Brief Report

Oromucosal \(\Delta^9\)-Tetrahydrocannabinol/Cannabidiol for Neuropathic Pain Associated with Multiple Sclerosis: An Uncontrolled, Open-Label, 2-Year Extension Trial

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ABSTRACT

Background: Central neuropathic pain (CNP), pain initiated or caused by a primary lesion or dysfunction of the central nervous system, occurs in \(~28\%\) of patients with multiple sclerosis (MS). \(\Delta^9\)-Tetrahydrocannabinol/cannabidiol (THC/CBD), an endocannabinoid system modulator, has demonstrated efficacy for up to 4 weeks in randomized controlled trials in the treatment of CNP in patients with MS.

Objective: The purpose of this extension was to establish long-term tolerability and effectiveness profiles for THC/CBD (Sativex\(^\text{\textregistered}\), GW Pharmaceuticals plc, Salisbury, United Kingdom) oromucosal spray in CNP associated with MS.

Methods: This uncontrolled, open-label trial was an indefinite-duration extension of a previously reported 5-week randomized study in patients with MS and CNP. In the initial trial, patients were randomized to placebo or THC/CBD. Patients were only required to maintain their existing analgesia in the randomized study. In the open-label trial they could vary their other analgesia as required. All patients (placebo and THC/CBD) who completed the randomized trial commenced the open-label follow-up on THC/CBD (27 mg/mL: 25 mg/mL). Patients titrated their dosage, maintaining their existing analgesia. The primary endpoint of the trial was the number, frequency, and type of adverse events (AEs) reported by patients. Secondary endpoints included changes from baseline in 11-point numerical rating scale (NRS-11) neuropathic pain score, hematology and clinical chemistry test results, vital signs, trial drug usage, and intoxication visual analogue scale scores.

Results: Sixty-six patients were enrolled in the randomized trial; 63 (95\%) completed the randomized trial and 63 (95\%) entered the open-label extension. (race, white, 100\%; sex, male, 14 [22\%]; mean [SD] age, 49 [8.4] years [range, 27–71 years]). The mean (SD) duration of open-label treatment was 463 (378) days (median, 638 days; range, 3–917 days), with 34 (54\%) patients completing >1 year of treatment with THC/CBD and 28 (44\%) patients completing the open-label trial with a mean (SD) duration of treatment of 839 (42) days (median, 845 days; range, 701–917 days). Mean NRS-11 pain scores in the final week of the randomized trial were 3.8 in the treatment group and 5.0 in the placebo group. In the 28 (44\%) patients who completed the 2-year follow-up, the mean (SD) NRS-11 pain score in the final week of treatment was 2.9 (2.0) (range, 0–8.0). Fifty-eight (92\%) patients experienced ≥1 treatment-related AE. These AEs were rated by the investigator as mild in 47 (75\%) patients, moderate in 49 (78\%), and severe in 32 (51\%). The most commonly reported AEs were dizziness (27\%), nausea (18\%), and feeling intoxicated (11\%). Two treatment-related serious AEs (ventricular bigeminy and circulatory collapse) were judged to be treatment-related.

This study was presented in part at the 11th World Congress on Pain, August 21–26, 2005, Sydney, Australia; the 20th Consortium of Multiple Sclerosis Centres, May 31–June 3, 2006, Scottsdale, Arizona; the 16th European Neurological Society, May 27–31, 2006, Lausanne, Switzerland; the 2nd International Congress on Neuropathic Pain, June 7–10, 2007, Berlin, Germany; and the Annual Meeting of the Association of British Neurologists, April 11–13, 2007, Cambridge, United Kingdom.

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Both serious AEs occurred in the same patient and resolved completely following a period of discontinuation. Eleven (17%) patients experienced oral discomfort, 4 persistently. Regular oral examinations revealed that 7 (11%) patients developed white buccal mucosal patches and 2 (3%) developed red buccal mucosal patches; all cases were deemed mild and resolved. Seventeen (25%) patients withdrew due to AEs. The mean number of sprays and patients experiencing intoxication remained stable throughout the follow-up trial.

Conclusions: THC/CBD was effective, with no evidence of tolerance, in these select patients with CNP and MS who completed ~2 years of treatment (n = 28). Ninety-two percent of patients experienced an AE, the most common of which were dizziness and nausea. The majority of AEs were deemed to be of mild to moderate severity by the investigators. (Clin Ther. 2007;29:2068-2079) Copyright © 2007 Excerpta Medica, Inc.

