Articles

Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): multicentre randomised placebo-controlled trial

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Summary

Background Multiple sclerosis is associated with muscle stiffness, spasms, pain, and tremor. Much anecdotal evidence suggests that cannabinoids could help these symptoms. Our aim was to test the notion that cannabinoids have a beneficial effect on spasticity and other symptoms related to multiple sclerosis.

Methods We did a randomised, placebo-controlled trial, to which we enrolled 667 patients with stable multiple sclerosis and muscle spasticity. 630 participants were treated at 33 UK centres with oral cannabis extract (n=211), Δ^9-tetrahydrocannabinol (Δ^9-THC; n=206), or placebo (n=213). Trial duration was 15 weeks. Our primary outcome measure was change in overall spasticity scores, using the Ashworth scale. Analysis was by intention to treat.

Findings 611 of 630 patients were followed up for the primary endpoint. We noted no treatment effect of cannabinoids on the primary outcome (p=0·40). The estimated difference in mean reduction in total Ashworth score for participants taking cannabis extract compared with placebo was 0·32 (95% CI –1·04 to 1·67), and for those taking Δ^9-THC versus placebo it was 0·94 (–0·44 to 2·31). There was evidence of a treatment effect on patient-reported spasticity and pain (p=0·003), with improvement in spasticity reported in 61% (n=121, 95% CI 54·6–68·2), 60% (n=108, 52·5–66·8), and 46% (n=91, 39·0–52·9) of participants on cannabis extract, Δ^9-THC, and placebo, respectively.

Interpretation Treatment with cannabinoids did not have a beneficial effect on spasticity when assessed with the Ashworth scale. However, though there was a degree of unmasking among the patients in the active treatment groups, objective improvement in mobility and patients' opinion of an improvement in pain suggest cannabinoids might be clinically useful.

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See Commentary

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Introduction

Of the many symptoms encountered in multiple sclerosis, muscle spasticity (muscle stiffness as a result of increased pyramidal tone) and spasms occur in up to 90% of patients at some point. This symptom often leads to considerable distress from pain, reduced mobility, and interference with activities of daily living. Other disabling features of the disease include ataxia and tremor in up to 80% of patients, and sensory symptoms, including pain, in up to 50%.[1] Lower urinary tract dysfunction is present in more than 90% of people with long-standing multiple sclerosis,[2] with the most frequent symptoms being urinary frequency and urgency.[3] Although many symptoms resolve in the remitting phase of multiple sclerosis, spasticity, weakness, ataxia, and bladder symptoms are often characteristic of progressive disease and tend to worsen over time.

Symptomatic therapy often provides inadequate relief and can be limited by toxicity. As a consequence, people with multiple sclerosis have experimented with many alternative therapies, including cannabis, to ease their physical problems.[4,5] There is much anecdotal suggestion that cannabis and its major components, the cannabinoids, have beneficial effects on disease-related pain, bladder symptoms, tremor, and particularly spasticity,[6] but little scientific evidence exists for their efficacy. There is widespread unlicensed and often illegal use of cannabinoids in multiple sclerosis, involving various formulations and routes of administration, and estimates suggest[7] that between 1% and 4% of patients in the UK use cannabis for symptom relief.

The plant *Cannabis sativa* is complex and has more than 60 oxygen-containing aromatic hydrocarbon compounds, known as cannabinoids. Most of their effects seem to be mediated through cannabinoid receptors, two types of which have been isolated and cloned: CB_1[8] and CB_2.[9] CB_1 receptors are distributed widely in the nervous system, and seem to have a general role in the inhibition of neurotransmitter release, whereas CB_2 receptors are mainly found on cells of the immune system. The identification of a range of endogenous cannabinoids, the most important of which are thought to be 2-arachidonoylglycerol and arachidonoylethanolamide (anandamide),[10] has also provoked considerable interest, and there is some evidence[11,12] that cannabinoids have a neuroprotective action.

Four small, randomised, double-blind, placebo-controlled studies[13–16] have been undertaken to assess the effect of cannabinoids on spasticity related to multiple sclerosis, the largest of which[16] was a crossover study of 16 patients. The results suggest that cannabinoids produce subjective symptomatic improvement, but provide no objective evidence for efficacy. Our aim was to ascertain whether either Δ^9-tetrahydrocannabinol

(Δ^9-THC) or an ethanol extract of whole cannabis is effective for the treatment of spasticity and a range of other disease-related symptoms in patients with multiple sclerosis.

Methods

Patients

Between December, 2000, and October, 2002, we enrolled patients aged 18–64 years with clinically definite or laboratory-supported multiple sclerosis who, in the opinion of the treating doctor, had had stable disease for the previous 6 months, with problematic spasticity (Ashworth score of ⩾2 in two or more lower limb muscle groups). Since cannabinoids can potentially affect cardiac function (reducing heart rate and blood pressure), the exclusion criterion of ischaemic heart disease and the upper age limit were imposed. Furthermore, we made every attempt to stabilise factors that affect spasticity, so any physiotherapy regimen or medication likely to affect spasticity was optimised before the study and not altered in the 30 days before start of treatment. Patients with active sources of infection, or taking medication such as beta interferon, which could affect spasticity, were excluded, and we asked individuals not to have any immunisations associated with foreign travel over the 15 weeks of the study. Patients were also asked not to drive while they were receiving medication and, if unable to comply, were excluded. Other exclusion criteria included fixed-tendon contractures, severe cognitive impairment, past history of psychotic illness, major illness in another body area, pregnancy, use of Δ^9-THC at any time, and use of cannabis in the 30 days before the start of the study.

We recruited participants from 33 neurology and rehabilitation centres in the UK. We undertook the study on an out-patient basis, with each patient attending eight clinic visits over 15 weeks, including two pre-treatment visits (visits 1 and 2; see webtable 1 at http://image.thelancet.com/extras/03art9446webtable1.pdf for visit schedule). Potentially suitable patients were identified by the local investigator, referred by other clinicians, or self-referred as a result of publicity about the study. Prospective patients were invited to attend for screening 2–4 weeks before start of therapy. We reassessed individuals with respect to inclusion and exclusion criteria before trial treatment began. Patients who did not fulfil the criteria at either of the pre-treatment visits were excluded from the trial.

The study was approved by the South West multicentre research ethics committee and was undertaken under licence from the UK Home Office. All participants provided written informed consent.

