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Do cannabis-based medicinal extracts have general or specific effects on symptoms in multiple sclerosis? A double-blind, randomized, placebo-controlled study on 160 patients

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The objective was to determine whether a cannabis-based medicinal extract (CBME) benefits a range of symptoms due to multiple sclerosis (MS). A parallel group, double-blind, randomized, placebo-controlled study was undertaken in three centres, recruiting 160 outpatients with MS experiencing significant problems from at least one of the following: spasticity, spasms, bladder problems, tremor or pain. The interventions were oromucosal sprays of matched placebo, or whole plant CBME containing equal amounts of delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) at a dose of 2.5–120 mg of each daily, in divided doses. The primary outcome measure was a Visual Analogue Scale (VAS) score for each patient's most troublesome symptom. Additional measures included VAS scores of other symptoms, and measures of disability, cognition, mood, sleep and fatigue. Following CBME the primary symptom score reduced from mean (SE) 74.36 (11.1) to 48.89 (22.0) following CBME and from 74.31 (12.5) to 54.79 (26.3) following placebo [ns]. Spasticity VAS scores were significantly reduced by CBME (Sativex) in comparison with placebo (P =0.001). There were no significant adverse effects on cognition or mood and intoxication was generally mild.
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Introduction

Multiple sclerosis (MS) may lead to a wide range of impairments best managed through individualized interventions of many types. Complex drug combinations are sometimes necessary but these are often only partially effective or associated with unacceptable side effects. Consequently, drugs that can target several impairments at the same time are especially useful. For example amitriptyline may help pain, bladder symptoms, sleep and depression. Anecdotal animal and clinical data have all suggested that cannabis or cannabinoids may ameliorate pain, spasticity, muscle spasms and other symptoms in MS.[1–8] UK doctors have been barred from prescribing cannabis preparations since 1971 under the Misuse of Drugs Act. Illicit self-medication has continued[9,10] although hampered by variability in potency of supply and problems associated with both smoked and oral routes of delivery.

Cannabis contains more than 60 different oxygen-containing aromatic hydrocarbon compounds unique to the plant, known as cannabinoids. The principal psychopharmacological component in cannabis is Δ9-tetrahydrocannabinol (THC),[11] but other derivatives may have therapeutic or synergistic potential. Cannabidiol (CBD) is the most promising of these, especially as it is nonpsychoactive and may modulate the intoxicating and/or memory effects of THC.[12] The majority of cannabis available illicitly in the UK contains significant amounts of THC and CBD.[13]

Recently, standardized whole plant cannabis medicinal extracts (CBME) have become available for clinical research. Selective breeding and rigorous analytic procedures during extraction can be used to ensure purity and stability.[14] The oromucosal route lends itself to self-titration by the patient and provides a satisfactory pharmacokinetic profile.[15] Single case crossover studies have demonstrated that these CBMEs have the potential to reduce previously intractable symptoms, including pain, spasms and spasticity in patients with MS and other neurological conditions[16] with low levels of intoxication.

Nonetheless the evidence supporting the use of cannabinoids for symptom relief in MS remains inconclusive, even after a recently reported trial involving 657 patients,[17] and concerns about safety have not been resolved.[18,19] The current study is one of several designed to extend earlier work[16] in assessing the efficacy and tolerability of an oromucosal combined preparation of THC and CBD in the amelioration of multiple symptoms associated with MS.

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Methods

This randomized, placebo-controlled, double-blind parallel group study was conducted at three clinical centres in the UK with approval of the local research ethics committees. Patients were recruited through MS societies and referrals from outpatient clinics or general practitioners.

To be eligible, patients had to:

- have clinically confirmed MS of any type. This was undertaken through taking a history, undertaking a full examination, and full review of all hospital notes;
- have been stable over the preceding four weeks with no relapse, confirmed clinically on entry to the study;
- be on stable regular medication (i.e., not changed in the last four weeks);
- be willing to abstain from alternative cannabinoid use for seven days prior to screening and throughout the study; and
- volunteer one of the five target symptoms at a sufficient level of severity (see below).

Following informed consent, patients were screened for eligibility. This included having one of the chosen five target symptoms: spasticity, spasms, bladder problems, tremor or pain that was not obviously musculoskeletal. Each patient nominated the most troublesome of these as their primary symptom. Patients were asked to rate the severity of each target symptom on a Visual Analogue Scale (VAS) with anchors 'no problem' to 'very bad'. Patients were excluded if the primary symptom was rated at less than 50% of maximal severity.

