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A Multicentre, Double-Blind, Randomised, Parallel-Group, Placebo-Controlled Study of Effect of Long-Term Sativex® Treatment on Cognition and Mood of Patients with Spasticity Due to Multiple Sclerosis

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Abstract

Objective: When Sativex ® THC:CBD cannabinoid-based oromucosal spray was first approved as a prescription medicine for multiple sclerosis (MS) spasticity, there was some concern about its possible long-term impact on cognition and mood. The objective of this study was therefore to assess the long-term impact of Sativex on cognitive function and mood in MS patients with spasticity.

Methods: 121 patients were randomly assigned Sativex or placebo in a double-blind manner. Patients self-administered treatment daily for 48 weeks while maintaining anti-spasticity therapy. The primary endpoint was the difference between treatments in Paced Auditory Serial Addition Test (PASAT) score from baseline to end of treatment. Secondary measures included Beck Depression Inventory-II (BDI-II), Subject-, Physician- and Caregiver Global Impression of Change, and Columbia-Suicide Severity Rating Scale.

Results: 62 patients were randomised to Sativex and 59 to placebo. There was no difference in the effect of Sativex on PASAT and BDI-II scores compared with placebo. Subject-, Physician- and Caregiver-rated improvements in spasticity with Sativex were all statistically significant. The mean daily dose of Sativex declined gradually to 6.4 sprays per day.

Conclusion: Long-term treatment with Sativex was not associated with cognitive decline or significant changes in mood in this prone population sample. Sativex was efficacious and well tolerated across the study period and no new safety concerns were identified.

Keywords: Cannabidiol, Cognition, Delta-9-tetrahydrocannabinol, Endocannabinoid system, Multiple Sclerosis, Sativex, Spasticity

Abbreviations

AE: Adverse Event; ANCOVA: Analysis of Covariance; BDI-II: Beck Depression Inventory-II; CBD: Cannabidiol; CL: Confidence Limit; C-SSRS: Columbia-Suicide Severity Rating Scale; GIC: Global Impression of Change; MAS: Modified Ashworth Scale; PASAT: Paced Auditory Serial Addition Test; PP: Per Protocol; SAE: Serious Adverse Event; THC: Δ9-tetrahydrocannabinol

Introduction

Spasticity (muscle stiffness) affects around 80% of multiple sclerosis MS patients and is often classed as moderate to severe in magnitude, leading to significant impairment of the patient [1]. Current oral medication for the treatment of spasticity includes baclofen, tizanidine, dantrolene, benzodiazepines and anticonvulsants. However, despite widespread use of these agents, there is limited evidence of their efficacy [2,3]. The clinical need for new and effective treatments for spasticity is therefore clear.

The endocannabinoid system modulator Sativex (GW Pharma Ltd.) is formulated from plant-based extracts prepared from fully standardised chemotypes of Cannabis sativa L. plants developed to produce high and reproducible yields of the two principal cannabinoids, Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD), which are present at an approximate 1:1 fixed ratio in Sativex, with minor amounts of other cannabinoids and terpenes [4]. Notably, CBD has been shown to reduce the psychoactivity of THC [5].

Sativex is indicated as a treatment for adult patients with moderate to severe spasticity due to MS who have not adequately responded to other anti-spasticity medications. Previous clinical trials using Sativex

have demonstrated statistically significant and clinically relevant improvements in patient-reported severity of spasticity, while being well tolerated [6-9]. Importantly, efficacy has been shown to be maintained with long-term use of Sativex, with no deterioration of spasticity over a period of one year [10].

Both natural and synthetic cannabinoids have been shown to impair learning and memory in animals and humans, although pre-existing cognitive differences between cannabis users and nonusers makes interpretation of the human literature problematic [11]. In addition, there may be an association between long-term cannabis use and the development of suicidal ideations and depressive illness [12-14], suggesting that sustained administration of cannabinoids may promote the development of depression. The age of subjects (adolescent [15] vs. ageing brains [16]), the underlying disease [17] and blood THC concentrations [18] are factors to consider.