Key words: multiple sclerosis, open-label extension trial, cannabinoid, Sativex, Δ²-tetrahydrocannabinol/cannabidiol, central pain, neuropathic pain.

INTRODUCTION

Central neuropathic pain (CNP), pain initiated or caused by a primary lesion or dysfunction of the central nervous system, occurs in ~28% of patients with multiple sclerosis (MS), and in >90% of patients is daily, constant, and ongoing. However, prescription of agents such as antidepressants and anticonvulsants for CNP in MS is associated with recognized problems of central nervous system tolerability, and there have been few controlled studies of agents in this area as demonstrated by a systematic review conducted in March 2002 of MEDLINE, EMBASE, Science Citation Index, Cochrane Database of Systematic Reviews, and the Cochrane Controlled Trials Register using a detailed search strategy.4

Oral dronabinol monotherapy and adjunctive treatment with Δ²-tetrahydrocannabinol/cannabidiol (THC/CBD), an endocannabinoid system modulator, both have demonstrated efficacy for up to 4 weeks in randomized controlled trials in the treatment of CNP in patients with MS.5,6 The effect of long-term (months or years) treatments used in CNP is uncertain.7,8 The longest open-label study to date examined use of anticonvulsants for up to 6 months.3

THC/CBD* is derived from strains of Cannabis sativa plants developed to produce high and reproducible yields of THC and CBD, with trace amounts of other cannabinoids and terpenes in a solution containing ethanol, propylene glycol, and peppermint oil flavoring.5 THC and CBD comprise ≥90% of the total cannabinoid content of the extracts.

Health Canada has approved THC/CBD as adjunctive treatment for the symptomatic relief of neuropathic pain in MS in adults, under the Notice of Compliance with Conditions policy.10 Products approved under this policy have demonstrated promising benefit, are of high quality, and possess an acceptable safety profile based on a benefit/risk assessment for the approved use. Full licensing of such products is dependent upon additional clinical trials to verify the anticipated benefit. Here we present the results of 2-year follow-up treatment with THC/CBD in patients with MS and associated CNP.

PATIENTS AND METHODS

Initially the open-label study was approved by the Multi-Centre Research Ethics Committee for Scotland, Edinburgh, United Kingdom, and subsequently by the South Sefton Research Ethics Committee, Liverpool, United Kingdom. It was stipulated that patients should not drive during the course of the study. The study was conducted in accordance with both the Declaration of Helsinki11 and the principles of Good Clinical Practice.12

Patients

Adult patients with CNP syndromes associated with MS, as defined by the Poser criteria,13 were invited to participate in an initial 5-week, randomized, double-blind, placebo-controlled, parallel-group study conducted at the Walton Centre Clinical Trials Unit, Liverpool, United Kingdom. The results and detailed methods of that study have been reported previously.6 Patients were identified predominantly from a study validating the Neuropathic Pain Scale14 (NPS) in MS-associated CNP,15 the regional MS clinic, or by specialist referral.

Patients reaffirmed consent at the start of the open-label extension trial and their eligibility was recon-
firmed. A physical examination, including oral, was performed. Vital signs were recorded as well as full blood count, urea, electrolytes, liver function tests, serum calcium, and resting 12-lead electrocardiogram (EKG). Hematology samples were collected in 2-ml ethylenediamine tetraacetic acid tubes and shipped at ambient temperature to the central laboratory (Pivotal Laboratories Ltd., York, United Kingdom). Biochemistry samples were collected in 5-mL serum tubes, allowed to stand at room temperature for 15 minutes, then spun in a centrifuge at 1200g for ~15 minutes. After spinning, the serum was pipetted into a transport tube and shipped together with the hematology sample.

A urinary pregnancy test was conducted when appropriate. Vital signs were measured by a nurse using an aural thermometer for temperature, an electronic blood pressure cuff for pulse and blood pressure, and manual counting of the resting respiratory rate. All laboratory analyses were conducted by the central laboratory which complied with the National External Quality Assurance Scheme for the periodic analysis of external samples. Additionally, the laboratory conducted internal quality control per parameter for each batch of samples. The laboratory reference ranges were taken from the test manufacturer's literature or from the laboratory's own data, dependent upon the individual method. Standard whole blood biochemistry and serum hematology were analyzed using the SF-3000 and BM 917 analyzers (Sysmex Corporation, Kobe, Japan). Urine tests were performed at the study site, and samples were sent to the central laboratory for light microscopy and culture if any of the initial results were abnormal.

