30 % or more improvement in pain scores from their parent RCT baseline score. This is in line with the findings from the allodynia parent RCT, in which there was a statistically significant improvement in this outcome measure when THC/CBD spray was compared with placebo [17].

In the SGIC efficacy measure, the majority of patients reported an overall improvement in their PNP at the end of

treatment. This is in line with both parent RCTs, in which the improvements in favour of THC/CBD spray versus placebo reached statistical significance in the allodynia RCT [17], but not the diabetic neuropathy RCT [18]. Similar improvements in patient quality of life and pain intensity scores have been reported in other clinical trials of evoked pain using cannabinoids [11, 16, 23–25].

Sustained improvements from baseline were also observed in NPS and sleep quality 0–10 NRS scores. These findings suggest that efficacy is maintained with long-term THC/CBD spray treatment in the majority of patients, an encouraging finding in this normally treatment-resistant patient population. The importance of sleep in chronic pain states has been well documented [26, 27] and one of the main objectives for patients is to gain improved sleep [28], especially since neuropathic pain can be worse at night [29]. Improvements in sleep quality with THC/CBD spray have also been published in both short- and long-term clinical trials [13, 14, 16, 22] including the parent allodynia RCT to the current study, in which a statistically significant improvement in sleep quality was also observed [17]. In addition to THC/CBD spray, these improved sleep quality findings are also consistent with recent studies which looked at other cannabinoid medicines, such as smoked cannabis [24] and synthetic THC [25].

A further positive outcome was that, over the course of the study, there was no evidence of a tolerance developing towards THC/CBD spray, with the median number of daily sprays of THC/CBD spray reducing from 8.0 daily sprays after 1 month of treatment to 6.6 daily sprays during the last month of treatment. Furthermore, the incidence of AEs for this population, who had relatively severe neuropathic pain and were receiving polypharmacy, was reasonably low. The most common treatment-related AEs were dizziness and nausea. These reactions are both well characterised and easily managed and appear to have no long-term sequelae. The majority of AEs resolved and were considered to be either mild or moderate in severity. 23 % of patients discontinued THC/CBD spray due to AEs. By contrast, a meta-analysis of long-term opioid use for chronic non-cancer pain showed 34 % of patients discontinued strong oral opioids due to AEs [30]. No increase in intoxication was observed with long-term use of THC/CBD spray and no new significant safety issues were raised as a result of the study.

Two deaths were reported during this study, but neither was considered related to THC/CBD spray. Four SAEs were considered related to study treatment. These consisted of two events of amnesia, one event of paranoia and one event of suicidal attempt. All events had resolved by the end of the study with the exception of one event of amnesia. There was another event of suicidal ideation that was considered unrelated to THC/CBD spray.

The lifetime prevalence of suicidal ideation in the general population of Europe is estimated at 7.8 % [31]; in chronic pain, this prevalence has been reported to be approximately three times higher at 20 % [32]. Relative to control subjects, the risk of death by suicide was found to at least double in patients with chronic pain, with a lifetime prevalence of suicide attempts of between 5 and 14 % in individuals with chronic pain [32]. Pain and depression coexist [33, 34] as do depression and suicide [35, 36]. Therefore, it is not surprising that the prevalence of depression in chronic pain augments a higher risk of suicidal ideation and suicide attempts. During this 9-month study, the overall incidence of AEs of depressed mood and depression was reasonably low (≤3 %). The relatively high incidence of suicide attempts in the general chronic pain population and the other confounding factors in these two cases, which included previous suicide attempts, depression related to diabetes/chronic pain and difficult social circumstances, suggests a direct causality with THC/CBD spray is unlikely.

Study limitations

As this was an open-label study with no possibility of comparing with a placebo, it is possible that the observed maintenance of efficacy with THC/CBD spray could be attributable to causes other than the study medication. These include changes in the underlying disease across time or changes in the set of patients in the study- and efficacy-related withdrawals. As such, a randomised withdrawal study would further ascertain whether efficacy of THC/CBD spray is maintained after long-term treatment. This was attempted as an addition to the current study, yet no clear efficacy conclusions could be reached due to low numbers of participants (19 patients), many of which were non-responders to initial THC/CDB treatment.

Conclusions

In conclusion, neuropathic pain can be a distressful and disabling condition with existing management options providing insufficient relief for patients and often causing a significant number of side effects. The patients enrolled in this study had advanced long-lasting treatment-resistant disease and were significantly disabled. The results of this study show that THC/CBD spray is an efficacious option in neuropathic pain management that can be maintained for long-term use. Furthermore, patients who continue to use THC/CBD spray for the duration of the study do not increase their daily dose, nor do they seek to increase their use of other pain-relieving medications over time. This study meets the objectives described in the CHMP

neuropathic pain guidelines [19] regarding maintenance and/or development of tolerance to the effect of the medicine. The benefits for these patients seem to outweigh the risks of treatment and suggest that THC/CBD spray may provide an effective option for patients with neuropathic pain.

Conflicts of interest B. Hoggart, S. Ratcliffe, E. Ehler, K. H. Simpson, J. Hovorka, J. Lejčko and M. Serpell were all investigators in this study and received investigator fees from GW Pharma Ltd. accordingly for their participation in the study. GW Medical Writers L. Taylor, H. Lauder and S. M. Greenwood undertook the initial compilation and quality control review of the manuscript. Together with the other authors, the target journal was then agreed and all authors reviewed and contributed to the content of the manuscript and agreed upon the final submitted version. All intellectual property rights arising out of the current clinical study are vested in or exclusively licenced to GW.

Ethical standards The study was approved by the Institutional Review Boards or Ethical Committees in each of the countries in which it was run and was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines.

Informed consent All patients gave informed consent prior to their inclusion in the study and before any study-related procedures were carried out.

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Appendix B (Section H)

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RESEARCH PAPER

Cannabidiol inhibits paclitaxel-induced neuropathic pain through 5-HT$_{1A}$ receptors without diminishing nervous system function or chemotherapy efficacy

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Keywords
cannabidiol; paclitaxel; chemotherapy-induced neuropathic pain; CIPN; 5-HT$_{1A}$; breast cancer; cannabinoid; mechanical sensitivity

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BACKGROUND AND PURPOSE

Paclitaxel (PAC) is associated with chemotherapy-induced neuropathic pain (CIPN) that can lead to the cessation of treatment in cancer patients even in the absence of alternate therapies. We previously reported that chronic administration of the non-psychoactive cannabinoid cannabidiol (CBD) prevents PAC-induced mechanical and thermal sensitivity in mice. Hence, we sought to determine receptor mechanisms by which CBD inhibits CIPN and whether CBD negatively effects nervous system function or chemotherapy efficacy.

