

Long-term use of a cannabis-based medicine in the treatment of spasticity and other symptoms in multiple sclerosis

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The object of this study was to monitor the safety and efficacy of long-term use of an oromucosal cannabis-based medicine (CBM) in patients with multiple sclerosis (MS). A total of 137 MS patients with symptoms not controlled satisfactorily using standard drugs entered this open-label trial following a 10-week, placebo-controlled study. Patients were assessed every eight weeks using visual analogue scales and diary scores of main symptoms, and were followed for an average of 434 days (range: 21–814). A total of 58 patients (42.3%) withdrew due to lack of efficacy (24); adverse events (17); withdrew consent (6); lost to follow-up (3); and other (8). Patients reported 292 unwanted effects, of which 251 (86%) were mild to moderate, including oral pain (28), dizziness (20), diarrhoea (17), nausea (15) and oromucosal disorder (12). Three patients had five 'serious adverse events' between them – two seizures, one fall, one aspiration pneumonia, one gastroenteritis. Four patients had first-ever seizures. The improvements recorded and dosage taken in the acute study remained stable. Planned, sudden interruption of CBM for two weeks in 25 patients (of 62 approached) did not cause a consistent withdrawal syndrome, although 11 (46%) patients reported at least one of – tiredness, interrupted sleep, hot and cold flushes, mood alteration, reduced appetite, emotional lability, intoxication or vivid dreams. Twenty-two (88%) patients re-started CBM treatment. We conclude that long-term use of an oromucosal CBM (Sativex) maintains its effect in those patients who perceive initial benefit. The precise nature and rate of risks with long-term use, especially epilepsy, will require larger and longer-term studies. *Multiple Sclerosis* 2006; 12: 639–645. www.sagepub.co.uk

Key words: cannabis; chronic use; multiple sclerosis; safety

Introduction

Several studies have investigated the use of cannabis derivatives for the symptomatic treatment of patients with multiple sclerosis (MS) and other neurological conditions [1–10]. Results have been mixed, but these studies suggest that cannabinoids may produce improvements in spasticity, muscle spasm, neuropathic pain and lower urinary tract symptoms for at least some patients. These studies have been short, being restricted to treatment over 10–15 weeks.

Although cannabis and its derivatives seem to cause only transient acute toxicity, concerns

about long-term recreational use include possible detrimental effects on cognition [11], mental health [12], and dependency [13]. These concerns are derived from the use of street cannabis, which is of variable purity and potency and is usually smoked, with all the risks that this entails. Recreational smokers differ from medicinal users in at least one fundamental way: the former seeks psycho-active effects as the primary goal, whereas the latter usually tries to avoid it.

A systematic assessment of the safety and tolerability of cannabis-based medicines (CBM) over long-term treatment is an important component of the appraisal of their therapeutic potential. Therefore, we carried out a long-term follow-

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Received 25 May 2005; accepted 11 October 2005

up study involving patients who completed a previously reported acute, randomized, double-blind, placebo-controlled study of a particular CBM (Sativex) [7].

Methods

Patients entering the study had completed a six-week randomized, placebo-controlled, parallel group study followed by a four-week open-label period [7], in which CBM and placebo were administered by means of an oromucosal spray.

Patients had clinically confirmed MS of any type, with at least one of the following symptoms: spasticity, spasms, bladder-related problems, tremor or pain that was not obviously musculo-skeletal. On initial recruitment, at least one of these symptoms had to be of a severity recorded as ≥ 50 mm on a 100-mm visual analogue scale (VAS). Patients were excluded from the study if they had 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 a history of epilepsy. Patients were originally recruited by three hospital centres in the UK from out-patient clinics or referrals from MS societies and general practitioners. Those who wished to continue taking CBM and for whom this was considered safe and appropriate by the investigator, were given the option to enter this long-term, open-label assessment.

Throughout the extension study, patients completed a weekly symptom diary recording the severity of their MS symptoms and intoxication levels using VAS. On a daily basis, they recorded the number of sprays of study medication taken, and these figures were checked against the amount of drug given and returned. They attended a clinic at eight weekly intervals for a medical and nursing review which included VAS scores of the primary symptoms studied (one or more of spasticity, spasms, tremor, bladder problems, or pain).