The patient's most troublesome CNP and the time of day at which it was of maximum intensity were identified at the outset of the randomized trial. A daily 11-point numerical rating scale was completed throughout the trial for the identified pain and time. The 11-point numerical rating scale (NRS-11) of pain intensity ranges from 0 (no pain) to 10 (worst possible pain). Pain intensity score was determined by asking patients to indicate the single number that best represented their level of pain intensity. The psychometric properties of NRS scales are similar to visual analogue scales (VASs) and have been found to be valid and reliable, with strong associations to other pain rating scales. They have also been found to be responsive both to treatment-related reductions in pain and increases in pain-associated adverse events (AEs) of other treatments.

In the open-label follow-up trial, patients indicated their neuropathic maximum pain severity over the preceding week (0 = best possible; 10 = worst possible). Patients were instructed to equate “best possible” to the time before the start of their CNP. Patients were asked whether any AEs occurred since the previous visit at each follow-up trial visit, and if present, the investigators rated their severity (mild, moderate, or severe) and used their clinical judgment to assess their relationship to THC/CBD (unrelated, possibly-related, probably-related, and definitely-related). Serious AEs were defined as fatal, life-threatening, or those resulting in persistent or major disability/incapacity or prolonging hospitalization.

**Clinical Therapeutics**

**Trial Timetable and Dosing**

The follow-up extension was planned as an indefinite-duration, open-label, noncomparative, effectiveness and tolerability trial common to all patients who satisfactorily completed randomized controlled trials of THC/CBD (27 mg/mL Δ-9-THC:25 mg/mL CBD). This trial was to last until the trial medication or a suitable alternative was available on prescription or through a compassionate-use program, or until the termination of cannabinoid research by the study sponsor.

In the randomized study and open-label follow-up trials, patients underwent initial dosing under hospital supervision in the clinical trials unit on an outpatient basis. At the outset of the randomized trial, patients were randomized to THC/CBD or placebo, and at the outset of the open-label trial patients receiving placebo were commenced on THC/CBD. This was to be followed by home-dose titration of ≤8 sprays (THC 21.6 mg:CBD 20 mg) within any 3 hours and up to 48 sprays (THC 129.6 mg:CBD 120 mg) in 24 hours, with a maximum increase of 50% in the number of sprays tolerated in the previous 24 hour period. If intoxication was experienced, patients were advised to reduce or omit a dose. A maximum tolerated dose thus established was only exceeded cautiously by 1 or 2 additional sprays per day. Further details of the randomized study dose initiation and titration are published elsewhere. For all patients completing the randomized study, THC/CBD was retitrated from 0 following the exact methods above.

A phone call, performed by nursing staff, 14 to 20 days after the follow-up trial was initiated, in-
cluded specific queries regarding the patient’s titration of study medication, acceptability of dosing, AEs, changes in concomitant medication, and diary completion.

Patients were reviewed 4 weeks after initiation of the open-label trial and every 8 weeks thereafter when the following were assessed: investigator’s global assessment rating of neuropathic pain since trial entry (1 = much worse; 2 = worse; 3 = no change; 4 = better; 5 = much better); benefit from trial medication assessment (Yes/No); 100-mm intoxication VAS scores (0 = no intoxication and 100 = extreme intoxication); details of changes in medication, whether new or current, including usage of cannabis if any; and AEs, including their severity and relationship to the trial medication. Using their diaries, patients recorded the number of sprays of THC/CBD, the times at which they were taken daily between visits, and a weekly NRS-11 CNP rating score.

At weeks 28 and 52 and at 6-month intervals, a physical examination, blood tests (as listed previously), and a resting 12-lead EKG were repeated. At each visit, empty trial medication vials and symptom and dosing diaries were collected and replaced as appropriate. On the final visit, occurring either upon trial completion or withdrawal, all trial medication vials (used and unused) and diaries were collected.