Other exclusion criteria were a current or past history of drug or alcohol abuse, significant psychiatric illness other than depression associated with MS, serious cardiovascular disorder, significant renal or hepatic impairment or history of epilepsy. Patients could not be included if they had a planned visit abroad during the active study. Caution was exercised for patients taking drugs metabolized by certain cytochrome P450 enzymes, such as tricyclic antidepressants and anticonvulsants.

If eligible, patients were asked to consent to British Home Office notification of their participation, and had an ECG, and biochemical and haematological tests and (if appropriate) a pregnancy test.

Then a full assessment battery was undertaken by a specialist research nurse (see below). Patients were supplied with a run-in diary card of instructions to record symptoms on a daily basis. Most patients had tried other drugs for their symptom(s), and they were asked to continue concomitant medications throughout the study where possible.

Following the two-week base line period, patients returned to the study centre for review of eligibility, including further VAS completion for target symptoms. If the inclusion criteria were still fulfilled, dosing with randomized medication was initiated.

Patients were randomized by permuted blocks of size four, stratified by nominated primary symptom and centre. The pharmacist at each centre was provided with a randomization scheme for each primary symptom and assigned the treatments in sequential patient number order from the appropriate randomization list.

The study medication was whole plant extract containing equal proportions of THC and CBD. The CBME (Sativex) was presented in a pump action spray, delivering 2.7 mg THC and 2.5 mg CBD with each actuation. The placebo spray contained excipients only. All preparations incorporated a peppermint flavour and colouring to disguise the taste and appearance of CBME.

Supervision of the first dose, given in the clinic, was followed by instructions to titrate slowly during home dosing, aiming for optimal balance of symptom relief and unwanted effects. Guidelines were given for increments up to a maximum of 120 mg THC and 120 mg CBD per day with no more than 20 mg of each in any 3-hour period. Patients recorded the time and number of actuations per day, in a dosing diary. Regular telephone contact was maintained according to individual patient requirements and a brief safety visit was conducted after two weeks, to review dosing and adverse events.

After the six-week double-blind parallel group trial, patients returned to the study centre for a repeat of the full assessment battery. This was undertaken by a research nurse who was not involved in dosing advice and home contact with that patient, to ensure blinding. The assessments were carried out at the same time of day (morning) in the same order and by the same nurse for each patient throughout the trial where possible.

All patients were then offered active medication for a further four weeks. Retitration was necessary because for the placebo group this would have been a patient's first exposure to active medication.

At the end of this second period, a total of ten weeks dosing, patients had the opportunity to continue into an open-label long-term safety and tolerability study. The findings for the 137 patients who proceeded into the extension will be reported separately.

The full assessment battery comprised:

- 100 mm VAS for the primary target symptom, and for any other of the five target symptoms that were troublesome;
- Barthel Activities of Daily Living (ADL) index,[20] the Rivermead Mobility Index,[21] the short Orientation-Memory-Concentration Test,[22] the Adult Memory and Information Processing Battery test of attention adapted for patients with MS,[23] the General Health Questionnaire 28,[24] the Guy's Neurological Disability scale (GNDS),[25] the Beck Depression Inventory,[26] the Fatigue Severity Scale[27] and VAS to rate sleep: quality, amount and feelings on awakening;
- diary records using a VAS of spasm frequency, feeling of intoxication, and severity of each of the target symptoms on one nominated day each week;

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and, where appropriate:

- The modified Ashworth Scale of Spasticity[28] measured at wrist, elbow, knee and ankle and summed across all joints (total score = 20), a tremor ADL questionnaire,[29] the Nine-Hole Peg Test of manual dexterity,[30] a questionnaire on disability arising from urinary incontinence[31] and the time in seconds to walk 10 m.

The nominated primary symptom VAS score, henceforth referred to as the Primary Symptom Score (PSS), was compared between treatment groups using analysis of covariance (ANCOVA) with baseline primary symptom score as the covariate. The adjusted treatment means, treatment difference and the standard error of the mean difference (SE), *P*-value and 95% confidence interval for the treatment difference were presented. The VAS scores for each of the five individual primary symptoms and the sum of all five VAS scores for each patient (known as the Summed Symptom Score, scoring '0' where the patient did not experience the symptom) were analysed in the same way, as were the mean scores from daily diary cards recorded during the baseline and final two weeks of the active trial (i.e., weeks 5 and 6).