Procedures

We randomly assigned patients to receive one of two active treatments or placebo at visit 2, using MINIM (version 1.5).[17] Participants were allocated in a two-to-one-to-two-to-one ratio at trial entry to cannabis extract, cannabis extract placebo, Δ^9-THC, or Δ^9-THC placebo. Patients were randomly assigned by adaptive randomisation to minimise imbalance between centres and ambulatory status (defined as able to walk at least 15 m).[18,19] Once written informed consent had been obtained from an eligible patient, the investigator contacted the coordinating centre by telephone. The coordinating centre allocated the patient a trial number and then forwarded relevant details to the central trial pharmacy, where randomisation took place, using a dedicated stand-alone computer. The appropriate medication was dispatched directly to the centre. Throughout the study, the list of treatment allocation codes was kept at the central trial pharmacy, located separately from the coordinating office.

We were unable to make the active treatments look identical, so each had its own matched placebo. Matching of active and placebo capsules was assessed by an independent panel before the start of the study to ensure there was no obvious difference between them. Active treatment consisted of either synthetic Δ^9-THC (Marinol, Solvay Pharmaceuticals, Atlanta, USA) or a cannabis extract, containing Δ^9-THC and cannabidiol as the main cannabinoids (Cannador, Institute for Clinical Research, IKF, Berlin, Germany). Capsules were manufactured to contain 2·5 mg of Δ^9-THC equivalent, 1·25 mg of cannabidiol, and less than 5% other cannabinoids per capsule. Independent capsule analysis was undertaken to assess concentrations of Δ^9-THC and cannabidiol at various time points over the course of the study. Results showed Δ^9-THC concentrations varied within 2% of 2·5 mg per capsule over 9 months, with similar low degrees of variation in mean cannabidiol concentrations. Placebo capsules contained the respective vegetable oil vehicle. Dose of study medication was based on bodyweight, with a maximum possible dose of 25 mg daily (table 1). Medication was taken twice daily, after food. All other medication was taken as usual, except other oil-based capsules—eg, evening primrose oil—which we asked patients to take separately from trial medication to avoid possible interference with absorption.

The study started with a 5-week dose titration phase (visits 3 and 4) because of the well recognised considerable interindividual variation in the tolerated dose with oral administration of cannabinoids. During this period, we asked patients to increase their dose by one capsule (2·5 mg Δ^9-THC equivalent) twice daily at weekly intervals. If side-effects developed, patients were advised not to increase the dose, and if side-effects were considered intolerable, the dose was reduced. Weeks 6–13 constituted a plateau phase, during which participants remained on a stable dose of medication (visits 5, 6, and 7). During week 14, patients reduced their medication by one capsule twice daily each day until they were off study medication. Patients remained off trial medication during week 15, and a final assessment was undertaken at the end of this week (visit 8).

Patients were scheduled to attend clinic visits at the same time of day wherever possible to reduce the effect of any diurnal variation in spasticity. If rescheduling of visits was needed for any reason, arrangements were made for patients to attend within 1 day of the scheduled visit date if possible. To detect any illicit cannabis use, urine

	Bodyweight			
	30–49 kg	50–69 kg	70–89 kg	>89 kg
Daily target dose (number of capsules)	4	6	8	10
Cannabis extract	16 (2·34 [1·44])	87 (4·78 [1·78])	78 (5·79 [2·33])	30 (7·99 [2·86])
Δ^9-THC	13 (3·22 [1·12])	80 (4·58 [1·80])	84 (6·30 [2·10])	28 (6·56 [3·27])
Placebo	14 (3·57 [1·24])	94 (5·21 [1·46])	75 (7·11 [1·89])	31 (8·47 [2·23])

Data are number of patients (mean [SD] dose received) unless otherwise indicated.

Table 1: **Dose of study medication**

samples were collected at visits 2, 5, 6, and 8 and assayed for cannabinoids at a central laboratory by ELISA. Blood samples for cannabinoid assay, using gas chromatography and mass spectrometry, were collected at baseline and all subsequent visits from about 150 patients at the two largest centres, for convenience (unpublished data). To maintain blinding at the coordinating centre in Plymouth, all blood and urine results were held at an independent site (MRC Clinical Trials Unit, London) until statistical analysis began.

Our primary outcome measure was the change in spasticity related to multiple sclerosis, using the Ashworth score of spasticity.[20] Assessment of the Ashworth score was made at six visits: two pre-treatment (visits 1 and 2), three whilst on treatment (visits 5, 6, and 7), and one after discontinuation of treatment (visit 8). The Ashworth score is an assessment of biological impairment, rather than disability or handicap, and is dependent on the estimation of the doctor or physiotherapist. The score consists of a 5-point scale (0=normal, 1=slight catch when the limb is moved, 2=anything more than a catch but not restricting movement, 3=considerable increase in tone limiting passive flexion, 4=limb rigidity in flexion or extension). We assessed ten muscle groups on each side of the body (elbow flexors, extensors, pronators and supinators; wrist and finger flexors; hip adductors, knee flexors and extensors, and foot plantar flexors). The reliability of the Ashworth score depends on assessor experience, thus we made every effort to ensure that the same assessor monitored spasticity in individual patients at all visits. Assessors attended one of six regional training sessions or received individual instruction to ensure uniformity in application of the Ashworth score. We provided all centres with a training video demonstrating the Ashworth assessment. Each patient was assessed supine on a couch, or as close to this position as was tolerated, after resting for 15 min. The limb was moved rapidly in the direction required by assessment. As spasticity can change with passive limb movement, the number of movements of each joint was kept to a minimum. After a muscle spasm, the Ashworth score can increase greatly for some minutes, we therefore asked assessors to wait for 5 min after a spasm before reassessing that limb. The presence of more than seven beats of clonus on examining a joint was taken as implying at least grade 2 spasticity.