The study medication was a whole plant extract prepared from genetically distinct chemical varieties (chemovars) of *Cannabis sativa L.* This medicine (Sativex) contains approximately equal amounts of the two cannabinoids delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) which together make up at least 90% of the total cannabinoid content. Other constituents present in the extracts, which may themselves have therapeutic properties [14], include minor cannabinoids, terpenes, fatty acids, carotenoids, sterols and flavonoids. The medication was delivered by a pump-action oromucosal spray containing THC (27 mg/mL) and CBD (25 mg/mL) with excipients and peppermint flavouring. Each activation

delivered 0.1 mL (2.7 mg THC+2.5 mg CBD). In both the acute study and at the beginning of the extension phase, patients self-titrated their dose depending upon symptom resolution or side effects up to a permitted maximum of 48 sprays/day.

Sixty-two patients who had received Sativex for at least one year and whose dose had been stable for the previous two weeks were asked to participate in a planned abrupt interruption of the study medication, and 25 agreed to do so; several others declined because they did not wish to risk the return of well-controlled symptoms. The purpose of this was to explore the possibility of a withdrawal syndrome and to determine whether MS-related symptoms would reappear. Participating patients were asked to stop CBM abruptly and to record any changes over a period of up to 14 days, to assess the time course of any changes. Patients could re-start medication at any point, or could decide to remain off medication.

European Union Good Clinical Practice guidelines require all new clinical events to be recorded as 'Adverse Events', regardless of actual or presumed cause, and any that result in prolonged hospitalization or persistent or significant disability, or are considered life-threatening or fatal are defined as 'Serious'. The clinical investigator is required to judge whether or not each serious adverse event is related to the experimental preparation. We report the adverse events here using these methods and data.

Results

One hundred and thirty-seven patients (89% of the 160 patients recruited into the original study [7]) entered this extension study and this analysis includes all data up to 30 November 2003. The remaining patients were similar to the 137 included in terms of disability: mean (SD) Barthel ADL index score [15], was 16.3 (3.5) against 14.9 (5.9), and mean (SD) Guy's Neurological Disability Scale [16], scores were 19.3 (9.0) against 20.7 (7.2). Patients entered the extension study in a staggered manner over many months because they completed the acute study at different times. The mean duration of study participation was 434 days (range: 21–814) for patients remaining on treatment ($n=79$) and 225 for the 58 patients who stopped (range: 21–801). Demographic data and duration of CBM treatment are shown in Table 1. Figure 1 shows the flow of patients through the study.

Figure 2 and Table 2 present data from a cohort of 73 patients who had completed at least one year's treatment and contributed data to every time point. Baseline refers to VAS score at entry into the acute study. It can be seen that the large reductions

Table 1 The study population ($n = 137$)

Variable	Data
Age years, mean (range)	50.5 (27.5–73.8)
Female	83 (61%)
Previous cannabis use	
Recreational	28 (21%)
Medicinal	53 (39%)
Tobacco smoker	39 (28%)
Alcohol intake – male	
None	28 (33%)
<21 units/week	34 (63%)
>21 units/week	2 (4%)
Alcohol intake – female	
None	31 (37%)
<21 units/week	44 (53%)
>21 units/week	8 (10%)
Duration of follow-up (weeks)	
2–6	3 (3%)
7–12	11 (8%)
13–26	21 (15%)
27–52	10 (7%)
>52	92 (67%)

recorded at 10 weeks (ie, following the acute study) are maintained over one year of treatment. The average number of doses taken daily by this group remains constant or slightly reduces over time (Figure 3).

Non-serious adverse events are shown in Table 3, and serious adverse events are shown in Table 4. During the period under review, the 137 patients reported a total of 292 unwanted effects, of which 251 (86%) were of mild to moderate intensity. The most common treatment-related adverse event was a sore mouth (20.4%) and eight patients also had an 'oromucosal disorder' (ie, visible changes in the mucosa). No psychiatric events or changes were noted, and only six patients complained of a cognitive change (altered attention).

During follow-up, 22 patients were recorded as experiencing 33 'serious adverse events'. In 19 patients (28 events), the event was considered unrelated to CBM, but in three patients (five events) it was considered at least possibly related to CBM – two patients experienced seizures and one of these patients subsequently died from aspiration pneumonia. The third patient experienced loss of balance possibly related to CBM and sustained an ankle injury. She continued taking CBM and, three months later, developed diarrhoea and vomiting necessitating overnight hospital assessment. This resolved the following day and the patient continued with CBM treatment. Two further patients died in the course of the study, as a result of lung cancer and breast cancer, respectively. A total of four patients had seizures; all were taking other medica-

tions which increases the risk of epilepsy, such as anti-depressant medication.