EXPERIMENTAL APPROACH

The ability of acute CBD pretreatment to prevent PAC-induced mechanical sensitivity was assessed, as was the effect of CBD on place conditioning and on an operant-conditioned learning and memory task. The potential interaction of CBD and PAC on breast cancer cell viability was determined using the MTT assay.

KEY RESULTS

PAC-induced mechanical sensitivity was prevented by administration of CBD (2.5 – 10 mg·kg^{-1}) in female C57Bl/6 mice. This effect was reversed by co-administration of the 5-HT$_{1A}$ antagonist WAY 100635, but not the CB$_1$ antagonist SR141716 or the CB$_2$ antagonist SR144528. CBD produced no conditioned rewarding effects and did not affect conditioned learning and memory. Also, CBD + PAC combinations produce additive to synergistic inhibition of breast cancer cell viability.

CONCLUSIONS AND IMPLICATIONS

Our data suggest that CBD is protective against PAC-induced neurotoxicity mediated in part by the 5-HT$_{1A}$ receptor system. Furthermore, CBD treatment was devoid of conditioned rewarding effects or cognitive impairment and did not attenuate PAC-induced inhibition of breast cancer cell viability. Hence, adjunct treatment with CBD during PAC chemotherapy may be safe and effective in the prevention or attenuation of CIPN.

Abbreviations
CB, cannabinoid; CBD, cannabidiol; CI, combination index; CIPN, chemotherapy-induced peripheral neuropathy; CPP, conditioned place preference; CRM, cremophor; PAC, paclitaxel; THC, tetrahydrocannabinol; TRPV, transient receptor potential vanilloid

Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is a serious dose-limiting side effect associated with several commonly used chemotherapeutic agents, including taxanes, platinum agents and vinca alkaloids. CIPN occurs in 30–40% of patients but incidences can approach 75% with certain regimens. Common peripheral sensory symptoms include paresthesias and dysesthesias, pain, numbness and tingling, and sensitivity to touch and temperature. Motor symptoms include weakness and gait and balance disturbances (Visovsky *et al.*, 2007). In most cases, CIPN is only partially reversible with cessation of treatment and in the worst cases damage can be permanent. To date, no one drug or drug class is considered to be safe and effective for treatment of CIPN (Lynch *et al.*, 2004), making the identification of alternative effective analgesics a crucial medical need.

The exact mechanism of CIPN has not been fully elucidated and can differ across classes of chemotherapeutic agents. In general, these agents can affect cellular microtubules, disrupt mitochondrial function or impair DNA synthesis. Such assaults on peripheral nerves can lead to sensitization and spontaneous activity of these fibres (Xiao and Bennett, 2008), alteration of voltage-gated sodium and transient receptor potential vanilloid (TRPV) channel activity and expression (Adelsberger *et al.*, 2000; Gauchan *et al.*, 2009), dorsal column ascending fibre pathology (Cavaletti *et al.*, 1995), and infiltration of activated microglia and release of pro-inflammatory cytokines (Hu and McLachlan, 2002), ultimately leading to ascending pain pathway sensitization (Peters *et al.*, 2007). Functional changes to the descending inhibitory pain pathway can also result, altering noradrenaline and 5-HT signalling and further amplifying the effects of central sensitization (Baron *et al.*, 2010).

Cannabinoids suppress neuropathic pain induced by traumatic nerve injury, toxic insults and metabolic changes (for review, see Guindon and Hohmann, 2008). The mixed CB_1/CB_2 agonist WIN55,212-2 suppresses neuropathic nociception induced by the chemotherapeutic agent paclitaxel (PAC) through a CB_1-specific mechanism (Pascual *et al.*, 2005). WIN55,212-2 also suppresses vincristine-induced neuropathy through activation of both CB_1 and CB_2 receptors (Rahn *et al.*, 2007). Activation of CB_2 receptors partially attenuates vincristine-induced neuropathy (Rahn *et al.*, 2007) and fully attenuates PAC-induced neuropathy (Rahn *et al.*, 2008; Deng *et al.*, 2012) in rats. In humans, several studies have demonstrated anti-neuropathic effects of whole cannabis, Δ^9-tetrahydrocannabinol (THC), or its synthetic analogues nabilone or dronabinol (Pinsger *et al.*, 2006; Skrabek *et al.*, 2008; Ware *et al.*, 2010). However, several reports describe these effects as modest, while others have reported negative results (Wade *et al.*, 2004; Johnson *et al.*, 2010). Importantly, patients in the vast majority of studies also report several adverse events such as dizziness, dryness, sedation, disorientation and decreased concentration, and while these were not categorized as serious they probably limit the tolerability and compliance with such treatments.

One of the more successful cannabis-based pharmaceuticals for the treatment of pain is the buccal spray Sativex [1:1 formulation of THC and the phytocannabinoid cannabidiol (CBD)], approved in the EU and Canada for treatment of multiple sclerosis spasticity, with an additional license in Canada for use in multiple sclerosis-associated neuropathic pain and cancer pain. Sativex has recently entered directly into US late-stage trials because of its promising therapeutic uses, and has shown pain-relieving effects in two recent clinical trials: one for cancer pain (Johnson *et al.*, 2010) and one for neuropathic pain associated with multiple sclerosis (Langford *et al.*, 2013). However, the psychoactive side effects of Sativex mediated by THC may limit its broader utility in the clinic. For example, THC and Sativex have been determined to produce similar subjective and physiological effects (Johnson *et al.*, 2010; Karschner *et al.*, 2011). However, mounting preclinical evidence now demonstrates that CBD alone has anti-neuropathic effects (Costa *et al.*, 2007; Toth *et al.*, 2010; Xiong *et al.*, 2012; see Fernández-Ruiz *et al.*, 2013 for review). To date, no clinical trials have yet commenced to study the efficacy of the non-psychoactive CBD as a monotherapy for the treatment of neuropathic pain. We have recently reported that 14 days of administration of CBD prevents the onset of PAC-induced mechanical and thermal sensitivity in a female mouse model of CIPN (Ward *et al.*, 2011).

In the present set of experiments, we aimed to determine whether sub-chronic dosing regimen of CBD would prevent PAC-induced mechanical sensitivity while also determining whether this effect is mediated by activation of 5-HT_{1A} receptors. CBD binds to the 5-HT_{1A} receptor as an agonist with micromolar affinity (Russo *et al.*, 2005), and research has demonstrated potent anti-neuropathic effects with 5-HT_{1A} agonists (e.g. Colpaert, 2006). Indeed, intra-periaqueductal grey injection of CBD produces dose-dependent antinociception that is blocked by co-administration of the 5-HT_{1A} antagonist WAY100635 (Maione *et al.*, 2011). Lastly, we also sought to determine whether treatment with CBD would have any effects on conditioned reward, learning and memory, and the inhibitory activity of PAC on breast cancer cell viability.

