Efficacy of two cannabis based medicinal extracts for relief of central neuropathic pain from brachial plexus avulsion: results of a randomised controlled trial

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Abstract

The objective was to investigate the effectiveness of cannabis-based medicines for treatment of chronic pain associated with brachial plexus root avulsion. This condition is an excellent human model of central neuropathic pain as it represents an unusually homogenous group in terms of anatomical location of injury, pain descriptions and patient demographics. Forty-eight patients with at least one avulsed root and baseline pain score of four or more on an 11-point ordinate scale participated in a randomised, double-blind, placebo-controlled, three period crossover study. All patients had intractable symptoms regardless of current analgesic therapy. Patients entered a baseline period of 2 weeks, followed by three, 2-week treatment periods during each of which they received one of three oromucosal spray preparations. These were placebo and two whole plant extracts of Cannabis sativa L.: GW-1000-02 (Sativex®), containing Δ9-tetrahydrocannabinol (THC):cannabidiol (CBD) in an approximate 1:1 ratio and GW-2000-02, containing primarily THC. The primary outcome measure was the mean pain severity score during the last 7 days of treatment. Secondary outcome measures included pain related quality of life assessments. The primary outcome measure failed to fall by the two points defined in our hypothesis. However, both this measure and measures of sleep showed statistically significant improvements. The study medications were generally well tolerated with the majority of adverse events, including intoxication type reactions, being mild to moderate in severity and resolving spontaneously. Studies of longer duration in neuropathic pain are required to confirm a clinically relevant, improvement in the treatment of this condition.

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1. Introduction

Avulsion of nerve rootlets from the spinal cord following traction injuries to the brachial plexus frequently produces a highly characteristic pain syndrome. Constant, spontaneous crushing and burning pain is felt in the distal part of the anaesthetic limb and is often accompanied by shooting pain (Frazier and Skillern, 1911; Parry, 1980). It is not uncommon for the pain to persist for many years making this a difficult condition to treat. Options include empirical drug therapy, nerve transfer surgery and dorsal root entry zone (DREZ) lesions. There is a small body of evidence to support surgical intervention (Berman et al., 1998; Samii et al., 2001; Thomas and Kitchen, 1994). However, the published evidence on drug treatment is essentially anecdotal.

Many of our patients have given spontaneous reports regarding the efficacy of ‘street’ cannabis in treating the pain from brachial plexus avulsion. These have been in cases where the use of a wide range of anticonvulsants, opiates and tricyclic antidepressants have had only partial or no success. These reports led us to try nabilone on a number of occasions. This synthetic THC analogue is licensed in the United Kingdom as an antiemetic during

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chemotherapy. Unfortunately its use has been limited by problems with availability and more particularly a perception that psychotropic side effects were more common at analgesic levels than was the case with cannabis (Hirst et al., 1998). Whole plant extracts of Cannabis sativa L. contain a complex mixture of natural cannabinoids and other chemical compounds. These may interact to provide a superior therapeutic profile over single synthetic entities. It was therefore a logical step for us to test newly available pharmaceutical grade cannabis based medicines in patients with this condition. An additional reason for choosing this population of patients is that they are an unusually homogenous group in terms of anatomical location of injury, pain descriptions and demographics. They therefore represent an excellent human model of central neuropathic pain.

The main psychoactive ingredient of cannabis extract is Δ⁹-tetrahydrocannabinol (THC). This is an agonist at the CB1 receptor, which is found at many sites within the central nervous system (Pertwee, 2001). Some of its unwanted side effects may be modulated by another naturally occurring cannabinoid, cannabidiol (CBD) (McPartland and Russo, 2001). In this study we tested two whole plant extracts of Cannabis sativa L.; one with an approximate 1:1 ratio of THC:CBD, coded as GW-1000-02 (Sativex®) and a THC extract, coded as GW-2000-02. The extracts were used in an oromucosal spray containing 27 mg/ml THC and 25 mg/ml CBD and tested against an inactive placebo. Our primary question was whether GW-1000-02 reduced chronic pain, with GW-2000-02 assessed as a secondary objective. In addition to further pain related questionnaires, secondary questions also aimed to review improvement in overall quality of life. Patients report that they cope better with their pain during work or other activities that provide distractions whereas periods of relaxation and sleep are more problematic.