Intoxication scores were recorded on a daily basis by VAS, and are shown in Figure 4. Median scores were <5 out of 100 at all time points, and only three (2%) patients withdrew due to symptoms possibly associated with intoxication (confusion/somnolence; light headedness; somnolence).

Of the 25 patients who entered the two-week treatment interruption study, five (20%) resumed CBM before the end of 14 days because of re-emergence of marked MS symptoms. During the interruption, seven (28%) reported their MS symptoms to be much worse, 10 (40%) worse, five (20%) no change and three (12%) better. Three patients (12%) opted not to resume CBM treatment at the end of the two week interruption, two patients because their MS symptoms had not re-emerged and one because of a planned house move. No consistent withdrawal syndrome emerged, although 11 (44%) subjects did experience withdrawal-type symptoms. These patients reported at least one of the following during the withdrawal period – interrupted sleep (4; 16%); hot and cold flushes (4; 16%); tiredness (4; 16%); low mood (3; 12%); decreased appetite (2; 8%); emotional lability (1; 4%); vivid dreams (1; 4%); and intoxication (1; 4%).

Discussion

This open-label study on patients who selected themselves as gaining initial benefit from the cannabis-based medicine was designed to investigate its longer-term use in terms of safety, tolerability and maintenance of effects. It was not designed to assess efficacy. Thus, it complements recently published randomized-controlled trials [5–8], that demonstrate significant subjective improvement in spasticity and trends towards improvement in other MS symptoms. This study suggests that patients with MS who derive symptom relief from CBM in the first 10 weeks, generally maintain that symptom relief over an extended period of treatment without any increase in dose. Unwanted effects were common but rarely troublesome. Four patients (of 137) experienced seizures, but there were no other consistent major adverse events. There was no consistent withdrawal syndrome on abrupt cessation in a self-selected group of 25/63 patients, although just under half the patients experienced new symptoms that may have been related to withdrawal.

The loss of patients (58; 42%) during follow-up does compromise the study, but only 17 (12%) stopped due to adverse events, and most stopped for practical reasons or because there was no longer

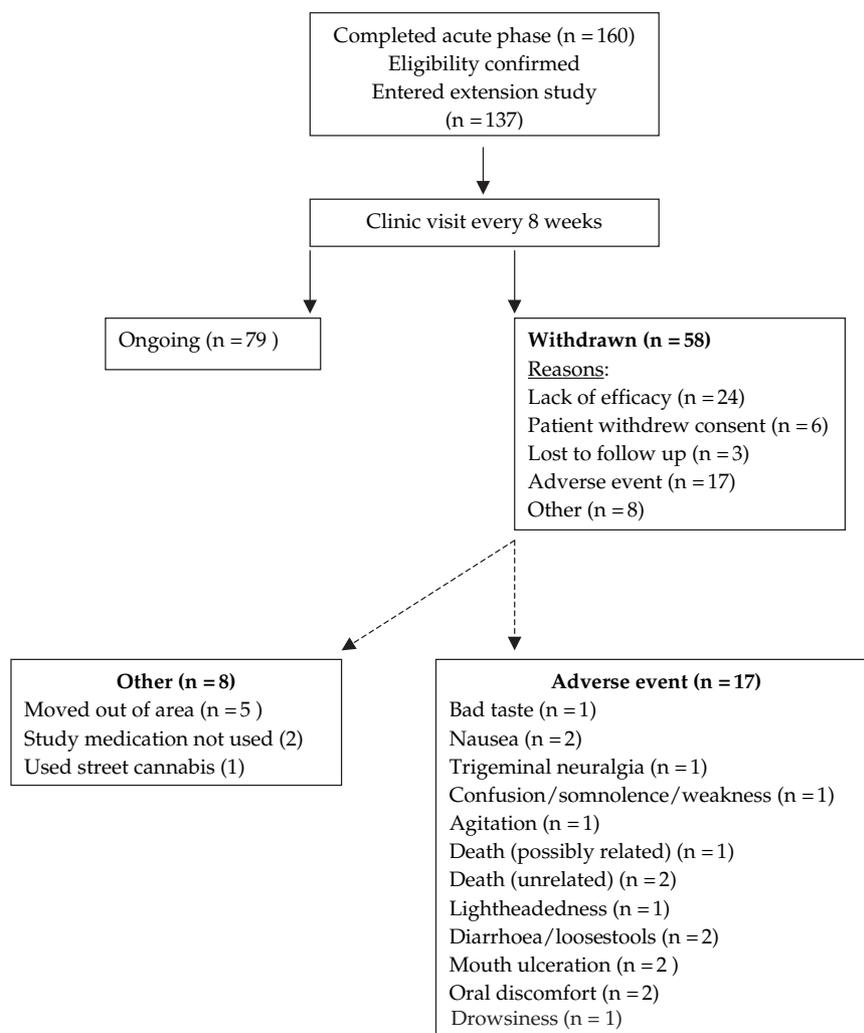


Figure 1 Study design and withdrawals.