Methods

Animals. Female C57Bl/6 mice weighing 16–20 g (Taconic Farms, Cranbury, NJ, USA; Jackson Labs, Chicago, IL, USA) were acclimatized to the temperature- and humidity-controlled vivarium and housed in groups of four for at least 5 days before initiation of behavioural studies. Artificial

lighting provided a reverse 12 h light/dark cycle (lights off 10:00 h). The animals had free access to dietary food and water except where noted. The total number of animals used was 240 and the procedures used were as humane as possible and complied with the guidelines of the Temple University Institutional Animal Care and Use Committee. All studies involving animals are reported in accordance with the ARRIVE guidelines for reporting experiments involving animals (Kilkenny *et al.*, 2010; McGrath *et al.*, 2010).

Drugs. PAC solution [Teva Parenteral Medicines: dissolved in 1:1 mixture of alcohol and cremophor (CRM)] was obtained from Temple University Hospital Cancer Center (Philadelphia, PA, USA). For cell viability studies in breast cancer cell lines, PAC was obtained from Sigma (St. Louis, MO, USA). CBD, morphine sulfate, and the CB_1 (SR141716A) and CB_2 receptor (SR144528) antagonist were provided by the National Institute on Drug Abuse drug supply program (Bethesda, MD, USA). WAY100635 was purchased from RBI. PAC was diluted in 0.9% saline. CBD was dissolved in a 1:1 mixture of ethanol and CRM (Sigma-Aldrich, St. Louis, MO, USA) and diluted with saline to a final ratio of 1:1:18 (ethanol : CRM : saline). Morphine and WAY100635 were dissolved in 0.9% saline. All injections were given i.p. in a volume of 10 $\mu L \cdot g^{-1}$ of body weight.

Mechanical allodynia

In the first set of experiments, mechanical allodynia was assessed in five groups of mice (n = 8 per group) using von Frey monofilaments of varying forces (0.07–4.0 g) applied to the mid-plantar surface of the right hind paw, with each application held in c-shape for 6 s using the up-down method of Dixon (1980). Mice were placed in individual Plexiglas compartments (Med Associates, St. Albans, VT, USA) on top of a wire grid floor suspended 20 cm above the laboratory bench top and acclimatized to the environment for 15 min before each test session. Baseline sensitivity to the monofilaments was assessed 1 day before the start of drug administration and continued weekly for 10 weeks. On experimental days 1, 3, 5 and 7, mice received the following two i.p. injections, spaced 15 min apart: group 1 – CRM vehicle, CRM vehicle; group 2 – CRM vehicle, 4.0 $mg \cdot kg^{-1}$ PAC; group 3 – CRM vehicle, 8.0 $mg \cdot kg^{-1}$ PAC; group 4 – 2.5 $mg \cdot kg^{-1}$ CBD, 8.0 $mg \cdot kg^{-1}$ PAC; 5.0 $mg \cdot kg^{-1}$ CBD, 8.0 $mg \cdot kg^{-1}$ PAC. Mechanical allodynia was not assessed on injection days. PAC and CBD doses were based on significant findings from Ward *et al.* (2011).

In the second set of experiments, mechanical allodynia was assessed in an identical manner to that described above. Four groups of mice were treated on experimental days 1, 3, 5 and 7 with three i.p. injections spaced 15 min apart: group 1 – saline, CRM vehicle, CRM vehicle; group 2 – saline, CRM vehicle, 8.0 $mg \cdot kg^{-1}$ PAC; group 3 – saline, 5.0 $mg \cdot kg^{-1}$ CBD, 8.0 $mg \cdot kg^{-1}$ PAC; group 4 – 1.0 $mg \cdot kg^{-1}$ WAY100635, 5.0 $mg \cdot kg^{-1}$ CBD, 8.0 $mg \cdot kg^{-1}$ PAC. Dose of WAY100635 was based on several studies investigating blockade of 5-HT_{1A} agonist-mediated behavioural pharmacological effects (e.g. Hagiwara *et al.*, 2008).

In the third set of experiments, mechanical allodynia was assessed 1 day before the start of drug administration and on day 15 following the first injections. Five groups of mice were treated on experimental days 1, 3, 5 and 7 with three i.p. injections spaced 15 min apart: group 1 – saline, CRM vehicle, CRM vehicle; group 2 – saline, CRM vehicle, 8.0 $mg \cdot kg^{-1}$ PAC; group 3 – saline, 5.0 $mg \cdot kg^{-1}$ CBD, 8.0 $mg \cdot kg^{-1}$ PAC; group 4 – 3.0 $mg \cdot kg^{-1}$ SR141716, 5.0 $mg \cdot kg^{-1}$ CBD, 8.0 $mg \cdot kg^{-1}$ PAC; group 5 – 3.0 $mg \cdot kg^{-1}$ SR144528, 5.0 $mg \cdot kg^{-1}$ CBD, 8.0 $mg \cdot kg^{-1}$ PAC. Doses of SR141716 and SR144528 were based on several studies investigating blockade of CB_1 and CB_2 agonist-mediated effects respectively (Rahn *et al.*, 2007; 2008).

Place conditioning

The conditioned rewarding effects of CBD and morphine were assessed using a standard mouse place conditioning procedure and Med Associates mouse three compartment place conditioning chambers (MED-CPP-3013). Mice received vehicle or morphine (2.5–10 $mg \cdot kg^{-1}$, i.p.; 15 min pretreatment) or vehicle or CBD (2.5–10 $mg \cdot kg^{-1}$, i.p.; 30 min pretreatment) on alternate days for 30 min conditioning sessions for 6 successive days. Vehicle injections were paired with the black compartment and the drug injections with the white compartment of the conditioned place preference (CPP) apparatus. On day 7, test sessions were conducted where mice in a drug-free state had 30 min free access to all chambers following an initial 5 min acclimation in the central grey compartment. The time spent in the drug- and vehicle-paired compartments was recorded on the test day and the data are presented as time spent in the drug-paired compartment.

Autoshaping

The effect of CBD (2.0–20 $mg \cdot kg^{-1}$, i.p.) on acquisition and retention of a conditioned learning task was assessed using a modified autoshaping procedure and Med Associates mouse operant conditioning chambers (ENV 307W) as described in Foley *et al.* (2008). Briefly, mice were weighed and food-restricted for 24 h before the experimental session. On the acquisition day, mice were placed inside a standard mouse experimental chamber, and the availability of a sweet liquid reinforcer (50% vanilla Ensure in tap water; Abbott Laboratories, Columbus, OH, USA) under a variable interval schedule was signalled by a tone. The mouse was reinforced with the vanilla Ensure if it made a nose-poke response into a centre dipper receptacle during an 8 s period following the tone. Each acquisition session lasted for 2 h or until 20 reinforced nose pokes were recorded. For the retention test, mice were placed back into the chambers 24 h following the acquisition session under the same conditions. In the present experiment, mice were pretreated with vehicle or CBD 30 min before the acquisition session.