Power calculations using data from the initial study[16] suggested that a minimum of 65 patients would be needed to detect a 10% shift in the primary symptom VAS score in comparison with placebo. Following external advice, a decision was taken to increase the size of the study in order to facilitate comparison of individual primary symptoms.

Multiple statistical comparisons were made, because in addition to being an RCT with a primary outcome, this was also an exploratory study. All *P*-values presented are for single comparisons, but readers should be aware that a Bonferroni correction for multiple comparisons applied to 11 measures would make $P = 0.0045$ the significant value for $\alpha = 0.05$.

Role of the funding source

GW Pharma Ltd contributed to the study design and was involved in collection of the data. Data handling and analysis were contracted by GW Pharma Ltd to an independent research organization.

Results

Two hundred and seventeen patients were screened, of whom 160 were found to be eligible for inclusion. The flow of patients can be seen in Figure 1.

Demographic and baseline data are shown in Table 1; there were no statistically significant differences between the groups although the active treatment group was slightly more disabled (difference in mean Barthel score 1.5/20).

The data from the six-week assessment and the results of calculating adjusted mean difference scores can be seen in Table 2 and diary card data for the primary symptoms are shown in Table 3.

The PSS improved in both groups, with no statistically significant difference between the groups. However patients with pain all showed a large effect that was almost identical in patients on active and on placebo, and when patients with pain as their primary symptom are removed, the difference between CBME and placebo becomes statistically significant (without Bonferroni correction; $P = 0.03$). Analysis of the summed symptom score gave similar results (data not shown).

At the end of the double-blind trial (at six weeks), patients on active treatment whose primary symptom had been spasticity showed a significant reduction in their VAS (even after Bonferroni correction; $P = 0.001$) in comparison with placebo. This was supported by diary data comparing entries from the baseline and final two weeks of the active trial ($P = 0.009$).

Although not statistically significant, the 10 m walking time improved more in the actively treated group, and greater improvements in VAS scores and in diary data were also seen for bladder control following CBME compared with placebo.

A statistically significant treatment difference in favour of CBME was seen in patients' assessment of the quality of sleep ($P = 0.047$), and a difference in favour of the placebo group was seen in the GNDS scores ($P = 0.048$). There were no significant differences between the groups on measures of cognition and mood.

The relative incidence of adverse effects in active and placebo groups, as submitted to regulatory authorities, is shown in Table 4.

The average amount of CBME taken over the first ten weeks in each group is shown in Figure 2, where it can be seen that patients in both groups increased dosage gradually, reaching a plateau at about four weeks, with patients in the placebo group tending to take higher doses.

The graph of intoxication shown in Figure 3 reveals a slight increase in level of intoxication from baseline at commencement of the active medication, which appears to reduce by week ten of dosing.

Discussion

This large, randomized, placebo-controlled trial ambitiously attempted to amalgamate outcome measures of five MS symptoms into a single PSS. Although the PSS following CBME reduced by 25.29 mm out of 100 mm and following placebo reduced by 19.35 mm out of 100 mm, this was not a statistically significant difference. However, the difference in spasticity score between CBME and placebo was statistically significant (-31.2 versus -8.4, $P = 0.001$), and this significance was maintained following a Bonferroni correction for multiple measures.