any benefit. Ninety-two subjects (67%) were followed for at least one year on the medication. Although the selective nature of this cohort limits the generalizability of the results and cautious interpretation is required, it nevertheless provides a large body of safety and tolerability data that is lacking for other licensed anti-spasticity drugs.

Only 25 of 62 eligible patients agreed to participate in the trial of sudden withdrawal of CBM. These are likely to be an unrepresentative sample, but the main intention of this procedure was to check for physiological or psychological dependence. We were reassured by the lack of any sudden adverse response to sudden withdrawal. It was noted that MS-related symptoms tended to return over five to 10 days, suggesting that the benefits were not entirely due to a placebo effect, and that the mechanism of action had a relatively long half-life.

All adverse events were recorded, regardless of causation. The great majority of serious events (19/22) were judged unrelated. It is notable that four people had seizures. Pre-existing epilepsy was an excluding factor for entry into the initial study, but patients with MS are at an increased risk of seizures, and these four patients were also taking other potentially epileptogenic drugs. The relationship between CBMs and seizures warrants further investigation. Routine formal assessment of psychiatric and cognitive status was not undertaken, but there was regular clinical assessment. No new psychiatric symptoms emerged and few new cognitive symptoms were recorded.

The low intoxication scores recorded throughout the months of treatment (Figure 4) support our strong clinical impression that patients wished to avoid psychoactive effects, and do not suggest that the benefits reported were simply the result of

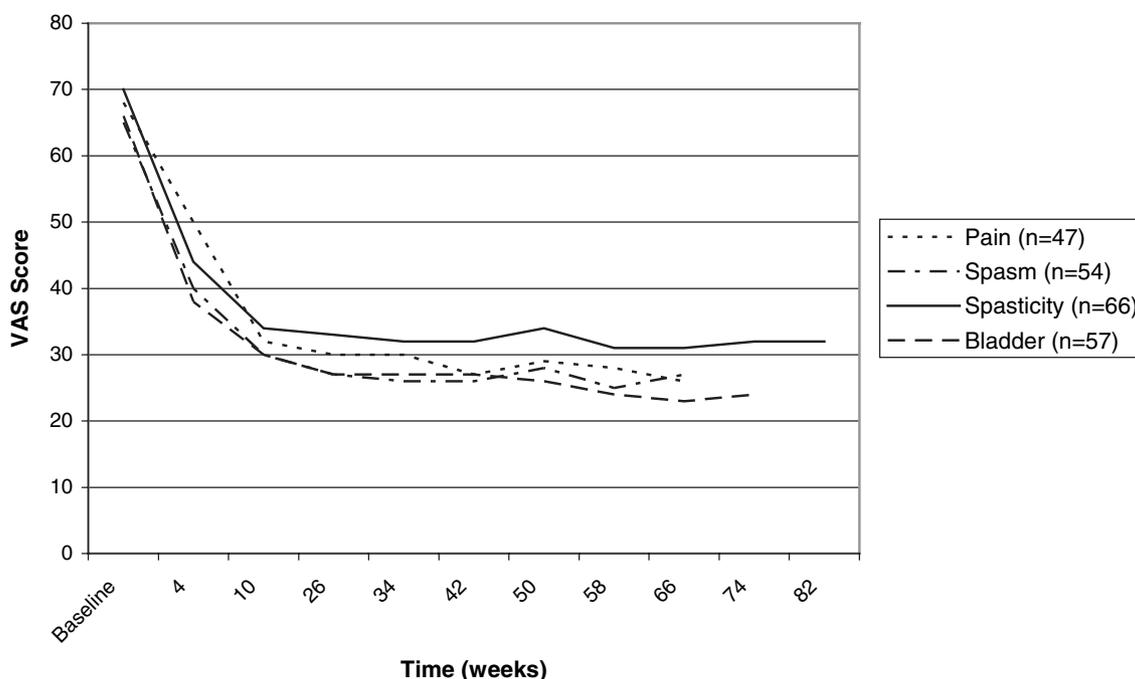


Figure 2 Patients who have completed at least one year’s treatment and with data at each point (n = 73).

patients feeling better due to intoxication. The acute study did not find any significant effects on mood [7].