Cell culture and treatments

The mouse and human breast cancer cell lines used were 4T1 (obtained from ATCC) and MDA-MB231-luc-D3H2LN (obtained from Caliper; Jenkins *et al.*, 2005) cells respectively. Cell lines were maintained at 37°C and 5% CO_2. In all experiments, the different cell populations were first cultured in RPMI media containing 10% FBS. Cells were then seeded into 96-well plates in 10% FBS and on the first day of treatment the media was replaced with vehicle control or drug in RPMI and 0.1% FBS as previously reported (McAllister *et al.*, 2005). The media with the appropriate compounds were replaced every 24 h.

MTT assay

Assays were performed as previously described (McAllister *et al.*, 2007). Cell viability (%) was calculated as the MTT absorbance of the treated cells/control cells × 100.

Pharmacological and statistical analyses

IC_{50} values were calculated using CompuSyn (Paramus, NJ, USA). To test for synergism, the combination index (CI) was also calculated using Compusyn where CI <1, = 1 and >1 indicates synergism, additive effect and antagonism, respectively, as previously described (Chou *et al.*, 1993; Chou, 2006) and as previously published by our group (Marcu *et al.*, 2010). Based on the classic isobologram for mutually exclusive effects relative to the end point of measurement, the CI value for x % inhibition is calculated as: $CI = (D)_1/(Dx)1 + (D)_2/(Dx)_2$.

$(D)_1$ PAC; $(D)_2$ represents CBD; $(Dx)_1$ and $(Dx)_2$ are the doses for x% growth that can be obtained using the IC_F equation described above. $(D)_1$ and $(D)_2$ are the concentrations in the combination which also inhibit cell growth by x % (Chou *et al.*, 1993).

Results

Mechanical allodynia

Treatment with either 4.0 or 8.0 mg·kg^{-1} PAC on alternating days for a total of four injections produced mechanical sensitivity in female C57Bl/6 mice. Peak sensitivity was achieved by week 2 post-treatment and lasted for the full 10 weeks of the study for the 8.0 mg·kg^{-1} PAC dose. Co-administration of either 2.5 or 5.0 mg·kg^{-1} CBD 15 min prior to each PAC injection prevented PAC-induced mechanical sensitivity. Two-way ANOVA revealed significant main effects of treatment [$F(4, 310) = 27.71$, $P < 0.0001$] and time [$F(9, 310) = 5.001$, $P < 0.001$] and no significant interaction ($F < 1.0$). Bonferroni post-tests revealed a significant increase in sensitivity in both the 4.0 and 8.0 mg·kg^{-1} PAC groups compared with Veh/Veh. In contrast, the PAC groups pretreated with either 2.5 or 5.0 mg·kg^{-1} CBD were not significantly different from Veh/Veh in their mechanical sensitivity (Figure 1).

Additional administration of the 5-HT_{1A} antagonist WAY 100635 (1.0 mg·kg^{-1}) before PAC and CBD treatment attenuated the reversal of PAC-induced mechanical sensitivity by CBD. Two-way ANOVA revealed significant effects of treatment [$F(3, 280) = 24.66$, $P < 0.0001$] and time [$F(9, 280) = 5.058$, $P < 0.001$] and no significant interaction ($F < 1.0$). Bonferroni post-test revealed a significant increase in the sensitivity of the PAC group and the WAY/CBD/PAC groups compared with Veh/Veh/Veh. In contrast, the Veh/CBD/PAC group did not differ significantly from the Veh/Veh/Veh group on mechanical sensitivity (Figure 2).

Conversely, additional administration of either the CB_1 antagonist SR141716 (3.0 mg·kg^{-1}) or the CB_2 antagonist SR144528 (3.0 mg·kg^{-1}) had no effect on the reversal of PAC-induced mechanical sensitivity by CBD as measured on day 15 post-initiation of treatment. One-way ANOVA revealed a significant effect of treatment [$F(8, 79) = 7.647$, $P < 0.05$]. Dunnett's multiple comparison test determined that only the Veh/Veh/PAC, WAY/CBD/PAC, SR1/Veh/PAC and SR2/Veh/PAC groups were statistically different from the Veh/Veh/Veh

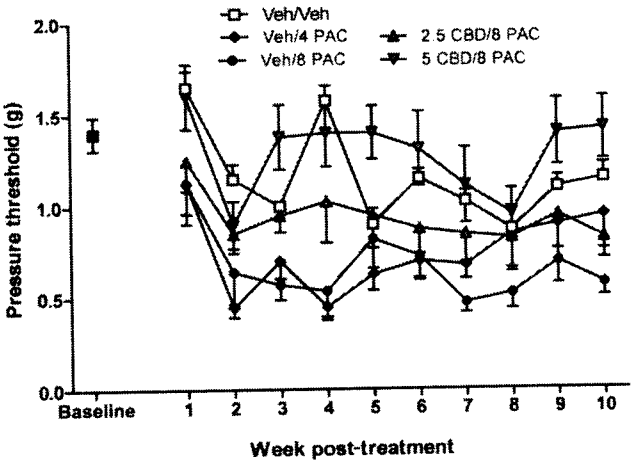

Figure 1

Effect of CBD pretreatment (2.5, 5.0 mg·kg^{-1}, i.p.) on PAC-induced mechanical allodynia in female C57Bl/6 mice. Baseline sensitivity to von Frey filaments was assessed on the day before drug administration and continued weekly for 10 weeks. Mice received the following two i.p. injections spaced 15 min apart on days 1, 3, 5 and 7: CRM vehicle, CRM vehicle; CRM vehicle, 4.0 mg·kg^{-1} PAC; CRM vehicle, 8.0 mg·kg^{-1} PAC; 2.5 mg·kg^{-1} CBD, 8.0 mg·kg^{-1} PAC; 5.0 mg·kg^{-1} CBD, 8.0 mg·kg^{-1} PAC. Two-way ANOVA revealed significant main effects of treatment [$F(4, 310) = 27.71$, $P < 0.0001$] and time [$F(9, 310) = 5.001$, $P < 0.001$] and no significant interaction ($F < 1.0$). Bonferroni post-tests revealed a significant increase in sensitivity in both the 4.0 and 8.0 mg·kg^{-1} PAC groups compared with Veh/Veh. In contrast, the PAC groups pretreated with either 2.5 or 5.0 mg·kg^{-1} CBD were not significantly different from Veh/Veh in their mechanical sensitivity. *X*-axis: time points pre- or post-day first injection. *Y*-axis: threshold pressure to elicit hind paw withdrawal from von Frey filament. Data points represent the mean and SEM, $n = 8$ per group.

control group ($P < 0.05$), showing significant mechanical allodynia (Figure 3). Furthermore, the ability of WAY to block CBD's anti-allodynic effect could not be attributed to the effect of WAY alone on PAC-induced mechanical sensitivity, as WAY itself did not potentiate the effect of PAC alone (WAY/Veh/PAC).