2. Methods

2.1. Subjects

Study participants were recruited between December 2001 and July 2002 from patients treated at the Royal National Orthopaedic Hospital (RNOH) in Stanmore. This is the UK national referral centre for patients with brachial plexus injury. Most patients had previously been treated by the Peripheral Nerve Injury Unit at the RNOH and had also attended the pain clinic.

Men and women aged 18 years or more, with at least one avulsed brachial plexus root and with the injury occurring ≥18 months previously were included. Patients who scored four or above on a zero to 10 eleven point ordinal pain severity scale at Visits 1 and 2 and had a pattern of pain that in the investigator’s opinion had been stable over the previous 4 weeks were eligible. No analgesics were prohibited; all permitted concurrent medication had to have been stable during the previous 4 weeks and was to remain stable during the study. Patients were required to stop any cannabis or cannabinoid use at least 7 days prior to entry into the study.

Patients with a history of any of the following were ineligible: schizophrenia, other psychotic illness or significant psychiatric illness, other than depression associated with chronic illness; serious cardiovascular disease; significant renal or hepatic impairment; epilepsy or convulsions; significant history of substance abuse; known adverse reaction to cannabis or the product excipients; surgery within 2 months (6 months for nerve repair). Female patients who were pregnant, lactating or at risk of pregnancy were also excluded. Concurrent use of levodopa, sildenafil and fentanyl during the study was not permitted due to the theoretical inhibition of selected cytochrome P450 isoforms by CBD. For similar reasons the dose of amitriptyline was restricted to a maximum of 75 mg per day.

Patients were not allowed to drive within 4 h of a dose of the study drug or if they felt intoxicated in any way (see Discussion).

The local ethics committee at RNOH approved the study. The study was conducted according to the International Conference on Harmonisation of Good Clinical Practice guidelines and the Declaration of Helsinki with respect to informed consent.

2.2. Study design and treatment

This was a single centre, double-blind, randomised, placebo-controlled, three period crossover study. All patients self-administered GW-1000-02, GW-2000-02 and placebo, with each medication given for a minimum of 14 days with the visit window allowing flexibility in clinic appointment timing up to a maximum of 20 days. Patients were randomly allocated by a computer generated list to the six possible sequences of receiving the three study medications. Although the treatment sequence was blinded, sealed code break envelopes, one for each patient, containing information on the treatment sequence were available if necessary. Blinding was maintained throughout the study.

After the initial contact, patients attended for their first visit. During this visit patients gave consent and underwent a full eligibility screen including physical examination, vital signs, and a battery of baseline assessments as described in Section 2.3. Patients recorded their baseline symptoms in a diary then returned for a second visit, 7–24 days later, for randomisation and dose introduction. Patients were instructed on how to self-medicate and were monitored in clinic over 4 h, on the dosing day at the start of each period, while they took up to four initial doses. Patients returned for their next visit 2 weeks later for end of period assessments and to receive the next medication. This process was repeated at a fourth visit, 2 weeks later. Two weeks after this, patients attended for a fifth and final visit that included
a clinical assessment and end of study assessments. A flowchart of the study plan is shown in Fig. 1.

Depending upon their clinical response to the dose of study medication given in the clinic each patient was advised to take between four and eight sprays the next day. Patients were instructed not to increase their total daily number of sprays by more than 50% of the number taken during the previous 24 h. Patients were allowed to titrate freely within the following limits, according to subjective symptom relief and adverse events (AEs). The maximum permitted dose was eight sprays (THC 21.6 mg or THC 21.6 mg/CBD 20 mg or placebo) at any one time or within a 3-h period and 48 sprays (THC 129.6 mg or THC 129.6 mg/CBD 120 mg or placebo) within any 24 h period.

At the final visit patients were given the choice to stop the medication or receive GW-1000-02 within an open label extension study. The purposes of this extension included collection of long-term safety and efficacy data and prevention of patients feeling the need to seek illegal sources of cannabis. The extension study is still in progress.

This paper has been presented according to the CONSORT guidelines (Moher et al., 2001).