In response to reports of 2 cases of possible leukoplakia neither of which was confirmed histologically (1 case subsequently resolved, and a causal relationship to the study medication was not established in the other), the trial protocol was amended 1 year after the first patient entered the open-label follow-up trial. The amendment required a reduction in the interval between examinations of the oral mucosa and buccal cavity from twice a year to once at each study visit. If lesions were observed, treatment was interrupted until complete resolution occurred. Patients who reported oral discomfort were advised to vary the application site within the mouth and to refrain from spraying onto sore or inflamed mucus membranes. If patients developed prolonged soreness or a clinically significant mucosal lesion, and the soreness or lesion completely resolved on interruption of the spray, then the risk/benefit ratio was considered when reintroducing the treatment. If, in the opinion of both the investigator and patient, the patient was gaining clinically significant benefit from THC/CBD, such patients were advised to try “indirect spraying” of THC/CBD into a milky drink and consume it. Patients adopting this method were advised to cautiously retitrante, given that this represented a different route of administration. If patients developed prolonged soreness or a new lesion (or loss of effect) following a trial of indirect spraying, they were withdrawn from treatment. Patients who withdrew from the trial because of severe or prolonged oral discomfort or development of visible lesions in the mouth were followed up until complete resolution had occurred.

**Primary and Secondary End Points**

The primary end point of the trial was the number, frequency, and type of AEs reported by patients. Secondary end points included changes from baseline in NRS-11 neuropathic pain score, hematology and clinical chemistry tests results, vital signs, trial drug usage, and intoxication VAS scores.

**Statistical Analyses**

As this was a noncomparative trial, no formal hypothesis testing was performed. The results were described by summary statistics. The intention-to-treat population was composed of any patient who administered ≥1 spray of THC/CBD and had ≥1 assessment. For those patients who withdrew from the trial, the last-observation-carried-forward (LOCF) method was used. The per-protocol (PP) population consisted of all patients completing the open-label trial. No corrections for multiple comparisons were made.

**RESULTS**

Sixty-four (97%) of the 66 patients enrolled completed the 5-week randomized trial, and 63 (95%) entered the open-label extension trial. Demographic details are outlined in Table I. Patient disposition throughout both the randomized and open-label phases of the trial are shown in Figure 1. Sixty-two patients commenced with the open-label trial on the same day as they finished the randomized trial. One patient delayed participation in the open-label study due to an elective operation. Two female patients who received THC/CBD in the randomized trial failed to complete it due to treatment-related AEs, and 1 female patient who received THC/CBD chose not to enter the open-label trial for personal reasons. No hospital admissions were required as a result of supervised initial dosing in either the randomized or open-label trial. The mean (SD) duration of open-label treatment was
Table I. Demographic characteristics and 11-point numerical rating scales (NRS-11) pain scores of those patients with multiple sclerosis (MS) receiving Δ8-tetrahydrocannabinol/cannabidiol (THC/CBD) or placebo at the time of their initiation into the randomized controlled trial and those entering the THC/CBD open-label trial.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Treatment in Double-Blind Study</th>
<th>Open-Label Extension Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>THC/CBD (n = 31)</td>
<td>Placebo (n = 32)</td>
</tr>
<tr>
<td>Age, y</td>
<td>Mean (SD)</td>
<td>50 (6.8)</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>37-64</td>
</tr>
<tr>
<td>Sex, no. (%)</td>
<td>Female</td>
<td>25 (81)</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>6 (19)</td>
</tr>
<tr>
<td>Weight, men, kg</td>
<td>Mean (SD)</td>
<td>83.2 (8.3)</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>70.4-94.5</td>
</tr>
<tr>
<td>Weight, women, kg</td>
<td>Mean (SD)</td>
<td>67.0 (11.8)</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>51.0-105.0</td>
</tr>
<tr>
<td>History of cannabis use, no. (%)</td>
<td>Medicinal</td>
<td>13 (42)</td>
</tr>
<tr>
<td></td>
<td>Recreational</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Duration of MS, mean (SD), y*</td>
<td>10.4 (7.3)</td>
<td>12.6 (8.1)</td>
</tr>
<tr>
<td>NRS-11 pain scores</td>
<td>At randomized trial baseline</td>
<td>6.6 (1.6)</td>
</tr>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>2.6-9.7</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>3.8 (2.1)</td>
</tr>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>0.1-8.3</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>3.4 (1.9)</td>
</tr>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>0-7.0</td>
</tr>
</tbody>
</table>

*On entry to the double-blind randomized trial.

463 (378) days (median, 638 days; range, 3–917 days), with 34 (54%) patients completing >1 year of treatment with THC/CBD and 28 (44%) patients completing the open-label trial with a mean (SD) duration of treatment of 839 (42) days (median, 845 days; range, 701–917 days). Among all withdrawals, the mean duration of treatment was 162 (221) days (median, 66 days; range, 3–751 days). Seventeen (25%) patients withdrew due to AEs. Thirteen (46%) of the 28 patients completing the open-label trial had previous exposure to cannabis, 3 (11%) recreationally. All 63 patients who entered the open-label study were white, 22 (35%) smoked tobacco, and 18 (29%) were of child-bearing potential.