As Sativex is cannabinoid-based, this study was done as part of the risk management plan required by the European regulatory agencies, with the primary objective of evaluating whether Sativex may have long-term adverse effects on cognitive function or mood in patients with MS spasticity. The efficacy of long-term Sativex use on the severity of spasticity was also evaluated.

Methods

Study design

This 50-week (two-week titration period, 46-week maintenance period, two-week end of treatment follow-up period) multicentre, double-blind, randomised, parallel group, placebo-controlled study was conducted in six centres in the Czech Republic. The study was approved by the relevant Independent Ethics Committee and was conducted in accordance with the principles of the Declaration of Helsinki and the ICH GCP guidelines. All patients were aged 18 or over and provided written informed consent.

Inclusion and exclusion criteria

Inclusion criteria: To be eligible, patients had to have clinically diagnosed MS of any subtype, with at least moderate levels of MS spasticity, which was not wholly relieved with current anti-spasticity therapy; be on a stable medication regimen (i.e., not changed in the last three months or four weeks for disease-modifying or anti-spasticity/cognition medications, respectively); be willing to abstain from alternative cannabinoid use for 30 days prior to screening and throughout the study.

Exclusion criteria: Patients were excluded if they: had any current or past history of drug or alcohol abuse or significant psychiatric illness, other than depression associated with MS; were hypersensitive to cannabinoids or any of the excipients used; were female and of child bearing potential or male whose partner was of child bearing potential, unless willing to ensure effective contraception was used throughout the study; were female and pregnant, lactating or planning pregnancy; had received an investigational medicinal product within 12 weeks of screening; had any concomitant disorders or abnormalities that could either put the patient at risk, affect the patient's ability to participate or influence the result of the study.

Study medication and procedures

Following eligibility screening, patients were randomly assigned Sativex (GW Pharma Ltd., UK) or placebo and baseline assessments were performed. Study medication was delivered using a pump-action oromucosal spray. Each 100 µL spray of Sativex delivered 2.7 mg THC and 2.5 mg CBD. Each spray of matching placebo delivered excipients plus colorants. Patients were restricted to a maximum permitted dose of 12 sprays/day. Patients self-titrated during the first 14 days, up-titrating through a predefined escalation scheme to their optimal dose, based on efficacy and tolerability. On-treatment visits occurred at the end of weeks 12, 24, 36 and at end of treatment (week 48) or earlier if patients withdrew. A follow-up visit occurred 14 days after end of treatment or withdrawal.

Concomitant medications

Patients continued any established anti-spasticity therapy and were prescribed any concomitant medications deemed necessary to provide adequate supportive care, except for those which could affect the primary endpoint unless medically necessary.

Study endpoints

Primary endpoint: The primary variable for analysis was the mean change from baseline to end of treatment in Paced Auditory Serial Addition Test (PASAT)-I and -II combined total score[19]. The primary clinical hypothesis of this study was one of non-inferiority of Sativex when compared with placebo in its effect on cognition associated with MS as measured by PASAT.

Secondary endpoints: Secondary efficacy endpoints included the mean changes from baseline to the end of treatment in Modified Ashworth Scale (MAS) total score[20], 10-metre walk time (ambulatory patients), the number of visits to a healthcare professional during the last 12 weeks of treatment (compared with the 12 prior to screening), and Subject-, Physician- and Caregiver Global Impression of Change (GIC).

Safety endpoints

Along with the primary endpoint, additional safety endpoints included changes in mood assessed using the Beck Depression Inventory-II (BDI-II) [21], instances of suicidal ideation and behaviour assessed using the Columbia-Suicide Severity Rating Scale (C-SSRS) [22], the incidence of adverse events (AEs) and serious adverse events (SAEs), clinical laboratory sampling (haematology, biochemistry and urinalysis), vital signs and oral examination.

Sample size

The planned sample size for this study was 120 patients (60 receiving Sativex, 60 receiving placebo). This sample size was adequate to confirm the non-inferiority of Sativex with a clinically relevant reduction delta of 10%, assuming there was no difference between treatments in the actual change in cognition and also assuming a standard deviation for treatment difference of 10.0, using a one-tailed 2.5% significance level and power of 90%.