Secondary outcome measures included the Rivermead mobility index,[21] a timed 10 m walk, and four self-completion questionnaires—the United Kingdom neurological disability score (UKNDS),[22] the Barthel index,[23] the general health questionnaire (GHQ-30),[24] and a series of nine category-rating scales. The Rivermead mobility index and timed walk were assessed at the same six time points as the Ashworth score. The UKNDS, Barthel index, and GHQ-30 were administered once pre-treatment (before visit 2) and once at the end of the treatment phase (before visit 7). The category rating scales were administered at the end of the treatment phase only. For this assessment, we asked patients to assess how their symptoms had been over the previous week compared with how they were just before the study started. Categories included irritability, depression, tiredness, muscle stiffness, tremor, pain, sleep, muscle spasms, and amount of energy. At the end of the 15 weeks (visit 8), the treating doctor also asked participants four specific questions about the overall effect of medication on changes in spasticity, tremor, pain, and bladder function. We calculated the Kurtzke expanded disability status score (EDSS)[25] before and after treatment to provide a widely accepted measure of overall degree of disability in the trial population.

The study coordinating team, all investigators, the data monitoring committee, and patients were unaware of the treatment allocation for the duration of the study. Because of the potential for loss of patient blinding with active medication, a treating doctor and an assessor had to be present at each centre, plus deputies to cover for absence. The treating doctor monitored dose, side-effects, and patients' well-being, and the assessor (usually a physiotherapist) ascertained the Ashworth score, timed the 10 m walk, and administered the Rivermead mobility index. Assessors remained unaware of any discussion of dose or side-effects and, when assessing patients' spasticity, were asked not to have access to their assessment scores from previous visits. We assessed degree of blinding at the end of the study (visit 8) by asking patients and study personnel which treatment they thought patients had received. Because it was not possible to match all capsules in the study, some patients might have guessed that they were on either the Δ^9-THC placebo or the cannabis-extract placebo, which is why the exclusion criterion of previous exposure to Δ^9-THC was included. We felt the degree of unmasking and bias from this cause was likely to be small compared with any unmasking as a result of side-effects.

Our study was undertaken under a Doctors and Dentists Exemption Certificate from the UK Medicines Control Agency. A pilot study was done in Plymouth on a cohort of 24 patients to test the procedures and to monitor closely any adverse events. During the dose titration phase of the pilot study, patients were contacted by the Plymouth coordinating centre by telephone every 3 days, and an extensive checklist of questions with respect to adverse events was administered. In all other centres, standard adverse-event monitoring took place at each visit with classification according to International Conference on Harmonisation good clinical practice definitions. The coordinating centre in Plymouth was notified of any serious adverse events immediately; data were then forwarded to the data monitoring and ethics committee. For the purposes of this study, any hospital admission was regarded as a serious adverse event, even if it was related to multiple sclerosis and not necessarily unexpected.

Statistical analysis

To identify an appropriate sample size, we based our power calculations on the assumption that the standard approach of using total Ashworth score as the primary endpoint to measure spasticity would be adopted. A double-blind, placebo-controlled UK trial of the antispasticity agent tizanidine[26] reported a baseline Ashworth score with a mean of about 17. The placebo group showed a decrease in Ashworth score of 1·2 whereas the treatment group showed a decrease of 4·4. The power calculations for our study assumed that the combined placebo group, the cannabis extract group, and the Δ^9-THC group would have mean decreases of 1·2, 4·4, and 2·8, respectively (corresponding to placebo, tizanidine, and the mean of placebo and tizanidine). A rate of 3% of illegal use of cannabis was assumed in the placebo and Δ^9-THC groups with a loss to follow-up rate of 20%, distributed evenly across the three groups.

With these assumptions, recruitment of 220 patients in each group provided 90% power to detect a significant difference at the 5% level in the one-way ANOVA, assuming an SD of 8 for the change in Ashworth score.[27]