Tolerability

Sixty (95%) patients experienced ≥1 AE. Fifty-eight (92%) patients experienced a treatment-related AE throughout the open-label trial. AEs were rated as mild, moderate, or severe in 47 (75%), 49 (78%), and 32 (51%) patients, respectively, in the open-label phase. The treatment-related AEs that occurred in
Randomized to double-blind trial (n = 66)

Completed (THC/CBD*) (n = 32)
Discontinued (n = 1)
Withdrew consent (1)

Entered open label (n = 31)
Discontinued (n = 9)
Adverse event (5)
Withdraw consent (3)
Lack of efficacy (1)

Completed 1 year of treatment (n = 22)
Discontinued (n = 2)
Withdraw consent (2)
Completed <2 years of treatment (n = 1)

Completed (placebo) (n = 32)
Discontinued (n = 3)
Adverse event (1)
Withdraw consent (1)
Noncompliance (1)

Completed 1 year of treatment (n = 12)
Discontinued (n = 3)
Adverse event (1)
Withdraw consent (1)
Noncompliance (1)

Completed 2 years of treatment (n = 19)
Discontinued (n = 1)
Withdraw consent (1)

Completed 2 years of treatment (n = 9)
Discontinued (n = 20)
Adverse event (11)
Withdraw consent (5)
Lack of efficacy (2)
Driving (2)

Completed open-label study (n = 28)

Figure 1. Patient disposition throughout a 5-week trial in which patients were randomized to receive Δ9-tetrahydrocannabinol/cannabidiol (THC/CBD) or placebo and the open-label trial in which all patients received THC/CBD. *Trademark: Sativex® (GW Pharmaceuticals plc, Salisbury, United Kingdom).

>5% of patients are listed in Table II. Ten (16%) patients experienced an MS relapse (2 were mild, 7 moderate, and 1 severe), and a further 10 patients reported a subjective aggravation of their MS (8 mild and 2 moderate).

Age, sex, and MS-related disability were similar in all patients whether they completed the trial or withdrew. Previous exposure to cannabis (13 [46%] vs 21 [60%]) and smoking status (6 [21%] vs 16 [46%]) were both lower in patients who completed the trial compared with those who withdrew.

In view of the oromucosal administration of THC/CBD, the upper gastrointestinal treatment-related AEs, each of which occurred in 1 (2%) patient, were as follows: upper abdominal pain, angular cheilitis, aphthous stomatitis, gastroesophageal reflux disease,
Table II. Treatment-related adverse events (AEs) occurring in >5% of patients with multiple sclerosis (MS) receiving Δ9-tetrahydrocannabinol/cannabidiol.

<table>
<thead>
<tr>
<th>AEs</th>
<th>Patients, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>11 (17.5)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6 (9.5)</td>
</tr>
<tr>
<td>Mouth plaque</td>
<td>6 (9.5)</td>
</tr>
<tr>
<td>Vomiting, NOS</td>
<td>5 (7.9)</td>
</tr>
<tr>
<td>Constipation</td>
<td>4 (6.3)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>4 (6.3)</td>
</tr>
<tr>
<td>Mouth ulceration</td>
<td>4 (6.3)</td>
</tr>
<tr>
<td>Tooth discoloration</td>
<td>4 (6.3)</td>
</tr>
<tr>
<td>General disorders and administration-site conditions</td>
<td></td>
</tr>
<tr>
<td>Feeling intoxicated</td>
<td>7 (11.1)</td>
</tr>
<tr>
<td>Edema, peripheral</td>
<td>6 (9.5)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4 (6.3)</td>
</tr>
<tr>
<td>Weakness</td>
<td>4 (6.3)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>17 (27.0)</td>
</tr>
<tr>
<td>Balance impaired, NOS</td>
<td>6 (9.5)</td>
</tr>
<tr>
<td>Headache, NOS</td>
<td>5 (7.9)</td>
</tr>
<tr>
<td>MS aggravated</td>
<td>5 (7.9)</td>
</tr>
<tr>
<td>Respiratory, thoracic, and mediastinal disorders</td>
<td></td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>4 (6.3)</td>
</tr>
</tbody>
</table>

NOS = not otherwise specified.

halitosis, dry lips, lip pain, oral discomfort, oral mucosal disorder, oral pruritus, stomatitis, coated tongue, tongue discoloration, throat irritation, cough, dry throat, nasal congestion, and oral fungal infection. Oral candidiasis and dysgeusia both occurred once as all-causality AEs. Application-site burning occurred in 2 (3%) patients.