Methods of assigning patients to treatment groups and blinding

Randomisation was done by an independent statistician using a computer-based algorithm, in which treatment allocation was assigned using balanced, randomly permuted blocks. The randomisation scheme involved patient numbers being assigned sequentially by the investigator staff.

Study medication was presented in brown-plastic-coated 5.5 mL glass vials. Both Sativex and placebo contained peppermint oil to blind the smell and taste. The placebo also contained colorants to match the appearance of Sativex. Patients, investigators and caregivers were all blinded to the treatment allocation.

Statistical methods

All randomised patients who received at least one dose of study medication and yielded on-treatment efficacy data were included in the safety analysis set. The per protocol (PP) analysis set was used as an additional for analysis of the primary endpoint only, and excluded patients with compliance issues. All summaries and statistical analyses were performed using SAS Version 9.1.3. Statistical comparisons of data between treatment groups used two-tailed statistical tests at the 5% significance level, unless stated otherwise. PASAT total scores were evaluated by analysis of covariance (ANCOVA), with the baseline value as covariate and treatment and centre as factors. Sativex was deemed to be non-inferior to placebo (i.e., to have no adverse effect on cognition) if the lower one-sided 97.5% confidence limit (CL) of the estimated treatment difference (Sativex–placebo) was greater than-10%.

Changes from baseline to the end of treatment were compared between treatment groups using ANCOVA for the BDI-II, MAS and timed 10-metre walk. Models included treatment and centre group as factors and baseline values as covariate. For data found to be non-normal in distribution, changes in the two treatment groups were compared using the Wilcoxon Rank Sum test. The BDI-II was summarised and analysed in the same way as the primary endpoint using the safety analysis set. Sativex was deemed to be non-inferior to placebo (i.e., to have no adverse effect on mood) if the upper one-sided 97.5% CL of the estimated treatment difference (Sativex–placebo) was less than +5%. For the number of visits to a healthcare professional and the GIC outcomes, the two treatment groups were compared using ordinal logistic regression and the cumulative proportional odds model, with treatment group as factor.

Results

The study took place between January 2012 and May 2013. In total, 121 patients were screened and randomised to treatment at six study centres. Of these, 62 received Sativex and 59 received placebo. A total of 98 patients completed the study and 23 withdrew (Figure. 1).

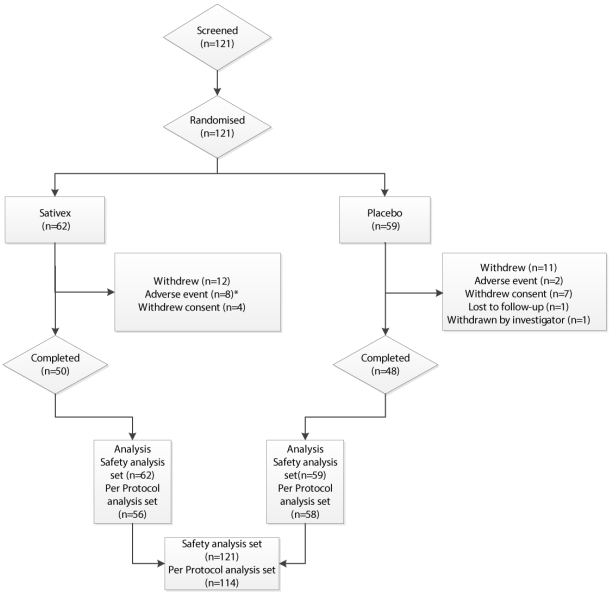

Figure 1: Disposition of patients enrolled in the study.

The overall withdrawal rate was the same in the active and placebo treatment groups. The baseline mean duration of MS was identical between treatment groups and the mean duration of spasticity was highly similar, with no notable differences in the proportions of patients with each MS subtype, the most common of which was relapsing/remitting MS for both groups (Table 1). From the first- to the last three months of the study, the median (mean [SD]) number of daily sprays decreased from 8 (7.6 [3.1]) to 6 (6.4 [3.1]) in the Sativex group and remained at 10 (9.5 [2.4/2.6]) in the placebo group. The median duration of treatment was 336 days for both groups.