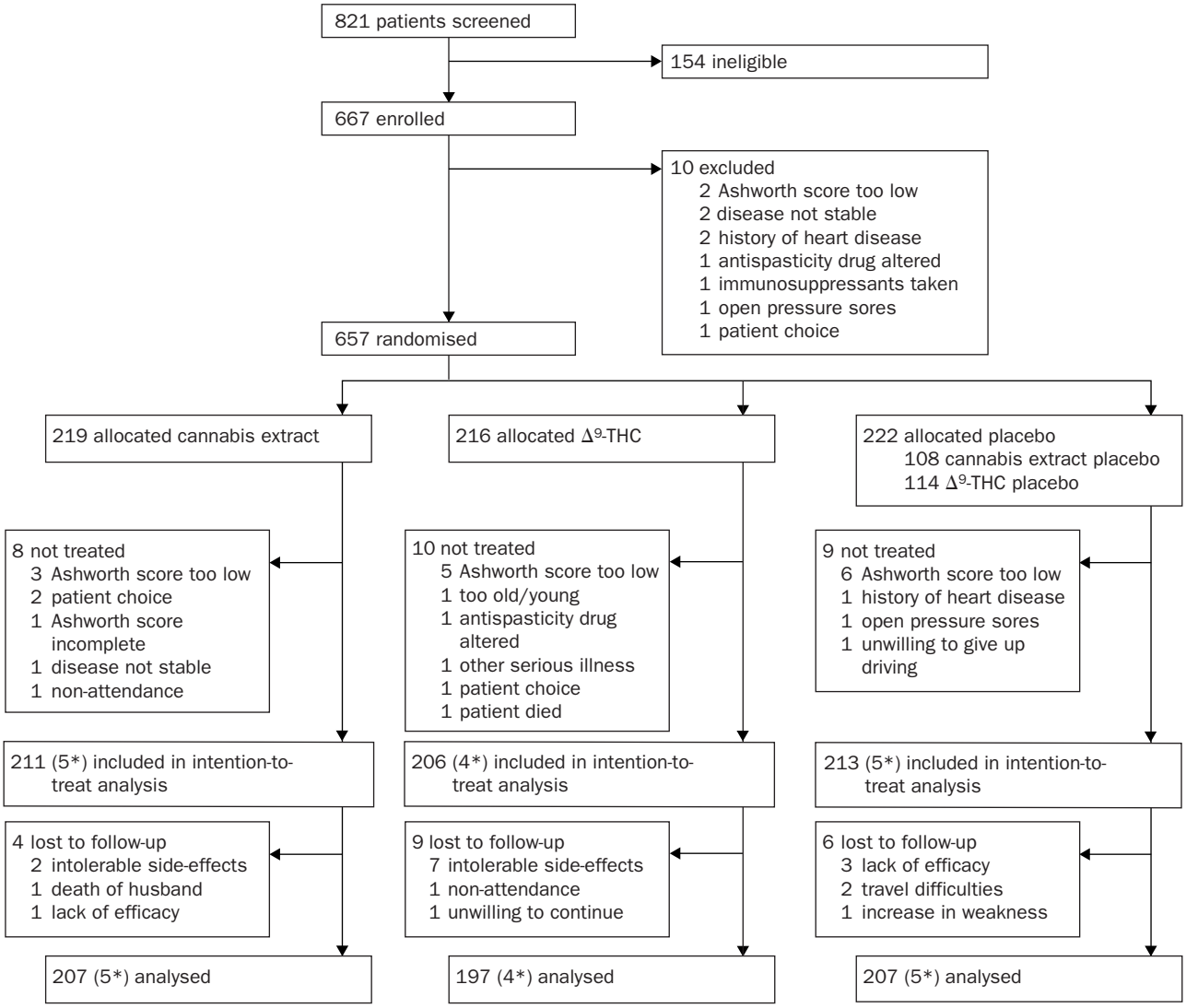

Figure 1: **Trial profile**
*Patients with low Ashworth score already started on treatment.

This calculation assumed there was no difference between placebo groups and that it was valid to combine them. This assumption was validated before the placebo groups were combined. No interim analysis was planned or done.

To minimise data-entry errors, we used a double data-entry system. All decisions with respect to primary outcome data were finalised and agreed by a blind data review panel before unblinding. We used S-Plus 2000 Professional and SAS version 8e software for analysis. Data analysis was by intention to treat and was undertaken in accordance with an analysis plan drawn up and agreed by the trial steering committee before unblinding. We judged a p value of 0·05 significant.

As planned, we compared the cannabis extract placebo and Δ^9-THC placebo groups in terms of changes in Ashworth scores, Rivermead mobility index, and walk times. Since no evidence of any differences was noted between placebo groups, they were combined into a single placebo group for all further analyses. The primary outcome, mean change from baseline in Ashworth score, was then compared, using analysis of variance, with treatments as fixed effects. We also added centres and ambulatory status to the model.

The analysis of times taken to complete a 10 m walk for mobile patients is complicated by the absence of data from patients who were physically unable to walk at one or other assessment. Initial analysis of these data suggested the effects were relative rather than additive and that a log-transformed ratio of walk time (baseline/follow-up) was appropriate. For patients who were ambulatory at baseline but unable to walk at follow-up, we assumed a suitably small value for the log ratio representing longer walk time at follow-up, so that patients who were unable to walk at follow-up had the lowest rank. We analysed data with the Kruskal-Wallis test and used non-parametric methods to produce 95% CIs for the median.

The Rivermead mobility index, UKNDS, Barthel index, and GHQ-30 were each analysed with non-parametric analysis of variance to compare the groups. We analysed patients' perception questions and category rating scales with contingency table analysis. No adjustments were made for multiple comparisons.

Two substudies were incorporated into the main CAMS programme. These focused specifically on lower urinary tract symptoms (CAMS-LUTS) and psychological effects of cannabinoids (CAMS-PEC). The results from both studies will be published separately.

	Treatment group					
	Cannabis extract (n=211)		Δ⁹-THC (n=206)		Placebo (n=213)	
	Number of patients	Mean (SD)/% of group	Number of patients	Mean (SD)/% of group	Number of patients	Mean (SD)/% of group
Sex						
Male (n=217)	76	..	63	..	78	..
Female (n=413)	135	..	143	..	135	..
Age (years) (n=630)	211	50·5 (7·6)	206	50·2 (8·2)	213	50·9 (7·6)
Height (cm) (n=624)	209	167·5 (9·3)	205	167·9 (9·8)	210	168·0 (10·4)
Weight (kg) (n=630)	211	71·7 (15·9)	206	71·2 (16·5)	213	71·6 (15·9)
Body-mass index (kg/m²) (n=624)	209	25·6 (5·6)	205	25·2 (5·2)	210	25·4 (5·1)
Mean baseline Ashworth						
Upper-body muscles (n=629)	211	5·0 (4·8)	206	5·9 (5·6)	212	5·4 (4·9)
Lower-body muscles (n=630)	211	16·8 (6·0)	206	16·7 (6·6)	213	16·1 (5·8)
All muscle groups (n=630)	211	21·8 (8·7)	206	22·6 (10·1)	213	21·4 (8·5)
Form of multiple sclerosis						
Relapsing/remitting (n=33)	6	3%	14	7%	13	6%
Primary progressive (n=145)	53	25%	43	21%	49	23%
Secondary progressive (n=452)	152	72%	149	72%	151	71%
Ambulatory status						
Able to walk with or without aid (n=303)	103	49%	95	46%	105	49%
Unable to walk (n=327)	108	51%	111	54%	108	51%
EDSS						
0–3·5 (n=3)	0	0%	1	0·5%	2	1%
4–5·5 (n=23)	6	3%	9	4%	8	4%
6–6·5 (n=299)	104	49%	94	46%	101	47%
7–9 (n=299)	99	47%	99	48%	101	47%
Missing (n=6)	2	1%	3	1·5%	1%	1%

Table 2: **Baseline characterisics**

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Figure 1 shows the trial profile. Of the 630 patients included in the intention-to-treat analysis, follow-up data on the primary outcome was obtained for 611 (97%). Completion and return of data for the secondary outcome measures was also generally high, with data available for analysis from 84–91% of patients, including for the four questions posed at the end of study.

Table 2 shows the baseline characteristics of the participants. Patients' demographics in the intention-to-treat sample were matched across the different treatment groups except that proportionately fewer patients with relapsing/remitting multiple sclerosis were allocated to cannabis extract than to the other treatment groups. Since relapsing/remitting multiple sclerosis represents only 5% of the total sample, however, this imbalance is unlikely to have greatly affected our results.