Patients entering this open-label extension study had opted to continue from a previous acute study, and so are a selected group of patients who thought they had benefited (137 out of an initial total of 160). Symptom relief was assessed using subjective VAS. The validity of these scales used on a repeated-measure basis is not known, but the authors considered this approach clinically pertinent for assessment of the variable symptom combination encountered by patients with MS. This study is representative of clinical practice, where only patients who consider a treatment beneficial will continue taking it.

This study indicates that community use of CBM is viable in the long-term. Patients were generally able to self-titrate their dose, with guidance, to achieve symptom relief without unacceptable adverse effects. The oromucosal spray lent itself to a flexible, patient-centred approach to dosing. Carers were able to give the medication to patients who had impaired dexterity. Careful monitoring of quantities used showed no evidence of drug misuse by any patient. Individuals who were more sensitive to unwanted effects, and those who could not achieve useful symptom relief without adverse effects, withdrew during the initial acute study. Withdrawal during the extension study tended to be due either to unwanted effects or to a change in their most troublesome symptoms over time, such

Table 2 VAS scores for patients who completed at least one year

Weeks	Pain (n = 47)	Spasm (n = 54)	Spasticity (n = 66)	Bladder (n = 57)
Baseline	68.1 (10.6)	65.1 (14.7)	69.5 (15.7)	65.6 (17.6)
4	50 (24.9)	39.6 (22.8)	44.1 (24.5)	38.0 (20.0)
10	31.9 (19.6)	30.7 (21.0)	34.2 (20.6)	29.5 (22.1)
26	30.2 (20.8)	27.4 (17.3)	33.0 (21.1)	26.8 (18.7)
34	29.8 (20.3)	26.2 (18.4)	31.8 (22.7)	26.7 (21.7)
42	26.6 (19.1)	25.9 (20.1)	31.6 (23.6)	26.9 (21.2)
50	29 (22.1)	27.6 (21.9)	34.1 (22.0)	26.3 (20.7)
58	27.8 (19.1)	24.5 (19.1)	31.3 (20.4)	23.6 (18.9)
66	26.4 (18.7)	26.7 (18.1)	31.0 (20.7)	23.4 (19.9)
74			31.6 (21.6)	23.5 (20.1)
82			31.8 (20.4)	

Mean (SD); number constant for each time point.

Approximately half the patients would have received placebo up to six weeks. Thereafter, all patients received CBM.

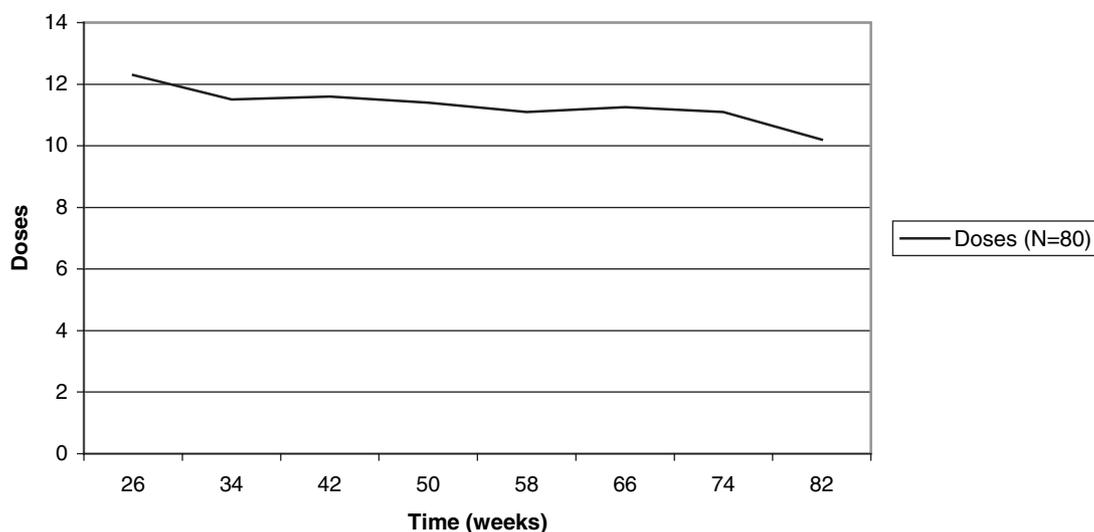


Figure 3 Mean number of doses daily for patients completing 82 weeks treatment.

that they were no longer deriving benefit. Patients tended to stabilize at a dose of approximately 11 sprays daily (equivalent to 30 mg THC and 28 mg CBD).