Place conditioning and autoshaping

There was no effect of CBD on time spent in the white, CBD-paired compartment compared with CRM vehicle control, although there was a trend towards a decrease in the time spent in the CBD-paired compartment at the highest dose tested. One-way ANOVA revealed no significant effect of treatment [$F(3, 31) = 2.477$, n.s.]. By comparison, morphine treatment significantly increased the time spent in the white, morphine-paired compartment compared with saline vehicle control [$F(3, 30) = 15.66$, $P < 0.0001$] (Figure 4). Furthermore, CBD treatment had no effect on the time to earn 10 reinforcers during the acquisition [$F(3, 32) < 1$] or retention [$F(3, 25) = 1.692$, n.s.] sessions (Figure 5).

CBD enhances PAC inhibition of breast cancer cell viability

Multiple studies now show that CBD can act as a direct antitumor agent against aggressive cancers (Massi *et al.*,

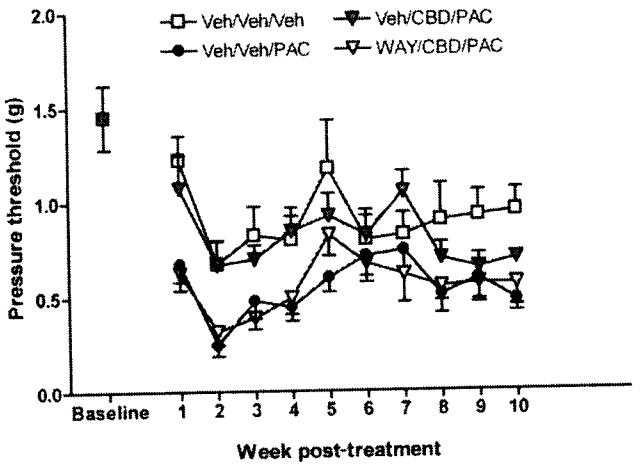

Figure 2

Effect of WAY100635 pretreatment (1.0 mg·kg^{-1}, i.p.) on CBD prevention of PAC-induced mechanical allodynia in female C57Bl/6 mice. Baseline sensitivity to von Frey filaments was assessed on the day before drug administration and continued weekly for 10 weeks. Mice received the following three i.p. injections spaced 15 min apart on days 1, 3, 5 and 7: saline, CRM vehicle, CRM vehicle; saline, CRM vehicle, 8.0 mg·kg^{-1} PAC; saline, 5.0 mg·kg^{-1} CBD, 8.0 mg·kg^{-1} PAC; 1.0 mg·kg^{-1} WAY100635, 5.0 mg·kg^{-1} CBD, 8.0 mg·kg^{-1} PAC. Two-way ANOVA revealed significant effects of treatment [$F(3, 280) = 24.66$, $P < 0.0001$] and time [$F(9, 280) = 5.058$, $P < 0.001$] and no significant interaction ($F < 1.0$). Bonferroni post-test revealed a significant increase in the sensitivity of the PAC group and the WAY/CBD/PAC groups compared with Veh/Veh/Veh. In contrast, the Veh/CBD/PAC group did not differ significantly from the Veh/Veh/Veh group on mechanical sensitivity. *X*-axis: time points pre- or post-day first injection. *Y*-axis: threshold pressure to elicit hind paw withdrawal from von Frey filament. Data points represent the mean and SEM, $n = 8$ per group.

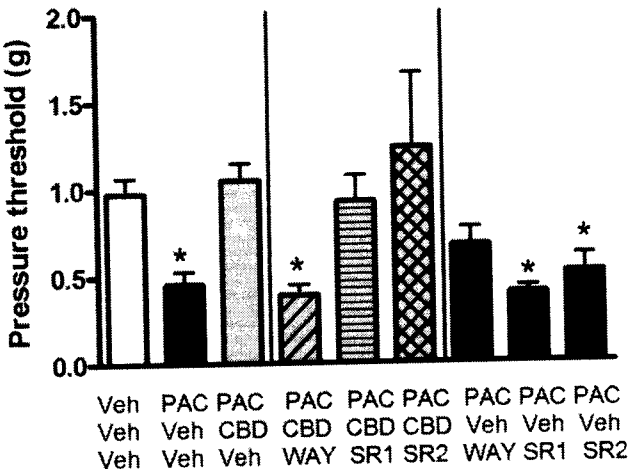

Figure 3

Effect of CB_1 (SR141716; SR1) or CB_2 (SR144528; SR2) receptor antagonism on CBD prevention of PAC-induced mechanical allodynia in female C57Bl/6 mice. Sensitivity to von Frey filaments was assessed on day 15 post-treatment. Mice received the following three i.p. injections spaced 15 min apart on days 1, 3, 5 and 7: saline, CRM vehicle, CRM vehicle; saline, CRM vehicle, 8.0 mg·kg^{-1} PAC; saline, 5.0 mg·kg^{-1} CBD, 8.0 mg·kg^{-1} PAC; 1.0 mg·kg^{-1} WAY, 5.0 mg·kg^{-1} CBD, 8.0 mg·kg^{-1} PAC; 3.0 mg·kg^{-1} SR141716, 5.0 mg·kg^{-1} CBD, 8.0 mg·kg^{-1} PAC; 3.0 mg·kg^{-1} SR144528, 5.0 mg·kg^{-1} CBD, 8.0 mg·kg^{-1} PAC; 1.0 mg·kg^{-1} WAY, CRM, 8.0 mg·kg^{-1} PAC; 3.0 mg·kg^{-1} SR141716, CRM, 8.0 mg·kg^{-1} PAC; 3.0 mg·kg^{-1} SR144528, CRM, 8.0 mg·kg^{-1} PAC. One-way ANOVA revealed a significant effect of treatment [$F(8, 79) = 7.647$, $P < 0.05$]. Dunnett's multiple comparison test determined that only the Veh/Veh/PAC, WAY/CBD/PAC, SR1/Veh/PAC and SR2/Veh/PAC groups were statistically different from the Veh/Veh/Veh control group ($P < 0.05$). *X*-axis: treatment. *Y*-axis: threshold pressure to elicit hind paw withdrawal from von Frey filament. Data points represent the mean and SEM, $n = 8$ per group.