The study included patients of all ages with a wide range of impairments and was not restricted by level of disability. Only patients who may have had specific
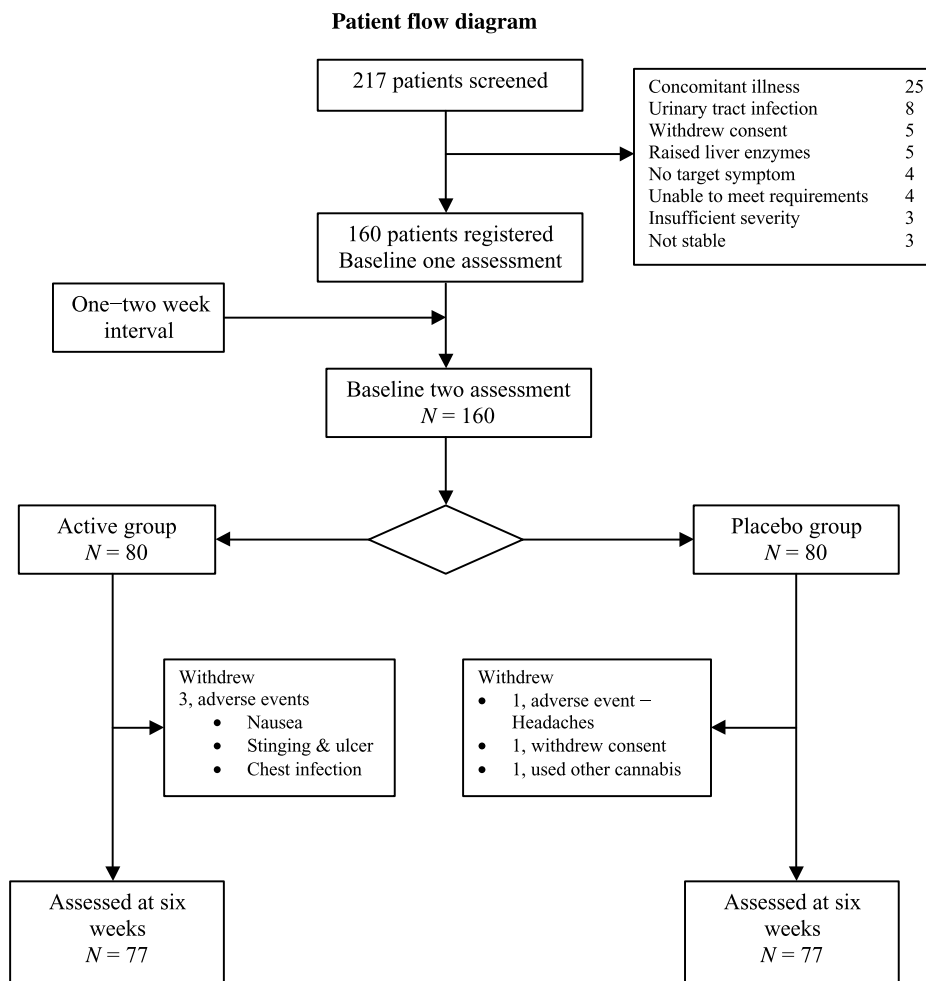
Patient flow diagram

Figure 1 *Patient flow diagram.*

contraindications to the use of CBME were excluded. The results should therefore be relevant to most patients with MS. However there are some weaknesses that need discussion.

One potential weakness is the combination of scores from different symptoms as a primary outcome measure. No tool has been developed to measure the efficacy of an intervention across a range of MS symptoms, as previously no intervention has been expected to have such a wide-ranging effect. Implementation of an identical measure for each key symptom permitted the creation of the PSS. This enabled us to use a measure personalized to each individual patient, a process similar to goal attainment scaling.[32,33] Although most of the validation of VAS has been conducted in the measurement of pain,[34] VAS was felt to be an appropriate measure in the other symptom groups. It had adequate sensitivity and had been demonstrated to be an effective measure of subjective endpoints in the pilot study,[16] but the clinical significance of any change is unknown. The approach of combining scores across different symptoms does allow patients to select their symptoms and might detect any general or multi-symptom benefits, but it also assumes that each symptom is equal in terms of responsiveness to cannabis and in terms of variability, and these assumptions may well not be true.

Five primary symptoms were studied, and consequently the number of patients with each individual symptom was small. The largest primary symptom category was spasticity, identified by 39 people. The assumptions were that the estimate of variability was large enough to encompass the most variable symptom and that each symptom category responded in a similar way to the medication. In retrospect these assumptions were incorrect, especially for pain, and when patients with pain as their primary symptom are removed from the analysis of changes in the PSS, the difference between CBME and placebo becomes significant (only before Bonferroni adjustment; $P = 0.03$). The large placebo effect for pain may have been explained by the patient group recruited, many of whom were self-referred, had not received regular specialist review and may not have been treated with licensed neuropathic pain medications.