With respect to analysis of Ashworth scores, 81% (n=513) of patients had the same assessor throughout or had a different assessor at just one visit (cannabis extract 82% [n=173], Δ⁹-THC 82% [n=168], placebo 81% [n=172]). The primary outcome was defined as the change from baseline (mean of two baseline pre-treatment visits) to the end of the 13-week treatment period (visit 7). In accordance with the protocol, missing Ashworth scores at visit 7 were replaced by carrying forward the most recent Ashworth score available during the treatment phase. 39 scores were carried forward; 28 from visit 6 and 11 from visit 5, distributed across treatments (12 cannabis extract, 17 Δ⁹-THC, ten placebo). Primary outcome data were not available for 46 patients originally randomised (12 cannabis extract, 19 Δ⁹-THC, 15 placebo). There was no evidence of an effect of treatment on change in total Ashworth score from baseline to 13 weeks' follow-up (p=0·29 with adjustment for ambulatory status and centre, p=0·40 without adjustment). Mean (SD) changes in total Ashworth scores (baseline minus follow-up) were 1·24 (6·60), 1·86 (7·95), and 0·92 (6·56) for cannabis extract, Δ⁹-THC, and placebo, respectively. Corresponding figures for upper-body muscle groups were –0·05 (4·11), 0·48 (4·70), and –0·11 (4·04), and for lower-body muscle groups were 1·29 (4·37), 1·39 (5·21), and 1·04 (4·20). Figure 2 shows estimates (95% CI) for the treatment effect adjusted for centre and for ambulatory status; with both active treatments there is a small (less than 3 points) though insignificant improvement over placebo.

There was no evidence of a treatment effect on changes in lower-body (adjusted for centre and ambulatory status p=0·71, unadjusted p=0·74) or upper-body (p=0·20 and p=0·31) components of the Ashworth score, and no evidence of any interaction effect between centre and treatment, between ambulatory status and treatment, or between baseline Ashworth score and treatment.

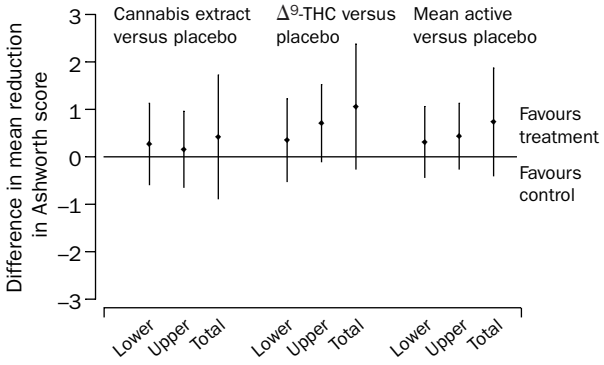

Figure 2: **Changes in Ashworth scores from baseline to 13 weeks' follow-up, adjusted for ambulatory status and centre effects**

Estimates (95% CI) shown for lower-body, upper-body, and total scores

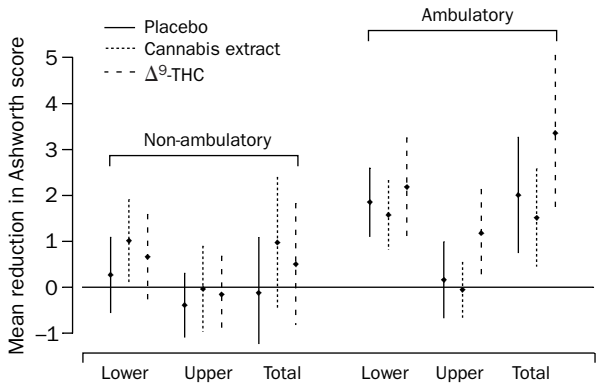

Figure 3: **Effect of ambulation on Ashworth scores by treatment group**
Mean (95% CI) for reduction in lower-body, upper-body, and total scores.

Both centre (p<0·0001) and ambulatory status (p=0·002) had a significant effect on change in Ashworth score (figure 3). The estimated mean reduction in total Ashworth score for ambulatory patients relative to non-ambulatory patients was 1·78 adjusted for treatment and centre (95% CI 0·6–2·9). There was an improvement in the mean scores with treatment, occurring in all treatment groups, including placebo (figure 4).

With respect to secondary outcome measures, 322 patients provided at least one baseline walk time. Of these, seven (one cannabis extract, three Δ⁹-THC, three placebo) dropped out of the trial. Walk times were obtained from 278 patients at visit 7. 20 patients were unable to walk (eight cannabis extract, five Δ⁹-THC, seven placebo) and very large walk times were substituted for these individuals. If patients forgot their walking aids at visit 7, walk times were carried forward from visit 6 (four patients) or visit 5 (one patient). Follow-up walk data for visits 5, 6, and 7 were missing for 12 patients. There was a significant treatment effect on walk time from baseline to visit 7 (p=0·015). The median time taken to walk 10 m was reduced from baseline to follow-up by 12% with Δ⁹-THC (95% CI 6–21) compared with a reduction with cannabis extract of 4% (0–10) and placebo of 4% (–2 to 7). Figure 5 shows the median walk time by visit and treatment group for patients who provided walk-time information at all six assessor visits.

We used category rating scales to assess whether patients felt their symptoms had improved while on treatment relative to before start of treatment, with the rating scale only being completed if patients were affected by that particular symptom. Patients felt that symptoms of pain, sleep quality, spasms, and spasticity had improved while on active treatment, though no effect was noted with respect to irritability, depression, tiredness, tremor, or energy (table 3).

There was no evidence of a treatment effect in any of the other secondary outcome measures (Rivermead mobility index, Barthel index, GHQ-30, and UKNDS; see webtable 2 at http://image.thelancet.com/extras/03art9446webtable2.pdf for raw data). For all measures except the Rivermead mobility index (where the baseline represented the mean of visits 1 and 2), the comparison between treatments was for the change from visit 2 (before treatment) to visit 7 (end of 13 week period on treatment).

At visit 8 (post-treatment) the treating doctor asked the patient specific questions about whether treatment had improved pain, tremor, spasticity, or bladder symptoms. Table 4 shows the patients' responses to these questions. More patients perceived an improvement in spasticity and pain when taking the active treatments than when taking placebo. Difference in perception of improvement in tremor was not significant and no treatment effect on bladder symptoms was identified. Although there was no stratification for these specific symptoms between groups, the groups were broadly balanced for these symptoms apart from bladder symptoms, where there were fewer patients with urinary symptoms in the group taking Δ⁹-THC.

There was a significant association between the actual treatment and the treating doctors' assessment of whether the patient was on active treatment (p<0·001). According to the treating doctors' assessment, 71% (n=140) of the cannabis extract group, 66% (n=119) of the Δ⁹-THC group, and 43% (n=85) of the placebo group were on active treatment. Similarly there was an association between the actual treatment and the patients' view of what they had taken (p<0·001). According to patients' reports, 77% (n=151), 77% (n=139), and 50% (n=98) of the cannabis extract, Δ⁹-THC, and placebo groups, respectively, thought that they had been on active treatment.