2013). Therefore, there is the potential for CBD to produce synergistic, additive or antagonist effects when combined with PAC. We studied these potential interactions by evaluating the effects of the drugs alone and in combination on breast cancer cell viability. 4T1 and luciferase-labelled MDA-MB231-luc-D3H2LN (LN 231) cells were treated for 2 days with a range of concentrations of either PAC or CBD and the ability of the drugs to inhibit cell viability was assessed using the MTT assay (Figure 6A). In this assay, CBD was more potent than PAC at inhibiting cell viability and CBD acted as a full agonist whereas PAC acted as a partial agonist. PAC could not fully inhibit cell viability even up to concentration of 50 μM. PAC began to precipitate out of solution in the MTT assay at the higher concentration range which precluded us from further concentrating the drug. The average values from the concentration response curves which were then used to derive medium-effect plot parameters including the dose-reduction index were calculated (Table 1). Using the calculated IC_{50} values, various dose ratios of CBD and PAC were combined in both 4T1 and LN 231 cells and viability was evaluated (Figure 6B and C). The use of higher dose ratios was limited by the solubility of PAC; however, this did not affect the calculation of a CI. As shown in Figure 6D, the combination of CBD and PAC led to an additive and synergistic inhibition of cell viability in 4T1 and LN 231 cells respectively.

Discussion

We had previously reported that a 14 day dosing regimen of CBD (5.0 and 10 mg·kg^{-1}) prevented the onset of PAC-induced mechanical and thermal sensitivity (Ward *et al.*, 2011). In the present study, we determined that both 2.5 and 5 mg·kg^{-1} CBD treatment, administered only before each of the four PAC injections of a standard dosing regimen for inducing CIPN in rodents, also prevents the development of PAC-induced mechanical sensitivity in female C57Bl/6 mice. The present study further demonstrated that 5-HT_{1A} receptors are partially involved in the neuroprotective effect of CBD in this model, in that co-administration of the 5-HT_{1A} antagonist blocked the preventive effect of CBD on PAC-induced mechanical sensitivity. In contrast, neither the CB_1 antagonist SR141716 nor the CB_2 antagonist SR144528 affected the efficacy of CBD, suggesting its neuroprotective effect was not mediated by activation of CB_1 or CB_2 receptors. Furthermore,

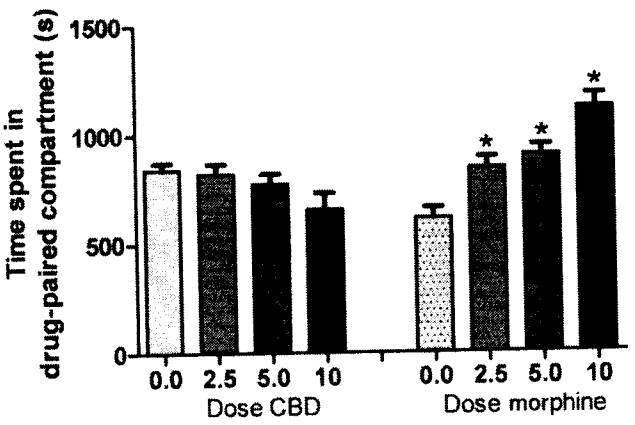

Figure 4

Ability of CBD (2.5–10 mg·kg^{-1}, i.p.) or morphine (2.5–10 mg·kg^{-1}, i.p.) to produce place conditioning in female C57Bl/6 mice. Mice received vehicle or morphine (2.5–10 mg·kg^{-1}, i.p.; 15 min pretreatment) or vehicle or CBD (2.5–10 mg·kg^{-1}, i.p.; 30 min pretreatment) on alternate days for 30 min conditioning sessions for 6 successive days. One-way ANOVAS revealed no significant effect of CBD treatment [$F(3, 31) = 2.477$, n.s.] and a significant effect of morphine treatment on time spent in the white compartment compared with saline vehicle control [$F(3, 30) = 15.66$, $P < 0.0001$]. *X*-axis: treatment. *Y*-axis: the time spent in the drug-paired (white) compartment on the treatment-free test day.

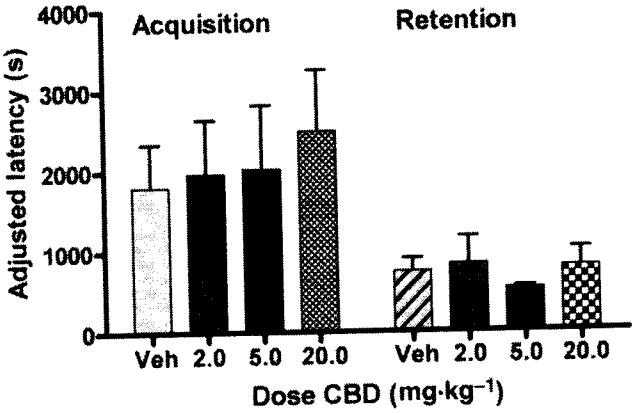

Figure 5

Effect of CBD administration (2.5–20 mg·kg^{-1}, i.p.) on acquisition and retention of a conditioned food reward task. Nose-poke responses are reinforced when made within 8 s following a tone signalling availability of the sweet liquid reinforcer (50% vanilla Ensure in tap water). Each session lasted for 2 h or until 20 reinforced nose pokes were recorded. CBD treatment had no effect on the time to earn 10 reinforcers during the acquisition [$F(3, 32) = <1$] or retention [$F(3, 25) = 1.692$, n.s.] sessions. *X*-axis: treatment. *Y*-axis: the time elapsed between the first earned reinforcer and the tenth reinforcer.

treatment with the antagonists alone did not further exacerbate PAC-induced mechanical sensitivity. In addition, CBD did not produce conditioned rewarding effects using the place conditioning procedure, nor did it produce deficits in acquisition or retention of an operant learning task using the autoshaping procedure. Lastly, CBD did not attenuate the anti-neoplastic effect of PAC on breast cancer cells in culture. Indeed, at optimal concentrations, CBD + PAC combinations produce additive to synergistic inhibition of breast cancer cell viability.

Cannabinoids represent a promising pharmacotherapeutic strategy for treatment of neuropathic pain considering that available alternatives are not always successful in the clinic. A putative role for cannabinoids in the amelioration of established PAC-induced CIPN has recently been demonstrated. Pascual *et al.* (2005) showed that the non-selective cannabinoid agonist WIN 55,212-2 reduced an established thermal hyperalgesia and tactile allodynia 22 days post-PAC treatment in rats, and that this effect was blocked by the CB_1 antagonist SR141716, suggesting the involvement of the CB_1 receptor; the potential participation of the CB_2 receptor in mediating this effect, however, was not investigated. The anti-neuropathic efficacy of non-selective CB agonist therapies, including the THC : CBD combination Sativex, appears promising; nonetheless, unwanted side effects, mainly the production of psychoactivity produced through activation of CB_1 receptors, remain a hindrance to their wider use (Johnson *et al.*, 2010; Karschner *et al.*, 2011; but see Langford *et al.*, 2013). The efficacy and safety of CB_2 selective agents in humans for treatment of neuropathic pain remain to be determined. Activation of CB_2 receptors has been shown to suppress established chemotherapy-induced CIPN in rats (Naguib *et al.*, 2008; Rahn *et al.*, 2008; Deng *et al.*, 2012). In the study of Rahn *et al*, CB_2 agonist administration was most effective at 30 min post-injection, with mechanical sensitivity re-emerging 60 min following agonist administration, suggesting that repeated administration would be necessary to treat the CIPN symptoms in the long term.