There are several minor features that could be criticized. All patients had the clinical diagnosis of MS confirmed, but we did not specifically categorize the type of MS because there is no evidence to support the validity (or reliability) of categorization and because it is unlikely to

Table 1 Demographic data

Variable	Active group n = 80	Placebo group n = 80
Oxford	46	46
Northampton	15	14
London	19	20
Age years (mean, SD, range)	51.0 (9.4); 27–74	50.4 (9.3); 27–74
Male:female	33:47	28:52
Previous 'medicinal' cannabis	30	32
Previous recreational cannabis	13	21
Primary symptom:		
Spasms	20	18
Spasticity	20	19
Bladder control	15	17
Pain	18	19
Tremor	7	7
Experienced symptom:		
Spasms	54	58
Spasticity	72	68
Bladder control	57	62
Pain	40	51
Tremor	26	28
Standardized assessments		
Barthel ADL index /20	14.2 (6.1) [n = 79]	15.7 (5.4) [n = 80]
Rivermead Mobility Index /15	7.1 (5.0) [n = 80]	8.2 (4.6) [n = 80]
Ashworth score /20	5.0 (3.7) [n = 76]	4.6 (4.4) [n = 74]
GNDS /60	20.8 (7.6) [n = 74]	21.6 (7.5) [n = 75]
SOMC /28	25.0 (3.2) [n = 79]	24.5 (4.6) [n = 79]
AMIPB number correct in four minutes	22.4 (8.2) [n = 75]	20.9 (8.6) [n = 74]

AMIPB: Adult Memory and Information Processing Battery; SOMC: Short Orientation Memory and Concentration Test.

predict responsiveness to symptomatic treatment. Patients were clinically stable. We did record the level of disability using well validated measures, but not using the Expanded Disability Status Scale (EDSS) in view of its limitations. We failed to assess the degree of blinding of our patients and outcome assessors, but we did make every effort to ensure blinding. We did not check on whether patients were taking other forms of cannabis, and although patients were asked not to change other medication over the first six weeks, they may have done so. Both of these variables would have tended to reduce any differences between placebo and experimental groups.

The patients had no difficulty in adopting a self-titration dosing regime which took up to four weeks. This generally enabled optimization of symptom relief at a dose not associated with troublesome adverse effects. Dose-limiting effects most commonly noted clinically were intoxication and excessive reduction in lower limb tone. Although anticipated with the use of THC-containing medication, the occurrence of intoxication was unpredictable due to variation between patients in level of sensitivity. Subjective experiences ranged from mild drowsiness and disturbance in attention to disorientation and a feeling of drunkenness. The experience of excess tone reduction in ambulatory patients was similar to that associated with use of other anti-spasticity agents. These effects were easily resolved with dose reduction and generally patients could stabilize at an acceptable level, resulting in few withdrawals.

Local discomfort at the application site with mouth ulceration in five patients was probably related to the ethanolic formulation. Oromucosal application was chosen to facilitate quicker and more sensitive titration of the