2.3. Outcome measures

2.3.1. Primary measure

The primary measure of efficacy was a standard eleven point ordinal pain severity scale ranging from zero ‘Best Imaginable’ to 10 ‘Worst Imaginable’, recorded in the daily diary. This was recorded as an eleven point Box Scale (BS-11) where patients ticked one of a row of boxes above the numbers 0–10 (Jensen et al., 1986, 1989). Baseline was taken as the average of these scores for the last 7 days before dosing. The on-treatment scores were the average of the last 7 days of each of the 2-week treatment periods, to minimise carry over effects from the previous period. Based on previously published work, it was assumed a priori that a difference of at least two points in the BS-11 pain score between the active and placebo phases would represent a clinically significant change (Farrar et al., 2001).

2.3.2. Secondary measures

At each clinic visit, patients recorded a pain review score on a BS-11 scale. On this scale patients recorded the severity of their pain over the previous 7 days.

Sleep quality was measured using a BS-11 scale from zero ‘Best Imaginable’ to 10 ‘Worst Imaginable’. Sleep disturbance (number of times woken due to pain) was measured using a four point categorical scale of none, once, twice, more than twice. Both these measures were recorded daily in the patient diaries. Patients also recorded the number of medication sprays taken during each 24-h period.

The short form McGill questionnaire (SF-MPQ), Pain Disability Index (PDI) and General Health Questionnaire-12 (GHQ-12) were administered at Visit 2 (baseline), Visits 3 and 4 (medication crossover) and Visit 5 (end of study) (Banks, 1983; Melzack, 1987; Tait et al., 1987).

2.3.3. Safety measures

A visual analogue scale (VAS) intoxication score was recorded at each visit along with AEs that were reported on open questioning. A physical examination was performed at Visits 1 and 5. Standard full blood count, urea, electrolytes, liver chemistry, urinalysis and 12 lead ECG were performed at Visits 1 and 5 or upon withdrawal. Additionally at Visit 1 a full medical history was taken from all patients including recording all concomitant medications. Female patients of child-bearing age were given a urine based pregnancy test at Visits 1 and 5.

2.4. Statistics

The sample size was based on the primary variable of the BS-11 pain scale. Based on the limited previous published work for this condition an approximate within patient standard deviation of 2.4 was assumed. Assuming a drop out rate of 20%, 48 patients were required to detect a mean two point difference in change from baseline in pain score between the cannabis based medicines and placebo with \( \alpha = 0.05 \) and a power of 90% using a two sided significance test. The intention to treat population consisted of all the patients who entered into the study, were randomised.
and had on treatment study data collected for at least 3 days from a treatment period. Any patients who received at least one dose of study drug were included in the safety analysis population.

No washout period was used between the three treatment periods. Any carry over effect was unlikely to be for greater than 2–3 days so the first week of titration for each period would be sufficient to counteract any carry over with efficacy comparisons being made by averaging the variables over the last 7 days of treatment. By 24 h post-dose the plasma level of the major efficacy constituents of GW-1000-02 is usually at or below the lower limit of quantification. In trials conducted to date using GW-1000-02, the putative effective half-lives of CBD, THC and 11-hydroxy THC (the main metabolite of THC) have been calculated to be in the order of 100, 85 and 130 min, respectively (Guy, 2003).

Analysis of variance (ANOVA) was used to compare each cannabis based medicine to placebo. The model included factors for patient, treatment and period. The significance of the overall treatment effect was assessed using the $F$-test from the ANOVA. The model used was as follows:

\[
\text{Outcome measure (e.g. BS-11 Pain Score)} = \text{Patient} + \text{Treatment} + \text{Period}
\]

During the course of the study and prior to unblinding it was decided that the primary comparison would be: GW-1000-02 with placebo. GW-2000-02 compared with placebo was considered secondary.

### 3. Results

#### 3.1. Patient characteristics

A total of 48 patients were randomised, of these 46 were male. The average age was 39 years (range 23–63 years).

#### 3.2. Dosing

The mean number of sprays taken daily during the analysis period is presented in Fig. 2.

#### 3.3. Withdrawals

Of the 48 patients randomised three withdrew before completing the study. One patient experienced nausea and vomiting during placebo administration, another withdrew due to an episode of feeling faint whilst taking GW-1000-02, the last patient withdrew due to feelings of anxiety and paranoia, experienced whilst taking placebo.