The study was not designed to investigate the efficacy of long-term CBM use in the management of co-existing symptoms. However, the results suggest that in patients who report symptomatic improvement during short-term treatment, the apparent benefit is likely to be maintained over a longer time-scale without the need for increases in dose. Patients' reports of oral irritation, though

possibly confounded by mouth dryness from other causes, suggest that alternative formulations may be desirable for extended use.

In conclusion, this study has shown that CBM (Sativex) can be used in the long-term without tolerance or intoxication, and with maintenance of subjective symptomatic relief. Further investigation

Table 3 Most frequently occurring (>4% subjects) unwanted effects considered possibly/probably/definitely related to CBM in 137 patients

Unwanted effect	No. of patients (%)
Oral pain	28 (20.4)
Dizziness	20 (14.6)
Diarrhoea	17 (12.4)
Nausea	15 (10.9)
Oral mucosal disorder	12 (8.8)
Bad taste	11 (8)
Dry mouth	9 (6.6)
Fatigue	9 (6.6)
Headache	9 (6.6)
Somnolence	9 (6.6)
Constipation	8 (5.8)
Vomiting	8 (5.8)
Tooth discoloration	7 (5.1)
Weight loss	7 (5.1)
Balance impaired	6 (4.4)
Disturbance in attention	6 (4.4)
Lethargy	6 (4.4)
Loose stools	6 (4.4)
Raised Gamma-glutamyltransferase	6 (4.4)

Table 4 Serious adverse events (SAEs) recorded (some patients had more than one)

Relation to CBM	Possibly related	Unrelated
Total number of patients	3	19
Total number of SAEs	5	28
Seizures	2	2
Urinary tract infections	0	3
Vomiting	1	2
Impaired balance	1	1
Diarrhoea	1	1
Breast cancer	0	2
Relapse of multiple sclerosis	0	2
Pneumonia	0	2
Primary biliary cirrhosis	0	1
Osteomyelitis	0	1
Cellulitis	0	1
Decubitus ulcer	0	1
Deep vein thrombosis	0	1
Dehydration	0	1
Abnormal liver function test	0	1
Lung cancer	0	1
Lymphadenopathy	0	1
Muscle spasms	0	1
Muscle weakness	0	1
Pleurisy	0	1
Sepsis	0	1

An SAE requires one or more of – hospitalization; persistent or significant disability; considered life-threatening; death. The primary diagnosis given in the notes was used.

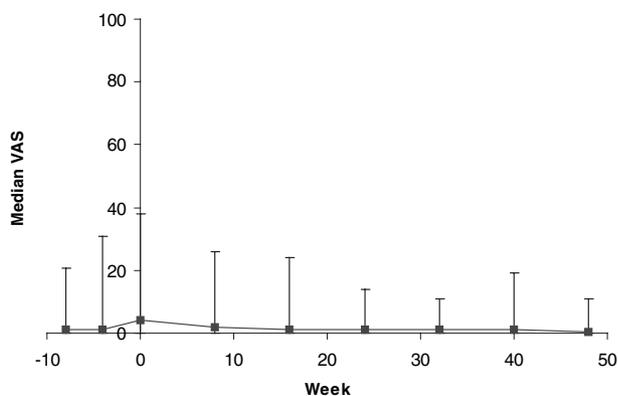


Figure 4 Median intoxication scores (displaying the 10th and 90th percentiles which represents the central 80% of data) for 92 patients completing at least 48 weeks of treatment.

into its effect on seizure threshold is warranted. Abrupt withdrawal of CBM was not associated with a specific or troublesome withdrawal syndrome, although MS-related symptoms that had been reduced tended to increase over seven to 10 days.

Acknowledgements

The study was funded by GW pharmaceuticals, and we are grateful for this funding and the ongoing co-operation of all the patients. We are grateful to Joan Atherton and Jane Hewitt for their input into the care and assessment of the Oxford patients and to Christine Staff, Jayne Sheppard, Caryn West, Elisa Visentin and Emma Snelson for collecting data from and supporting other patients.

Contributions: PR and DW initiated the study and took part in all aspects including design, choosing measures, 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 was in receipt of a research grant from GW Pharmaceuticals. DW's employer received money from GW for his time.

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