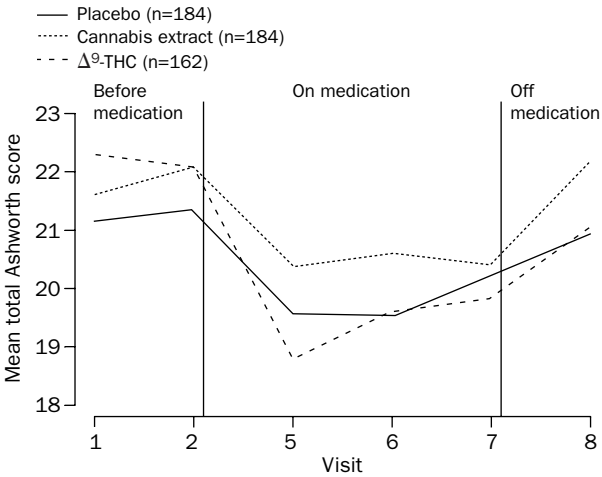

Figure 4: **Changes in Ashworth scores by visit and treatment group**
Mean (95% CI) for reduction in lower-body, upper-body, and total scores. Only cases in which observations on all muscles were available at all visits are included.

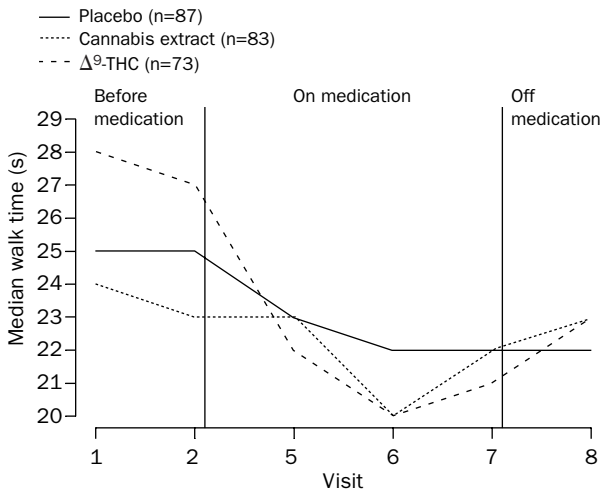

Figure 5: **Median 10 m walk times by visit and treatment group**
Only cases in which patients were ambulatory at baseline and walk information was available at all six visits included. In cases where patient was physically unable to walk a suitably large value was substituted.

	Response									p*
	Improvement			Same			Deterioration			
	Cannabis extract	Δ⁹-THC	Placebo	Cannabis extract	Δ⁹-THC	Placebo	Cannabis extract	Δ⁹-THC	Placebo	
Irritability (n=346)	46 (39%)	37 (33%)	31 (26%)	42 (36%)	42 (38%)	63 (54%)	30 (25%)	32 (29%)	23 (20%)	0·619
Depression (n=382)	43 (36%)	36 (29%)	38 (28%)	44 (37%)	47 (38%)	64 (47%)	33 (28%)	42 (34%)	35 (26%)	0·298
Tiredness (n=490)	46 (28%)	35 (22%)	37 (22%)	51 (31%)	46 (29%)	79 (47%)	68 (41%)	76 (48%)	52 (31%)	0·068
Spasticity (n=543)	95 (52%)	89 (51%)	67 (37%)	43 (23%)	40 (23%)	52 (28%)	46 (25%)	47 (27%)	64 (35%)	0·010
Shake/tremor (n=391)	49 (38%)	52 (41%)	45 (33%)	48 (38%)	44 (34%)	53 (39%)	31 (24%)	32 (25%)	37 (27%)	0·398
Pain (n=419)	68 (46%)	64 (50%)	42 (30%)	48 (32%)	43 (33%)	58 (41%)	32 (22%)	22 (17%)	42 (30%)	0·002
Sleep (n=479)	82 (50%)	71 (47%)	59 (36%)	62 (38%)	57 (38%)	79 (48%)	20 (12%)	24 (16%)	25 (15%)	0·025
Spasms (n=520)	96 (53%)	81 (49%)	67 (39%)	50 (28%)	49 (29%)	68 (39%)	34 (19%)	37 (22%)	38 (22%)	0·038
Energy (n=540)	61 (33%)	61 (35%)	45 (24%)	73 (40%)	63 (36%)	78 (42%)	49 (27%)	49 (28%)	61 (33%)	0·140

Data are number (% of treatment group). *Obtained by comparing three treatment groups on original 11-point rating scale.

Table 3: **Responses to category rating scales**

There was no association between the assessors' opinion of treatment and the actual treatment (p=0·72). The proportions viewed by the assessor as being on active medication in the three groups were 44% (n=90) cannabis extract, 39% (n=73) Δ⁹-THC, and 42% (n=86) placebo.

Compliance with study protocol was generally good. 592 patients provided pre-treatment urine samples, of which ten (2%) tested positive for cannabis. A small proportion of patients (cannabis extract 2% [n=4], Δ⁹-THC 2% [n=4], placebo 1% [n=2]) therefore probably took cannabis in the month preceding the trial, in contravention of the protocol. In the placebo group, three (2%) patients had positive urine tests at visit 5, and four (2%) were positive at visit 6. Concomitant medication was monitored during the course of the study. At the start of the study, 376 patients were taking medication for their spasticity, with no difference between the groups (128 cannabis extract, 120 Δ⁹-THC, and 128 placebo). During the 15 weeks of the study, a further 34 patients commenced medication for their spasticity (12 cannabis extract, 11 Δ⁹-THC, and 11 placebo).

Table 5 shows a summary of the serious adverse events reported, which on no occasion resulted in unmasking of treatment. Numbers of events are similar across the treatments, with slightly more events in the placebo group. Most of the events were expected in our study population. There was one death from pneumonia, occurring at week 13 in the Δ⁹-THC group. There were a large number of minor adverse events (table 6). As expected from the degree of unmasking among patients and the known side-effects of cannabinoids, there were more episodes of dizziness or light-headedness, and of dry mouth among the active groups. There were some differences between groups for gastrointestinal side-effects. Constipation seemed more frequent in the cannabis extract group, though there was no concomitant increase in hospital admissions for constipation (26 events, compared with nine in the Δ⁹-THC group and five in the placebo group). Diarrhoea was more common in both active groups (38 events in cannabis extract group and 36 in Δ⁹-THC) compared with placebo (15 events). Increased appetite was also an expected side-effect in treatment groups, although at low levels (four cannabis extract, six Δ⁹-THC, one placebo).