		Sativex (n = 62)	**Placebo (n = 59)**	**Total (n = 121)**
		Number (%) of patients		
Gender	Male	23 (37)	22 (37)	45 (37)
	Female	39 (63)	37 (63)	76 (63)
Ethnic origin	White/Caucasian	62 (100)	59 (100)	121 (100)
Previous cannabis use (at any time, including last year)		25 (40)	15 (25)	40 (33)
Spasticity 0-10 NRS score	1-3 (mild)	3 (5)	1 (2)	4 (3)
	4-6 (moderate)	22 (35)	24 (41)	46 (38)

		Sativex	Placebo	Total
	7-10 (severe)	37 (60) **(n = 62)**	34 (58) **(n = 59)**	71 (59) **(n = 121)**
		Mean (SD)		
Time since last cannabis use (years)		4.1 (3.13)	3.5 (3.23)	3.9 (3.14)
Age (years)		49.0 (8.95)	48.2 (10.38)	48.6 (9.64)
Body Mass Index (BMI) (kg/m2)		25.1 (3.77)	25.5 (4.82)	25.3 (4.30)
Weight (kg)	Male	82.7 (11.89)	89.0 (17.64)	85.7 (15.15)
	Female	69.0 (13.68)	67.0 (11.92)	68.0 (12.81)
Height (cm)		171.3 (9.86)	171.0 (9.91)	171.2 (9.84)
Spasticity 0-10 NRS score		6.7 (2.04)	6.7 (1.67)	6.7 (1.86)
Duration since diagnosis of MS (years)		13.9 (8.09)	13.9 (9.08)	13.9 (8.55)
Duration since onset of spasticity (years)		8.0 (6.08)	7.7 (6.57)	7.8 (6.30)
		MS Subtype (Number [%] of patients)		
Primary progressive		11 (18)	5 (8)	16 (13)
Secondary progressive		24 (39)	19 (32)	43 (36)
Relapsing/remitting		26 (42)	33 (56)	59 (49)
Progressive relapsing		1 (2)	2 (3)	3 (2)
NRS, Numerical Rating Scale				

Table 1: Patient demographics and baseline characteristics.

Concomitant medication

The anti-spasticity medications taken during the study are presented in Table 2. There were no major differences between treatment groups in the numbers of patients taking each class of anti-spasticity medication. The most frequently taken classes of other concomitant medication were glucocorticoids (47%), vitamin D and analogues (39%), calcium (37%), and selective serotonin reuptake inhibitors (36%).

Medication class/ name	Sativex (%)	Placebo (%)	Total (%)
Total patients taking at least one anti-spasticity medication	51 (82)	50 (85)	101 (83)
Adamantane derivatives	2 (3)	3 (5)	5 (4)
Benzodiazepine derivatives	14 (23)	15 (25)	29 (24)
Clonazepam	6 (10)	6 (10)	12 (10)
Bromazepam	3 (5)	3 (5)	6 (5)
Diazepam	1 (2)	0	1 (1)
Midazolam	1 (2)	0	1 (1)
Oxazepam	0	1 (2)	1 (1)
Tetrazepam	5 (8)	6 (10)	11 (9)
Benzodiazepine-related	2 (3)	0	2 (2)
Zolpidem	2 (3)	0	2 (2)
Magnesium	14 (23)	12 (20)	26 (21)
Other analgesics & antipyretics	10 (16)	12 (20)	22 (18)
Gabapentin	5 (8)	8 (14)	13 (11)
Pregabalin	5 (8)	4 (7)	9 (7)
Other centrally acting agents	42 (68)	38 (64)	80 (66)
Baclofen	35 (56)	30 (51)	65 (54)
Tizanidine	13 (21)	9 (15)	22 (18)
Tolperisone	0	5 (8)	5 (4)
Thiocolchicoside	0	2 (3)	2 (2)
Other nervous system drugs	1 (2)	2 (3)	3 (2)

Table 2: Anti-spasticity medications used by study patients.