On direct questioning, 11 (17%) patients experienced oral discomfort; transient in 6 patients, persistent in 4, and leading to trial withdrawal in 1. In another patient, persistent discomfort resolved, becoming transient later in the trial. On regular oral examinations, 7 (11%) patients developed white patches on their buccal mucosa, all of which were rated as mild. In 5 patients these were viewed as being probably related to treatment, in 1 patient definitely, and in another patient not related. Two patients developed red patches on their buccal mucosa associated with persistent oral discomfort, which were classed as mild and possibly related to THC/CBD administration. These resolved after temporary discontinuation, following a period of indirect spraying. Nine (14%) patients took THC/CBD via the indirect spraying method; 4 for development of white patches, 2 for red patches, and 1 for transient oral discomfort.

The most commonly reported nervous system treatment-related AEs were dizziness in 17 (27%) patients and impairment of balance in 6 (10%) patients. Nausea occurred in 11 (18%) and a feeling of intoxication in 7 (11%) patients.

Ten treatment-related psychiatric AEs occurred. Only euphoria and depressed mood (3 [5%] patients each) occurred in more than a single patient.

Serious Adverse Events and Adverse Events Leading to Withdrawal

AEs that led to 17 patients withdrawing from the trial were as follows: nausea (5 patients), weakness (3), dizziness (3), fatigue aggravated (3), feeling intoxicated (2), and vomiting, anorexia, ventricular bigeminy and circulatory collapse, oral discomfort, abnormal coordination, headache, impaired judgment, speech disorder, agitation, hallucination, and facial swelling each occurred once. Twelve serious AEs occurred in 10 (16%) patients, 2 of which, ventricular bigeminy and circulatory collapse, were judged to be treatment related. These occurred in the same patient and resulted in hospitalization. The patient made a complete recovery and was subsequently withdrawn from the trial.

Laboratory Results—Treatment-Related Adverse Events

Significant increases (defined as >20% of upper limit of normal) in white cell count, mean cell volume, and liver function tests each occurred in 2 patients, and there was a single instance of an increase in lymphocytes, neutrophils, alkaline aminotransferase, calcium, and potassium. No clinically significant changes in EKGs, pulse rate, or systolic or diastolic blood pressures were observed compared with baseline.

Changes in NRS-11 Pain Score

The mean (SD) NRS-11 score at trial completion or withdrawal (n = 62) was 4.05 (1.96) (range, 0–8.57)
using LOCF analysis for withdrawn patients or 4.21 (2.32) (range, 0–9.29) assuming that patients who withdrew had no change in their NRS-11 pain scores from the end of the randomized trial (Table I). The mean (SD) NRS-11 pain score in those completing the open-label study (n = 28) was 2.9 (2.0) (range, 0–8.0), a change from the randomized study baseline of −3.4 (1.8) (range, −7.0 to −0.1) (Figure 2).

**Dosing of Study Drug**

The mean (SD) number of sprays taken per day in the 34 patients reaching 1 year of treatment was 7.5 (5.7) (range, 1.3–21.9). In the last 6 full days of treatment, the mean (SD) number of sprays taken per day by all patients was 6.1 (5.2) (range, 0.3–24.8), equivalent to a mean dose of 16.5 mg of THC and 15.3 mg of CBD. This represents −1 (−0.94 [6.1]; range, −11.7 to 18.7) fewer sprays than at week 4 of the open-label trial, implying that there was no development of tolerance to THC/CBD. In the 28 patients who completed the study, the mean (SD) number of sprays taken in the final 6 full days of treatment was 6.5 (5.8) (range, 0.5–24.8), with 26 patients taking <11 sprays per 24 hours.

Approximately 45% of THC/CBD doses were administered between 6 PM and 12 AM (Figure 3). One or more patients took ≥1 spray in each hour-long dosing interval on ≥1 day in the final 7 full days of treatment.