	Treatment group			p
	Cannabis extract (n=197)	Δ⁹-THC (n=181)	Placebo (n=198)	
Symptom improvement				
Bladder				0·149
Yes	68 (44%)	67 (40%)	51 (33%)	
No	87 (56%)	97 (59%)	102 (67%)	
Pain				0·003
Yes	83 (57%)	64 (50%)	51 (37%)	
No	63 (43%)	64 (50%)	86 (63%)	
Tremor				0·052
Yes	58 (48%)	44 (40%)	43 (33%)	
No	64 (52%)	67 (60%)	89 (67%)	
Spasticity				0·003
Yes	121 (61%)	108 (60%)	91 (46%)	
No	76 (39%)	73 (40%)	107 (54%)	

Data are number (% of particular symptom within group). Not all patients responded to questions, particularly if that symptom was not a major problem for them.

Table 4: **Assessment of treatment benefit at visit 8**

Discussion

Treatment with cannabinoids did not improve spasticity associated with multiple sclerosis as measured with the Ashworth scale, but did result in some benefit in secondary outcome measures, assessing mobility and patients' perceptions of the effect of spasticity. These findings are consistent with those of smaller studies,[13–16] which showed some subjective, but no observer-verified, improvement in disease-related spasticity with use of cannabinoids. Our results should be considered in the context of a degree of patient unmasking in the active treatment groups.

Our aim was to assess spasticity with the Ashworth scale, and the power calculations were based on data from a previous study of tizanidine in multiple sclerosis.[26] The limitations of the Ashworth scale in measuring the highly complex symptom of spasticity are well known,[28] and there is a need to develop new patient-oriented scales to enable measurement of what matters to them.[29] One possible explanation for our results is that the Ashworth scale is too insensitive to identify small but clinically

	Treatment group			
	Cannabis extract (n=12)	Δ⁹-THC (n=18)	Placebo (n=20)	Total (n=50)
Adverse event				
Multiple sclerosis relapse or possible relapse	1	1	7*	9
Urinary tract infection	1	3	4	8
Pneumonia	1	2 (1 death)	1	4
Blocked/insertion of suprapubic catheter	1	1	2	4
Constipation	1		3	4
Grand mal seizures	1		1	2
Other	6†	11‡	2§	19
Total	12	18	20	50

*One patient had two relapses. One event each of: †urinary tract infection/relapse, collapse/bradycardia, fall at home, dizziness (inappropriate SAE report), abdominal pain of unknown cause, active duodenal ulcer and *Helicobacter pylori*; ‡collapse of unknown cause, possible transient ischaemic attack/syncope, viral gastroenteritis, chronic pleural effusion, pneumonia and renal stones, chest infection/urinary tract infection, cellulitis of leg/diarrhoea and vomiting, emergency hip replacement, disease progression (not relapse), urinary tract infection/diarrhoea and vomiting, back pain; and §deep-vein thrombosis, minor cerebrovascular event.

Table 5: **Frequency of serious adverse events**

	Treatment group					
	Cannabis extract		Δ⁹-THC		Placebo	
	Number of patients reporting symptom (% of total ITT patients)	Number of events reported	Number of patients reporting symptom (% of total ITT patients)	Number of events reported	Number of patients reporting symptom (% of total ITT patients)	Number of events reported
Adverse event						
Bladder	55 (26%)	80	49 (24%)	67	49 (23%)	73
Gastrointestinal tract	79 (37%)	132	62 (30%)	96	42 (20%)	65
Pain	51 (24%)	89	53 (26%)	76	69 (32%)	93
Depression or anxiety	20 (9%)	29	20 (10%)	22	18 (8%)	20
Vision	16 (8%)	18	12 (6%)	13	5 (2%)	8
Infection	34 (16%)	40	30 (15%)	37	36 (17%)	40
Dizzy or lightheadedness	105 (50%)	183	121 (59%)	209	38 (18%)	53
Dry mouth	42 (20%)	47	54 (26%)	60	14 (7%)	15
Weakness or reduced mobility	48 (23%)	66	52 (25%)	67	43 (20%)	53
Sleep	85 (40%)	121	73 (35%)	101	70 (33%)	93
Spasms or stiffness	69 (33%)	98	70 (34%)	102	70 (33%)	105
Tremor or lack of coordination	21 (10%)	24	25 (12%)	30	17 (8%)	22
Numbness or paraesthesia	14 (7%)	19	19 (9%)	23	14 (7%)	15
Miscellaneous	64 (30%)	95	58 (28%)	84	47 (22%)	73
Improvement in symptoms	3 (1%)	3	2 (1%)	3	1 (0·5%)	1
Total	706	1044	700	990	533	729

ITT=intention to treat. 558 patients reported adverse events: 196 cannabis extract, 193 Δ⁹-THC, 169 placebo.

Table 6: **Frequency of minor adverse events**

significant effects on spasticity. Nevertheless, we are confident that we have excluded any major observer-assessed effect on spasticity, and the Ashworth score is the most reliable and well-validated measure of spasticity, which has been used in previous studies.[26,30] Another explanation for our results is that we might not have achieved high enough systemic medication concentrations. Higher doses of drug might have achieved a greater effect on the Ashworth score, but most patients within the active treatment groups did not reach their target dose because of side-effects, suggesting that higher doses would not be tolerated. We are analysing serum concentrations of cannabinoids in a large subgroup of patients to examine the relation between serum concentrations and clinical effect.