Table 2 Adjusted mean differences in clinic visit scores over six weeks

Measure	Active	Placebo	Diff.	95% CI for difference	SE	P-value
PSS	−25.2 −25.29 [n = 79]	−19.35 [n = 77]	−5.93	−13.52, 1.65	3.84	0.124
Primary symptom: VAS						
Spasticity	−31.20 [n = 19]	−8.40 [n = 18]	−22.79	−35.52, −10.07	6.26	0.001
Spasms	−26.50 [n = 20]	−21.20 [n = 18]	−5.3	−19.81, 9.22	7.15	0.464
Bladder	−34.32 [n = 15]	−26.34 [n = 17]	−7.98	−27.44, 11.48	9.51	0.408
Pain	−11.44 [n = 18]	−20.17 [n = 18]	8.73	−10.39, 27.84	9.4	0.360
Tremor	−21.42 [n = 7]	−25.17 [n = 6]	3.75	−30.17, 37.68	15.22	0.810
Ashworth	−0.37 [n = 73]	−0.59 [n = 70]	0.22	−0.50, 0.94	0.365	0.548
GNDS	−0.93 [n = 66]	−2.74 [n = 63]	+1.81	+0.02, 3.60	0.91	0.048
GHQ total	−2.02 [n = 79]	−2.74 [n = 75]	+0.72	−2.38, 3.82	1.57	0.647
Fatigue Severity Scale	−0.26 [n = 78]	−0.14 [n = 76]	−0.12	−0.43, 0.18	0.15	0.427
Barthel ADL index	−0.38 [n = 78]	0.09 [n = 77]	−0.47	−1.01, 0.07	0.27	0.087
BDI	−2.14 [n = 78]	−2.83 [n = 77]	0.69	−1.11, 2.50	0.91	0.450
AMIPB	1.90 [n = 73]	2.01 [n = 70]	−0.11	−1.85, 1.64	0.88	0.904
Bladder questionnaire	−2.03 [n = 58]	−1.92 [n = 60]	−0.12	−1.77, 1.54	0.83	0.889
10 m time (s)	−2.78 [n = 38]	−0.74 [n = 47]	−2.35	−5.16, 0.46	1.41	0.070*
NHPT both (s)	−0.47 [n = 66]	+0.38 [n = 65]	−0.52	−1.58, 0.55	0.54	0.162*
VAS scales:						
Quality of sleep	−16.69 [n = 79]	−9.60 [n = 77]	−7.10	−14.11, −0.08	3.55	0.047
How much sleep	−13.93 [n = 79]	−9.40 [n = 77]	−4.53	−11.45, 2.40	3.50	0.198
Feeling upon waking	−9.56 [n = 79]	−8.20 [n = 77]	−1.36	−8.80, 6.07	3.76	0.717

*Wilcoxon rank sum test, as results not normally distributed; AMIPB: Adult Memory and Information Processing Battery; BDI: Beck Depression Inventory; CI: confidence intervals; GHQ: General Health Questionnaire; NHPT: Nine-Hole Peg Test; SE: standard error of the mean difference; SOMC: Short Orientation Memory and Concentration Test.

Table 3 Individual symptom VAS scores identified as primary as recorded on diary card; change between baseline two weeks and final two weeks

Measure	Active	Placebo	Diff.	95% CI for difference	Standard error	P-value
Primary symptom:						
Spasticity	−17.00	1.42	−18.4	−31.81, −5.01	6.59	0.009
Spasm frequency	−21.41	−20.14	−1.27	−16.85, 14.31	7.67	0.869
Spasm severity	−21.67	−21.59	−0.08	−17.28, 17.11	8.42	0.992
Bladder	−24.39	−11.10	−13.3	−29.10, 2.52	7.73	0.096
Pain	−9.83	−19.87	10.04	−7.14, 27.22	8.45	0.243
Tremor	−9.20	−5.12	−4.07	−42.06, 33.91	16.79	0.814

Table 4 Summary of treatment-related adverse events with greater than 4% incidence

| Adverse event	Active – n (%)	Placebo – n (%)
n	80	80
Dizziness	26 (32.5)	10 (12.5)
Disturbance in attention	7 (8.8)	0 (0)
Headache	7 (8.8)	13 (16.3)
Fatigue	12 (15)	3 (3.8)
Somnolence	7 (8.8)	1 (1.3)
Disorientation	6 (7.5)	0 (0)
Feeling drunk	4 (5)	0 (0)
Vertigo	5 (6.3)	0 (0)
Application site discomfort	21 (26)	18 (22.5)
Nausea	7 (8.8)	5 (6.3)
Diarrhoea	6 (7.5)	2 (2.5)
Mouth ulceration	4 (5)	1 (1.3)

medicine. Less irritant delivery mechanisms are now being developed.

This study should be viewed in parallel to the other large study recently published (the CAMS study).[17] The studies share many outcome measures including the Ashworth score, the Rivermead Mobility Index, the 10 m timed walk, the Barthel ADL index and the Guy's Neurological Disability Scale (although it was named the UK neurological disability scale in the CAMS study). Consequently, meta-analysis may be possible, accepting that the specific cannabis preparations were different. The patients in the CAMS study also covered a wide range of disability, though generally appear to have been more disabled than our study population. The placebo response was also quite large, and changes seen in the disability scales were similarly small.

The CAMS study primarily investigated spasticity, where it found little measurable benefit in the primary outcome (the Ashworth scale). However it also reported patient-assessed changes in four symptoms which were examined in our study; pain, spasticity, tremor and bladder control. As with our study, significant subjective improvements in spasticity were recorded, but in marked contrast to our study significant improvements in pain were also noted. There was a strong trend towards a benefit for tremor in their large sample of 365 patients, which was not apparent in our small subgroup of 13 patients. Finally they noted no significant effect on bladder symptoms, which is consistent with our findings.