#### Table 1

<table>
<thead>
<tr>
<th>Summary of brachial plexus injury and repair</th>
<th>Mean (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of root avulsions</td>
<td>3.6 (1–5)</td>
</tr>
<tr>
<td>Number of surgical interventions</td>
<td>1.73 (0–8)</td>
</tr>
<tr>
<td>Time since last surgical intervention (years)</td>
<td>5.0 (0.9–18.6)</td>
</tr>
</tbody>
</table>

#### Table 2

<table>
<thead>
<tr>
<th>Summary of concurrent analgesic medication</th>
<th>No of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gabapentin</td>
<td>16</td>
</tr>
<tr>
<td>Opiates</td>
<td>14</td>
</tr>
<tr>
<td>Tricyclic antidepressants</td>
<td>10</td>
</tr>
<tr>
<td>Tramadol</td>
<td>9</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>6</td>
</tr>
<tr>
<td>Other anticonvulsants</td>
<td>4</td>
</tr>
<tr>
<td>NSAIDS</td>
<td>2</td>
</tr>
<tr>
<td>SSRI</td>
<td>2</td>
</tr>
<tr>
<td>Alpha II blockers</td>
<td>1</td>
</tr>
</tbody>
</table>

Twenty two (45.8%) had previously used cannabis medicinally and 29 (60.4%) had used it recreationally. The pattern of injury, operative repair and time since last surgical intervention are shown in Table 1. Of the 45 completing patients, 36 (80%) entered the open label extension study, using GW-1000-02.

Patients were taking a variety of analgesic medication concurrently throughout the study, this is shown in Table 2. Forty patients (83%) were taking at least one concomitant medication, of these, eight patients were taking only one medication, 12 patients were taking two, four taking three, nine taking four medications and seven were taking five or more. Some patients may have failed previously tried analgesics.
and subsequently GW-2000-02. These are presented in Fig. 1. Data were therefore available for 48 patients who received placebo, 46 who received GW-1000-02 and 47 who received GW-2000-02.

3.4. Statistical issues

The appropriateness of the protocol specified statistical model was investigated by an inspection of the fitted residuals and no statistical issues were apparent. In addition, it is noted that neither the mean pain score nor the pain review score recorded at clinic visits provided any evidence of a treatment by period interaction effect. See discussion of carryover effects in Section 2.4.

3.5. Primary outcome measure

The difference in the mean diary BS-11 pain score between both study medications and placebo was statistically significant but did not reach the a priori assumed level for clinical significance of two boxes; GW-1000-02 compared with placebo equalled a reduction of 0.58 boxes ($P=0.005$, 95% CI: $-0.98$, $-0.18$ boxes) and GW-2000-02 compared with placebo gave a reduction of 0.64 boxes ($P=0.002$, 95% CI: $-1.03$, $-0.24$ boxes). Fig. 3 shows the mean daily pain score by day and Fig. 4 shows the mean daily pain scores during each period.

3.6. Secondary outcome measures

Table 3 shows the mean scores, $P$-values, and confidence intervals (given as the difference from placebo) for the secondary outcome measures. The sleep quality and sleep disturbance scores are the daily means over the last 7 days of each treatment period. The SF-MPQ scores, pain review BS-11 scores, PDI and GHQ-12 were recorded at the start of the study and the end of each treatment period. The present pain intensity (PPI) section of the SF-MPQ questionnaire was not analysed.

3.7. Numbers needed to treat

The numbers needed to treat (NNT) have been calculated according to the method described by Walter (2001). The NNTs for the diary BS-11 pain score are shown in Table 4 for threshold reductions in pain scores of one and two points as well as 30 and 50% against placebo (primary measure). Table 5 presents the same data for sleep quality.

Using a 30% decrease as the threshold for clinical relevance of pain relief the equivalent NNTs would be 9.0 (GW-1000-02) and 7.7 (GW-2000-02), respectively. At the 50% response level only one patient in the GW-2000-02 treatment group was classed as a responder (NNT 46) and none in GW-1000-02 group.