Based on growing preclinical literature, the myriad of CBD's pharmacological effects, from anti-neuropathic to anxiolytic and antipsychotic, may be mediated through either CB receptor-dependent and independent mechanisms or combinations thereof (Izzo *et al.*, 2009). It is important from both a basic science mechanistic as well as drug discovery perspective to identify which of these are necessary and/or sufficient for CBD's anti-neuropathic effects specifically. In the present study, we demonstrated that activation of 5-HT_{1A} receptors is necessary for the protective effect of CBD against PAC-induced neuropathic pain, in that pretreatment with WAY100635 blocked this effect. CBD acts as a direct agonist at 5-HT_{1A} receptors (Russo *et al.*, 2005; Alves *et al.*, 2010), and activation of the 5-HT_{1A} receptor in the rostroventromedial medulla plays an important role in modulating the descending inhibitory pain pathway (Colpaert, 2006; Viisanen and Pertovaara, 2010). Importantly, 5-hydroxytryptaminergic drugs presently represent one of the only drug classes showing efficacy in the treatment of neuropathic pain in human clinical trials (Finnerup *et al.*, 2010). 5-HT_{1A} agonism has also been shown to be neuroprotective via attenuation of microglial activation and oxidative stress (Collier *et al.*, 2011a,b), two immune alterations relevant to CIPN. Results from the present study failed to show a role for CB_1 or CB_2 receptor activation in CBD's anti-neuropathic effect. Although CBD has no appreciable affinity for CB_1 or CB_2 receptors, some evidence suggests that it can

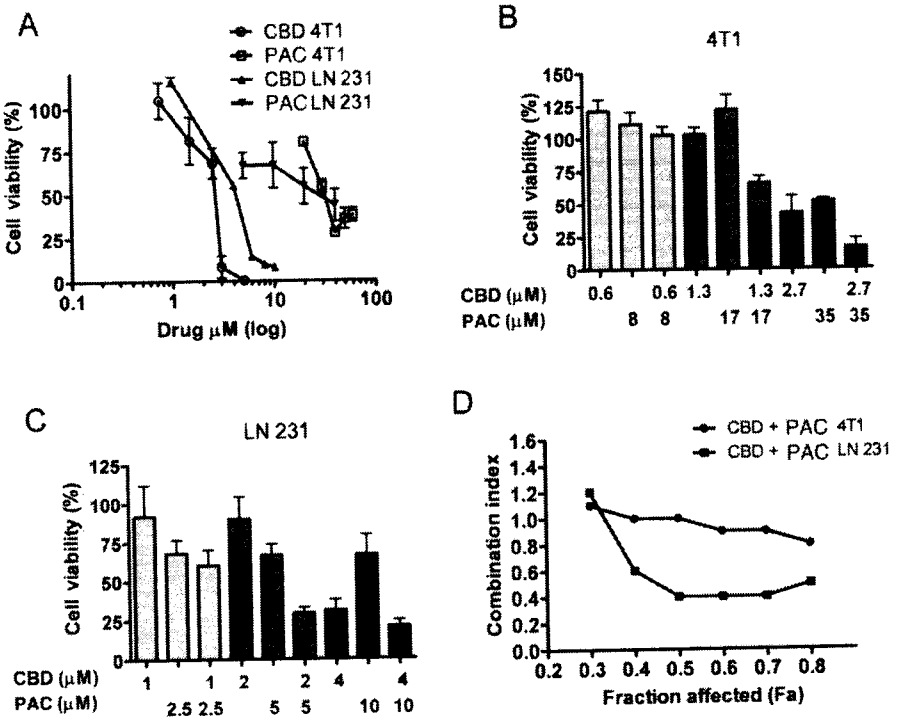

Figure 6

Treatments combining CBD and PAC produce additive to synergistic inhibition of breast cancer cell viability. Cell viability was measured using the MTT assay. (A) 4T1 and MDA-MB231-luc-D3H2LN (LN 231) cells were treated for 2 days with vehicle, CBD or PAC. Specific dose ratios of CBD and Pac where then combined in (B) 4T1 and (C) MDA-MB231-luc-D3H2LN cells. Cell viability (%) was calculated as the MTT product absorbance in the treated cells/control cells × 100. These data were used to calculate (D) CI values as described in Methods. A CI value of <1, 1 and >1 indicates synergism, additivity and antagonism respectively (Chou *et al.*, 1993). Data are the mean of at least three independent experiments; bars, ±SEM.

Table 1

Calculated median-effect plot parameters and DRI for drugs and drug combinations

		Median-effect plot parameters			DRI
Cell line	Chemotherapy	Dm	m	*r*	50% inhibition
4T1	CBD	2.7 μM	2.5	0.98	
	PAC	35 μM	1.8	0.86	2.0
	CBD + PAC	18 μM	3.0	0.99	
LN 231	CBD	4.1 μM	3.2	0.99	
	Pac	51 μM	0.3	0.92	15
	CBD + PAC	5.0 μM	2	1.0	

The median-effect dose (Dm), slope (m), linear correlation coefficient (*r*) and DRI (dose-reduction index) for drugs were calculated using Compusyn.

act as an indirect CB agonist via enhancement of eCB levels (Bisogno *et al.*, 2001; Campos *et al.*, 2013). However, our results are in agreement with the previous report by Comelli *et al.* (2008) demonstrating that CBD's anti-hyperalgesic effect did not involve CB_1 and CB_2 receptors. Others have shown that neither CB_1 nor CB_2 receptor activation was involved in CBD's neuroprotective (Sagredo *et al.*, 2007; 2011) or anti-inflammatory (Costa *et al.*, 2004) effects in other rodent models, whereas CBD-induced tail flick analgesia was blocked by co-administration of the CB_1 antagonist SR141716 (Maione *et al.*, 2011). CB_1 receptor involvement in the pharmacological effects of CBD on non-nociceptive behaviours has also been reported (Casarotto *et al.*, 2010; Do Monte *et al.*, 2013). Additionally, CBD binds with moderate affinity to TRPV1 (vanilloid) receptors and important nociceptive modulators, and anti-neuropathic effects of CBD have

been shown to depend upon TRPV1 activation (Comelli *et al.*, 2008), while acute antinociceptive effects have not (Maione *et al.*, 2011). Taken together with these other findings, our results suggest that specific pharmacological effects of CBD, such as its activity at 5-HT_{1A} and TRPV1 receptors, mediate CBD's anti-neuropathic effects, while its activity at other targets, including CB receptors, may be more important for other actions.