Given the relatively small number of patients with particular symptoms, and the large number of comparisons made, it is essential that all trends and apparent differences are viewed cautiously. For example patients in
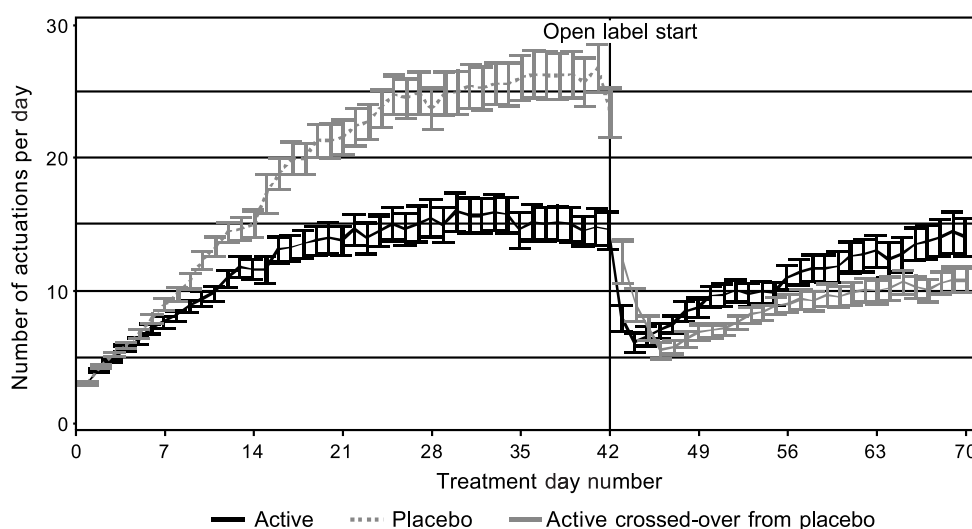
Figure 2 Mean number of actuations (±SE) per day.

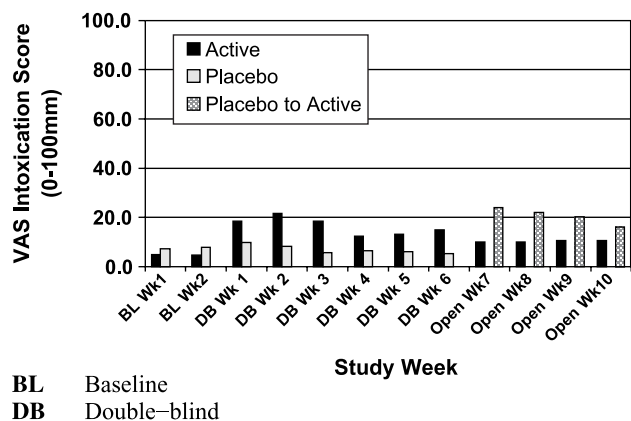**BL** Baseline
DB Double−blind

Figure 3 *Diary card intoxication scores.*

the placebo group appear to improve on the Guy's Neurological Disability scale more than patients on CBME, but the reverse is true for the Barthel ADL index. Consequently all differences in such items as sleep quality, bladder control, spasms and fatigue should be taken as possible indicators for future research, but no more.

In conclusion, the results of this study suggest that CBME (Sativex) is an effective treatment for spasticity associated with MS. The use of gradual self-titration of the dose allowed most people to achieve benefit without unduly troublesome side effects. Taking into account the results of the CAMS trial and our own preliminary study it is evident that further studies to clarify the precise role of CBME for people with MS are indicated, especially its potential for controlling several symptoms at the same time.

Contributions

PR and DW initiated the study and took part in all aspects including design, choosing measures and writing the paper. PM took part in some aspects of design and measures, and undertook medical screening and follow-up in Oxford. HH took part in some aspects of design and measure, and undertook many follow-up assessments, and trained other nurses. CB followed up many patients. All authors read and contributed to the final paper. DW is the guarantor.

Competing interests

PR is medical director of GW Pharmaceuticals who funded the study. HH and CB are employed by GW Pharmaceuticals. PM is in receipt of a research grant from GW Pharmaceuticals.

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