3.8. Tolerability and adverse events

The study medication was well tolerated by all patients with no serious AEs occurring throughout the study. There were more AEs experienced during the active medication periods than during the placebo period. However, the majority of AEs were mild or moderate in severity and resolved spontaneously. Intoxication VAS (100 mm) scores at the end of each dosing period were 1 mm for placebo, 5.9 mm for GW-1000-02 and 9.7 mm for GW-2000-02. Table 6 provides a summary of the number of patients experiencing the five most common treatment emergent, treatment related AEs by preferred term.
AEs that may indicate intoxication include: dizziness, somnolence, feeling drunk, euphoric mood, headache, nausea and lethargy. The incidence of these, based upon the treatment emergent, all causality AEs, does not differ greatly across the three treatment groups. Euphoric mood and feeling drunk were not experienced by the placebo group, dizziness was the most frequently experienced AE, see Table 6, with also the largest difference in incidence when either of the active medications is compared with placebo.

4. Discussion

This is the first randomised controlled trial of any drug used to treat pain resulting from brachial plexus avulsion injury. When treatment with study medications was compared to placebo the primary outcome measure (BS-11 pain severity score) failed to fall by the two points defined in our hypothesis. However, both this measure and measures of sleep showed statistically significant improvements. All patients remained on their existing medications throughout the study therefore this modest benefit is in addition to that provided by existing medications.

The lack of change in the PDI may reflect the patients’ underlying physical disability, which was not affected by the study medication.

A number of factors may have acted to confound the reliability of the results. The most problematic of these was the difficulty of guaranteeing full blinding although efforts were made to ensure that this was maintained. Many patients had previous experience of cannabis. Side effects suggestive of mild intoxication were more common in the active treatment phases when compared to placebo. Dysgeusia (bad taste) was also more common with active treatment. If patients associated these effects with the active drug this could have biased the study towards a positive outcome.

Patients were selected from the pain clinic and also by searching patient notes for mention of significant pain. Such a method may introduce bias although it is not clear whether any other selection method would have been better.

Patients continued to receive their regular analgesics throughout the study. As cannabis based medicines are likely to be used as adjunctive therapy we wanted the study design to reflect this. This may have reduced the measurable analgesic effect although conversely there is the possibility of synergistic effects with opiates (Lynch and Clark, 2003). Another reason for allowing patients to continue their regular analgesics was to improve the recruitment rate.

We chose a self-titration dosing schedule for several reasons. Data from human volunteer studies showed a high inter-subject variability in the bioavailability of GW-1000-02. Patients from previous studies had, due to symptom relief and tolerability, required the full range of dose, between 1 and 48 sprays per day (Notcutt et al., 2004; Wade et al., 2003). Self-titration also enabled patients, most of who were working and driving, to achieve their individual optimum therapeutic dose by balancing any analgesia against possible side effects and allowing them to vary the dose depending on their levels of pain, activity and to fit in with their lifestyle.

The sample size was sufficient to show a statistically significant change in the primary outcome measure. A larger sample and longer duration of treatment, would be required to comment more meaningfully on the true size of this effect (Moore et al., 1998). The extension study should provide this information in due course.

An important aspect of this study is the homogeneity of the study population. All injuries occurred at anatomically similar sites and pain descriptions were similar. The consistency of brachial plexus pain has been well described before (Bruxelle et al., 1988; Parry, 1980). It would be simplistic to suggest that the underlying mechanism of pain is the same in all patients following brachial plexus avulsion. There is much variation in the precise anatomical location of injury both in relation to the proximity of each avulsion to the spinal cord and the combination of nerve roots affected. There is evidence to suggest, however, that segmental deafferentation of the dorsal horn may be an important mechanism in the production of pain following avulsion injury. Both burst and continuous spontaneous firing of dorsal horn neurones have been reported following experimental avulsion injuries in the cat (Ovelmen-Levitt, 1988). Similar patterns of activity have also been recorded in man following spinal cord injury (Loeser et al., 1968). It has been suggested that such patterns of neuronal activity correlates with both the continuous and paroxysmal patterns of pain seen following avulsion injuries although this was not confirmed in a recent study (Guenot et al., 2003).