Spasticity is a complex symptom, which might be assessed differently by patients (who note the degree of stiffness) and doctors (who use the Ashworth score). Cannabinoids might affect patients' perceptions of spasticity, thereby improving their symptoms. This notion is supported by the finding of a significant difference between active and placebo groups with respect to patients' opinion that the medication had helped their spasticity, on both the overall effect question at the end of the study and the category-rating scales of muscle stiffness and spasms. Our results are also consistent with a report from a crossover study,[31] the findings of which indicated trends in reduction of spasms and improved mobility in 50 patients who received cannabis extract. The absence of subjective effect on tremor suggests that any treatment effect is unlikely to be mediated through a general masking of all negative symptoms, and there seems to be a differential effect in specific areas. Overall, the significant subjective effects on pain and muscle spasms, together with the patients' belief that these drugs helped spasticity, suggests there might be a reduction in the manifestations of spasticity, rather than an effect on muscle stiffness per se.

Our finding of a small improvement in 10 m walking time in ambulant patients is noteworthy, particularly since other measures, such as the Rivermead mobility index, indicated no effect of treatment. Assuming that no major effect on spasticity underlies this improvement, a reduction of discomfort during walking could explain these results. Further work is necessary to assess the mechanism of action by which cannabinoids seem to improve mobility in patients with multiple sclerosis.

To obtain the patients' perspective, pain was assessed with a category rating scale and an overall assessment at the end of the study. In both measures, there was a significant beneficial effect from treatment. This finding is consistent with previous data,[32] suggesting that cannabinoids are effective, if modest, analgesics. However, since many patients have indicated simple analgesia ineffective in pain control, we speculate that cannabinoids might have a more specific role in the management of chronic neuropathic pain. Results of studies done in animals[33] suggest that cannabinoids have analgesic action, which is independent of the opiate system. Furthermore, a report[34] has provided evidence for improvement in pain control and pain-related sleep disturbance in patients with multiple sclerosis who use a cannabis-based medicinal extract.

The main measures used by us to detect any overall effect on disability were the UKNDS and the Barthel index, which showed no significant effects between treatment groups. We chose the GHQ-30 as a measure of general psychological wellbeing or distress. If this class of drugs simply made people feel better, then we would expect to find differences on the GHQ-30, which we did not. Although we might have derived more information if we had used a range of other quality-of-life measures, both disease-specific and generic, we were conscious of demands on both patients and investigators, and therefore tried to keep assessments to a minimum to maximise recruitment and retention. Once again, the measures used might not have been sensitive enough to assess fully the effect of symptoms on degree of disability. It is noteworthy that our results do not agree with those of a previous smaller study,[16] which used the same cannabinoids as our study. In the earlier study, no evidence of any therapeutic effect was obtained using "subjects' global impression" and other measures. This finding could have been the result of inadequate dosing, since participants were only titrated up to a 5 mg twice-daily maximum dose.

The placebo response seen in our study was high, with almost half of patients feeling that their medication had improved spasticity after treatment for 13 weeks with placebo capsules. About 35% of patients in the placebo group felt their pain had improved, similar to figures obtained from, for example, treatments for acute migraine. The extent and duration of placebo response in

trials of multiple sclerosis should affect the design of future studies and the interpretation of previous studies in this unpredictable chronic disease. There was an expected unmasking of both treating doctors and patients, but blinding was maintained in the assessing individuals, suggesting that bias is unlikely to have occurred in the assessors' data.

We used oral capsules as the mode of medication delivery. There are inherent difficulties in predicting individual dose-response with cannabinoids, which is why a titration phase was incorporated into the study. Smoking cannabis results in more rapid and reproducible blood concentrations of cannabinoids than oral administration; this group of drugs are lipid soluble and lung inhalation also avoids liver metabolism and hence improves consistency of administration. We chose oral administration because it was considered unethical to expose individuals to the risks associated with smoking cannabis, and oral medication was readily available when the study was designed. Alternative routes of administration are being tested that might allow for more predictable dose-response relations.

There was no evidence for any distinction in terms of efficacy between Δ^9-THC and whole cannabis extract, and any differences observed in the data presented might simply indicate chance, since the study was not powered to detect such differences. Although these drugs were generally well tolerated, there were some slight differences in degrees of adverse events between groups, particularly in the number of gastrointestinal side-effects.

The finding of reduced hospital admissions for relapses in the two active treatment groups compared with placebo was unexpected. Our study was designed to assess the effects of cannabinoids on symptoms related to multiple sclerosis in individuals with fairly stable disease, so most patients had slowly progressive disease. Nonetheless, cannabinoid receptors are present on cells of the immune system, and the finding of a reduced relapse rate in what is commonly regarded as an autoimmune condition, is worthy of further investigation. This finding is consistent with some findings of studies of animal models of demyelinating conditions,[35] in which synthetic cannabinoids used in established disease significantly improved both neurological deficits as well as histological evidence of immune activation.

When assessing our results, it should be acknowledged that the degree of evidence for many of the commonly used drugs to combat symptoms is weak. A Cochrane review[36] of antispasticity agents for multiple sclerosis concluded that the paucity of evidence meant no recommendations could be made to guide prescribing, and that better outcome measures need to be developed. We used the findings of two studies,[26,27] using tizanidine to treat spasticity in patients with multiple sclerosis-related spasticity, in our power calculations. One study noted a difference in Ashworth scores comparing active treatment with placebo,[26] whereas the other showed no effect.[27] Neither of these studies detailed any difference in walking times, and even when a significant effect was obtained in the Ashworth score, there was no difference in pain measures or sleep quality on active medication.[26] Although there is slightly more evidence for the use of anticonvulsants in chronic pain syndromes,[37] few controlled trials have been published, and pain syndromes in multiple sclerosis have been poorly characterised.

Spasticity is a highly complex phenomenon, composed of both signs observable to assessors and symptoms reported by patients. Our results, using the Ashworth score as the primary outcome measure, exclude any major effect of treament of spasticity with cannabinoids, but the effect of spasticity and pain as assessed by patients indicates a symptomatic subjective clinical effect. There was also a beneficial effect on walking time. Our findings therefore provide some evidence that cannabinoids could be clinically useful in treatment of symptoms related to multiple sclerosis, but more work is necessary, using outcome measures that more adequately assess the effect of symptoms in chronic disease.

Contributors

All authors contributed to study design and protocol development. J Vickery was trial coordinator. H Sanders and D Wright did the statistical analysis. J Zajicek, J Vickery, H Sanders, and D Wright wrote the paper, with revisions and contributions from A Thompson, A Nunn, and P Fox. The UK MS Research Group entered patients into the study and provided helpful comments throughout the study and at the investigator meeting.

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Conflict of interest statement

None declared.

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