**Changes in Concomitant Analgesic Medication in Open-Label Study Completers**

Without a control group, changes in concomitant medications could not be evaluated; therefore, the following results are only descriptive. At the beginning of the open-label trial, the 28 patients who subsequently completed it were taking 31 medications for pain (range, 0–3) and 32 medications which may have had an effect on pain (range, 0–3) such as selective serotonin reuptake inhibitors or antispasmodics. In trial completers, 10 (32%) concomitant pain medications were reduced or stopped, 15 (48%) remained unchanged, and 6 (19%) were increased. Eleven (34%) medications possibly affecting pain were reduced or stopped, 16 (50%)...
remained unchanged, and the dose of 5 (16%) was increased. During the open-label trial, 14 (50%) patients temporarily commenced 31 new medications (12 different) indicated for any type of pain, including headache, stopping them before the end of the study, and 7 (25%) patients commenced a new medication for pain and continued it through the end of the study. Twenty (71%) patients temporarily commenced 31 new medications (14 different) which may have had an analgesic effect on their pain, and 7 (25%) commenced a new medication that may have had an effect on pain and continued it through the end of the study. Seventeen (71%) patients temporarily commenced 31 new medications (14 different) which may have had an analgesic effect on their pain, and 7 (25%) commenced a new medication that may have had an effect on pain and continued it through the end of the study. Twenty (71%) patients temporarily commenced 31 new medications (14 different) which may have had an analgesic effect on their pain, and 7 (25%) commenced a new medication that may have had an effect on pain and continued it through the end of the study. Seventeen (71%) patients temporarily commenced 31 new medications (14 different) which may have had an analgesic effect on their pain, and 7 (25%) commenced a new medication that may have had an effect on pain and continued it through the end of the study. Seventeen (71%) patients temporarily commenced 31 new medications (14 different) which may have had an analgesic effect on their pain, and 7 (25%) commenced a new medication that may have had an effect on pain and continued it through the end of the study. Seventeen (71%) patients temporarily commenced 31 new medications (14 different) which may have had an analgesic effect on their pain, and 7 (25%) commenced a new medication that may have had an effect on pain and continued it through the end of the study. Seventeen (71%) patients temporarily commenced 31 new medications (14 different) which may have had an analgesic effect on their pain, and 7 (25%) commenced a new medication that may have had an effect on pain and continued it through the end of the study. Seventeen (71%) patients temporarily commenced 31 new medications (14 different) which may have had an analgesic effect on their pain, and 7 (25%) commenced a new medication that may have had an effect on pain and continued it through the end of the study. Seventeen (71%) patients temporarily commenced 31 new medications (14 different) which may have had an analgesic effect on their pain, and 7 (25%) commenced a new medication that may have had an effect on pain and continued it through the end of the study. Seventeen (71%) patients temporarily commenced 31 new medications (14 different) which may have had an analgesic effect on their pain, and 7 (25%) commenced a new medication that may have had an effect on pain and continued it through the end of the study. Seventeen (71%) patients temporarily commenced 31 new medications (14 different) which may have had an analgesic effect on their pain, and 7 (25%) commenced a new medication that may have had an effect on pain and continued it through the end of the study. Seventeen (71%) patients temporarily commenced 31 new medications (14 different) which may have had an analgesic effect on their pain, and 7 (25%) commenced a new medication that may have had an effect on pain and continued it through the end of the study. Seventeen (71%) patients temporarily commenced 31 new medications (14 different) which may have had an analgesic effect on their pain, and 7 (25%) commenced a new medication that may have had an effect on pain and continued it through the end of the study. Seventeen (71%) patients temporarily commenced 31 new medications (14 different) which may have had an analgesic effect on their pain, and 7 (25%) commenced a new medicati

**DISCUSSION**

The results of this open-label trial of THC/CBD in patients with MS and CNP cannot be extrapolated beyond this population. Forty-four percent of patients completed ~2 years of treatment. The study protocol was common to all patients with disparate conditions and primary symptoms who completed a cannabinoid randomized controlled trial and was designed predominantly to provide chronic tolerability data. It is therefore devoid of symptom-specific outcome measures such as the NPS and mood scales used in the randomized phase, as well as quality-of-life and disability assessments. These might have helped define any additional benefits aside from an overall change in pain intensity. Open-label trials have been criticized for being prone to publication bias, denying patients standard available treatment, distorting the appearance of tolerability of a drug over months or years due to dropouts in the randomized phase, and merely enabling continued use of a new drug for compassionate purposes rather than to increase knowledge. Three (5%) of the 66 patients initially randomized into the double-blind trial did not enter the open label trial. There are no published randomized controlled trials of months' or years' duration supporting efficacy of pharmacologic treatments in CNP related to MS. In a 12-month follow-up to the 15-week, randomized, double-blind cannabinoids in MS (CAMS) study, during which patients and investigators remained for-