Can these proposed mechanisms be used to inform effective treatment? Neurosurgical treatment using the DREZ lesion was originally developed in the 1970s and continues to be used (Nashold and Ostdahl, 1979; Samii et al., 2001; Thomas and Kitchen, 1994). DREZ is an effective long-term treatment for brachial plexus avulsion pain producing long-term significant pain reduction in about two-thirds of patients. This strongly suggests that the dorsal horn is a significant site of ongoing pain generation following avulsion. Unfortunately DREZ is associated

<table>
<thead>
<tr>
<th>Preferred term</th>
<th>No. of patients</th>
<th>GW-2000-02</th>
<th>GW-1000-02</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>4</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>Somnolence</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Dysgeusia (bad taste)</td>
<td>1</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Nausea</td>
<td>3</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Feeling drunk</td>
<td>0</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>

Table 6
The five most common treatment emergent, treatment related adverse events

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with a significant rate of neurological complications limiting the use of this technique to only the most severe and refractory cases.

Surgical repair of avulsion injuries by nerve transfer has also been reported to lead to amelioration of pain (Berman et al., 1998). If this is a true causal relationship, the mechanisms are unclear.

Pharmacological treatment still remains the first line treatment for avulsion pain. In the absence of specific randomised trials this is based on their use in other neuropathic pain syndromes. Anticonvulsants, tricyclic antidepressants and opiates are the main drug groups used. The use of tricyclic antidepressants has frequently been limited by side effects that are unacceptable to this active group of patients. There is anecdotal evidence that opiates are only partially effective in a significant proportion of these patients (Berman et al., 1998).

Like the opioid system, the cannabinoids modulate pain processing at multiple sites within the central nervous system (Rice, 2001). Cannabinoids produce analgesia independently of opiates. Cannabinoid analgesia is well established in animal models of neuropathic pain (Bridges et al., 2001; Fox et al., 2001; Hamann and di Vadi, 1999; Herzberg et al., 1997; Mao et al., 2000). However, evidence for cannabinoid analgesia in man is limited. A recent systematic review revealed only two single subject case reports specifically looking at neuropathic pain (Campbell et al., 2001; Holdcroft et al., 1997; Maurer et al., 1990). However, evidence for cannabinoid analgesia in man is limited. A recent systematic review revealed only two single subject case reports specifically looking at neuropathic pain (Campbell et al., 2001; Holdcroft et al., 1997; Maurer et al., 1990).

Randomised controlled studies are only now starting to appear. The recently published CAMS study did show improvements in pain in multiple sclerosis with oral cannabis extract and also oral synthetic Δ9-THC when compared to placebo (Zajicek et al., 2003).

Like this study, a recent study of the effect of cannabis based medicines on neurogenic symptoms showed improved sleep quality (Wade et al., 2003). This may therefore prove a useful alternative to amitriptyline. It would be worthwhile to conduct studies comparing these two agents.

The adverse effects of smoked cannabis have been studied closely (Joy et al., 1999). When used recreationally cannabis does appear to have some potential for dependence (Ashton, 1999). There is also a consensus opinion that established mental illness may be aggravated by cannabis (Patton et al., 2002). For this reason, patients with a history of significant mental illness were excluded from this study. Heavy, regular recreational cannabis smoking at a young age in vulnerable subjects may be associated with an increased risk of subsequently developing schizophrenia (Arseneault et al., 2002; Zammit et al., 2002), but this remains a controversial issue. In assessing potential risk to medicinal subjects, it should also be borne in mind that the aim of the recreational user is to achieve intoxication, whereas, as seen in this study the aim of the medicinal user is to avoid it. No medication can be considered risk free. However, in the controlled setting there is no evidence that cannabis based medicine is less safe than other analgesic drugs.

Eighty percent of the patients considered the study drugs of sufficient benefit to warrant continuing into the extension study. This puts into context the clinical relevance of the modest drop in pain scores in a condition that is long lasting, difficult to treat and that has already proven refractory to our standard methods of treatment by both nerve repair and oral analgesics. The presented NNTs might be useful for clinicians to determine whether this drug would have a role in their practice. However, this must be set against the lack of consistency in outcome measures in central pain drug trials and consequently the difficulty in comparing NNTs across studies (Finnerup et al., 2002).

Further longer term studies of cannabis based medicines in central neuropathic pain are now required to demonstrate a clinically relevant, improvement in the treatment of this condition.

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