A novel strategy investigated in the present study is that of assessing the ability of CB-based pharmacotherapy to prevent the development of PAC-induced mechanical sensitivity as opposed to acutely reversing it. Other studies have demonstrated the ability of agents from other drug classes, including anticonvulsants (Xiao *et al.*, 2007), antidepressants (Xiao *et al.*, 2008) and opioids (Rahn *et al.*, 2008), to reduce CIPN symptoms in rodents, but to date no one drug or drug class is considered to be effective for reversal of CIPN (Lynch *et al.*, 2004). CIPN represents a neuropathic pain state with the unique possibility of aiming to prevent its onset with effective adjunctive treatment, as opposed to only attempting to reverse its symptoms following its onset. However, such investigations into prevention of PAC-induced CIPN in rodents are few. Interestingly, CBD has also recently been reported to protect against the onset of type I diabetic peripheral neuropathic pain (Toth *et al.*, 2010), hepatic ischaemia/reperfusion injury (Mukhopadhyay *et al.*, 2011), and retinal inflammation and degeneration (El-Remessy *et al.*, 2008) in rodent models. While clinical trials are ongoing investigating the anti-inflammatory effects of CBD as a monotherapy in disease states such as inflammatory bowel disease and graft versus host disease, its efficacy at preventing the onset of neuropathic pain in humans remains to be determined.

CBD represents a significant improvement in CB-based pharmacotherapy, in that CBD represents a cannabinoid that is regarded as being devoid of psychoactive euphoric effects. Surprisingly, however, a few preclinical studies to date have investigated CBD in reward models (e.g. Parker *et al.*, 2004). Here we demonstrated across a wider range of doses that CBD does not produce a CPP in C57Bl/6 mice using parameters that readily detect the conditioned rewarding properties of the same doses of morphine (Figure 4). CBD does, however, bind to several brain receptors and its anxiolytic and antipsychotic actions have been well characterized in animals and more recently in humans, so it is worth investigating whether CBD produces other CNS effects that would be considered adverse. An important pharmacological effect of CB receptor activation in addition to euphoria that has been extensively studied is disruption of learning and memory processes (see Lichtman *et al.*, 2002 for review). In the present study, we demonstrated that CBD across a wide range of doses did not impair acquisition or retention of an instrumental learning task. Interestingly, others have reported that CBD actually enhances certain types of learning, specifically extinction (Bitencourt *et al.*, 2008) and reconsolidation (Stern *et al.*, 2012). Determination of the effect of a putative anti-CIPN pharmacotherapy on learning and memory is important because cancer chemotherapeutics themselves are associated with a form of cognitive impairment in many cancer patients also known as 'chemofog' or 'chemobrain' (Argyriou *et al.*, 2011). CB agonists are likely to exacerbate these effects, while in contrast CBD should not affect cognition, and may therefore prove to be a more tolerable alternative as an adjuvant chemotherapy agent. In fact, as oxidative stress is a leading hypothesis regarding the mechanism underlying chemotherapy-associated cognitive impairment, the ability of CBD to reverse this phenomenon should also be investigated.

Finally, CBD has direct antitumor activity in multiple types of cancer (Massi *et al.*, 2013). We determined that at optimal concentrations, CBD in combination with PAC produces additive to synergistic inhibition of breast cancer cell viability. Our results in breast cancer cells are in agreement with a recent investigation demonstrating CBD could enhance the activity of first-line agents targeting prostate cancer in culture and *in vivo* (Aviello *et al.*, 2012). The doses that prevent PAC-induced allodynia in our model overlap with doses of CBD that attenuate breast cancer metastasis *in vivo* (McAllister *et al.*, 2011). This integrated approach to using CBD to prevent CIPN while directly and indirectly targeting tumour progression makes it a potential valuable therapeutic for the treatment of cancer patients undergoing treatments with first-line agents.

In summary, our data suggest that CBD is protective against PAC-induced neurotoxicity and that this effect is in part mediated by the 5-HT_{1A} receptor system. Furthermore, CBD treatment is devoid of other nervous system effects such as conditioned reward or cognitive impairment. CBD also did not attenuate the efficacy of PAC in inhibiting breast cancer cell viability. Taken together, adjunct treatment with CBD during PAC chemotherapy treatment may be safe and effective in the prevention or attenuation of CIPN.

Acknowledgements

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Conflict of interest

There are no conflicts of interest present.

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November 11, 2018

To: State of Connecticut Medical Marijuana Program Appendix C (Section I)

From:

[redacted]

[redacted]

This letter represents an appeal to approve medical marijuana in the state of Connecticut for the treatment of individuals with peripheral neuropathy. It is well-known that the various forms of peripheral neuropathy can cause disabling pain, numbness, paresthesia, dysesthesia, allodynia, and muscle weakness, all of which are often debilitating for those patients who are afflicted. Oftentimes, currently approved medications, procedural interventions, and rehab therapies are of limited efficacy or fraught with intolerable side effects. Other alternative treatments such as opioids, are well-known to have addictive properties and can even exacerbate the patient's symptoms through the phenomena of opioid-induced hyperalgesia, in which a patient's sensitivity to painful stimuli becomes enhanced.

Studies have shown that medical marijuana can be effective for neuropathic pain. It does not appear to have addictive properties. It has also been shown to reduce opioid-induced hyperalgesia. Medical marijuana is already approved for trigeminal neuralgia, postherpetic neuralgia, multiple sclerosis, and cancer. Cancer treatments such as surgery and chemotherapy are well-known to carry the risk of causing focal postoperative neuropathies and chemotherapy-induced polyneuropathies.

In general, there are a vast number of conditions which are associated with neuropathy. Hence, there are wide range of individuals who could potentially benefit from and improve their quality of life through treatment with medical marijuana.

Please give this matter all due consideration.

Sincerely,

[redacted]

Appendix C(Secti[redacted]

[redacted]

[redacted]

October 29, 2018

Connecticut Department of Consumer Protection
Medical Marijuana Program
450 Columbus Blvd, Suite 901
Hartford, CT 06103-1840

Dear Sir/Madam,

The medical marijuana program currently lists 22 disorders that qualify a patient for this drug. Many of the syndromes that meet that qualification are for disorders which are painful, and not otherwise successfully treated. These conditions include neuropathic pain associated with fibromyalgia, post herpetic pain, chronic regional pain, and neuropathic facial pain.

My office believes that painful neuropathies also are not adequately controlled by drug or alternative treatments and patients should be eligible for medical marijuana. Painful neuropathies can be debilitating and should be added as a qualifying condition.

Yours truly,

[redacted]

[redacted]

[redacted]

[redacted]

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