Primary endpoint: PASAT

In the assessment of cognitive function, the adjusted mean PASAT total score increased (improved) by 6.02 points from a mean baseline

score of 59.4 points in the Sativex group, compared with an adjusted increase of 7.49 points from a mean baseline score of 62.1 points in the placebo group. The estimated treatment difference was -1.47 points and the lower one-sided 97.5% CL was -6.41. Analysis of the PP subset yielded similar results, with an estimated treatment difference-1.57 points and a lower one-sided 97.5% CL - 6.57. In both sets, the lower one-sided 97.5% CL was greater than-10%, therefore Sativex was deemed to be non-inferior to placebo.

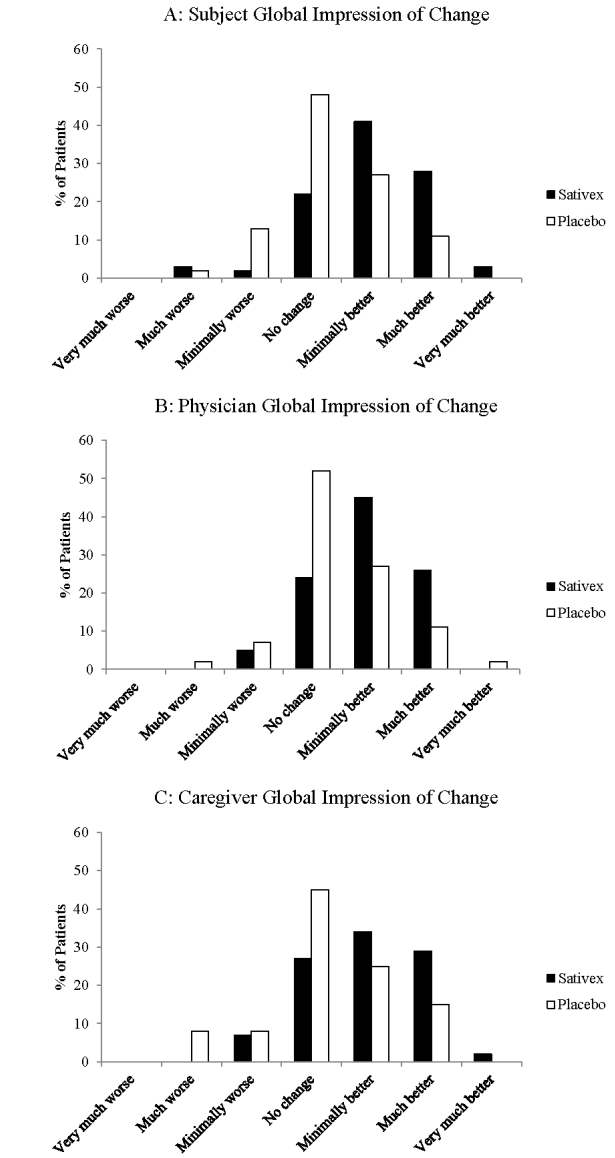

Figure 2: A: Subject Global Impression of Change at end of treatment, B: Physician Global Impression of Change at end of treatment, C: Caregiver Global Impression of Change at end of treatment.

Secondary efficacy analyses

In the efficacy analyses of Subject-, Physician- and Caregiver GIC, there was a statistically significant treatment difference in favour of Sativex compared with placebo in all cases (p=0.0001, p=0.002 and p=0.014, respectively) (Figure. 2, Table 3). The remaining secondary endpoints were non-significant but many were in favour of Sativex (Table 3).