**Intoxication**

A 100-mm intoxication VAS was completed by all patients at each study visit. The median VAS score for the patient population at all time points was 0, indicating that most patients had no feeling of intoxication at the time of their study visits. In those patients who did experience intoxication at the time of their study visit, the mean scores were low and remained stable between 3 and 6.
mally blinded, the authors did not define the etiology of pain but confirmed that a patient’s reduction in pain reported on category rating scales at 15 weeks was maintained. Prospective open-label trials in MS pain using anticonvulsants have been conducted, but the data are limited and do not allow evaluation of efficacy.3,30

The approval of THC/CBD for use in patients with MS and CNP in Canada10 in 2005 and a general license permitting doctors to prescribe THC/CBD as an unlicensed medicine on a named patient basis in the United Kingdom (UK Home Office, January 2006) merits analysis of its longer-term effects and tolerability. This follow-up trial, taking into account the recognized limitations of an open-label design with no control group, explores the response to THC/CBD in the 44% of patients who completed it.

Overall, there was a mean treatment duration of 463 days, representing ~80 treatment years. Twenty-nine (46%) patients withdrew from the trial within the first year, which was comparable to the 50% to 58% of patients in the CAMS trial who remained on treatment at 1-year follow-up.29 Age, disability (as determined by Expanded Disability Status Scale31), location and type of CNP, and previous exposure to cannabis did not predict which patients withdrew. Driving was not permitted during either the randomized or open-label trial, and although this was the recorded reason for trial withdrawal in 2 patients, it may have influenced ongoing trial participation in many patients. This may have compromised both the retention rates and apparent effects of THC/CBD. At the time of their withdrawal from the trial, 18 (51%) of the 35 patients still perceived benefit from THC/CBD.

Seventeen patients withdrew due to AEs; the most common of which were nausea, dizziness, weakness, and fatigue. The range of nervous system and psychiatric AEs was not unexpected for a centrally-acting medication, particularly in patients with MS with moderate to severe disability who constituted approximately two-thirds of the patients in our trial. THC/CBD was administered oromucosally and dissolved in an alcoholic solution, and oral AEs were therefore carefully sought. Although white and red patches on the buccal mucosa did occur, these all resolved, and with 1 exception for oral discomfort, patients were able to remain on THC/CBD by varying the site of its application and by indirectly spraying into milk in a minority of patients. One treatment-related serious AE occurred from which the patient made a full recovery. Intoxication was only assessed at the time of the clinic visit and therefore it is likely that higher levels of intoxication were perceived later in the day, which were not captured in the patients’ diaries.

All but 1 of the 28 patients who completed the follow-up study received >2 years’ treatment with THC/CBD. They represent a “best-case scenario” with due reference to the caveats regarding withdrawals outlined previously. In this group a sustained reduction in pain was observed. When all patients who withdrew from open-label treatment are assumed to have had no change in their NRS-11 pain scores from the end of the randomized trial, there is little difference from an LOCF analysis (Figure 2).

Given its oromucosal administration and avoidance of the first-pass effect, one potential advantage of THC/CBD over orally-administered cannabinoids is flexibility of dosing and a rapid onset of action. Pharmacokinetic studies have found that following buccal administration of THC/CBD, THC, CBD, and 11-hydroxy-Δ9-THC (the main metabolite in THC) appear in the plasma almost simultaneously from ~30 minutes after administration, although there is wide intersubject variability.32 About 45% of THC/CBD was administered between 6 PM and 12 AM perhaps reflecting the increase in CNP which is known to occur in the afternoon and early evening, which itself may reflect the patient's physical activity earlier in the day.2 In common with other analgesics, whether the action of THC/CBD is solely due to an effect on pain or in part as a result of promoting improved sleep, is open to question.

The investigators did not encourage patients to alter their existing analgesia unless they expressed a wish to do so or for other clinical reasons. The use of THC/CBD, per se, did not lead to either a major increase or decrease in the use of new analgesics, which over at least 2 years is perhaps a further indirect measure of sustained effectiveness in the PP population.

CONCLUSIONS

THC/CBD was effective, with no evidence of tolerance, in these select patients with CNP and MS who completed ~2 years of treatment (n = 28). Ninety-two percent of patients experienced an AE, the most common of which were dizziness and nausea. The majority of AEs were deemed to be of mild to moderate severity by the investigators.
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REFERENCES


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