	Sativex (mean)	Placebo (mean)	Treatment difference	95% CI (lower; upper)	p-value
	Primary endpoint				
Paced Audio Serial Addition test	6.02	7.49	−1.47	−6.41 (lower one-sided 97.5% CL)	(Non-inferior)
PP subset	5.90	7.47	−1.57	−6.57 (lower one-sided 97.5% CL)	(Non-inferior)
	Secondary endpoints				
Modified Ashworth Scale	−10.41	−8.05	−2.36	−6.09; 1.37	0.212
Timed 10-metre walk	8.58	3.70	4.88	−11.51; 21.27	0.556
Non-parametric analysis	−2 (median)	0 (median)	−1	−3; 0	0.088
Excluding estimated times	−1.45	−0.47	−0.98	−2.82; 0.86	0.293
Non-parametric analysis	−2 (median)	0 (median)	−1	−3; 0	0.118
Number of visits to a healthcare professional	-	-	1.186 (odds ratio)	0.605; 2.324	0.6198
Subject Global Impression of Change	-	-	4.017 (odds ratio)	1.963; 8.222	0.0001
Physician Global Impression of Change	-	-	3.066 (odds ratio)	1.514; 6.206	0.0019
Caregiver Global Impression of Change	-	-	2.785 (odds ratio)	1.229; 6.311	0.0142
	Additional safety endpoints				
Beck Depression Inventory-II	−2.84	−2.55	−0.29	2.33 (upper one-sided 97.5% CL)	(Non-inferior)

Table 3: Summary of primary, secondary and additional safety endpoint analyses showing adjusted mean change from baseline to the end of treatment data for Sativex versus placebo.

Safety and tolerability

Assessment of mood change using the BDI-II scale showed a decrease (improvement) of −2.84 points from an adjusted mean baseline score of 15.7 points in the Sativex group, compared with a decrease of −2.55 points from an adjusted mean baseline score of 13.5 points in the placebo group. The estimated treatment difference was

−0.29 points and, as the upper one-sided 97.5% CL was 2.33 (i.e., less than +5%), Sativex was deemed to be non-inferior to placebo.

The C-SSRS assessments revealed one patient receiving placebo was classed as having active suicidal ideation, but without intent (due to severe pain). There were no treatment-emergent effects on depression, suicidal ideations or suicidal behaviour in patients receiving Sativex.

All AEs experienced by patients during the study are presented in Table 4. Thirty-nine (62.9%) patients in the Sativex group and 19 (32.2%) in the placebo group experienced AEs. The most common treatment emergent treatment-related AEs in Sativex patients were vertigo in six [9.7%] patients, fatigue in five [8.1%] patients, and dizziness in five (8.1%) patients. Five patients in the Sativex group (8.1%) developed at least one SAE during the study, while there were no SAEs reported by any patients in the placebo group. One patient in the Sativex group had an SAE of acute myocardial infarction leading to their death, not considered to be related to study treatment. There were only three treatment-related SAEs (all occurring in one patient), all of which were mild in severity and resolved following interruption of study medication. All other SAEs were either mild or moderate in severity and recovered following continuation, interruption or cessation of study medication. There were no psychiatric AE safety signals identified in the study. No obvious trends were shown for biochemistry, haematology or urinalysis, and no changes in mean blood pressure and pulse rate were observed from baseline to final visit.

System organ class	**Sativex (n = 62)**	**Placebo (n = 59)**
Preferred term	Number (%) of patients	
Total patients with at least one AE	39 (62.9)	19 (32.2)
Mild	20 (32.3)	10 (16.9)
Moderate	16 (25.8)	7 (11.9)
Severe	3 (4.8)	2 (3.4)
Cardiac disorders	1 (1.6)	0
Ear and labyrinth disorders	6 (9.7)	0
Vertigo	6 (9.7)	0
Eye Disorders	0	1 (1.7)
Visual impairment	0	1 (1.7)
Gastrointestinal disorders	6 (9.7)	3 (5.1)
Diarrhoea	1 (1.6)	0
Dry mouth	2 (3.2)	0
Nausea	1 (1.6)	1 (1.7)
Oral mucosal erythema	0	1 (1.7)
Vomiting	1 (1.6)	0
General disorders and administration site conditions	8 (12.9)	2 (3.4)
Application site discomfort	1 (1.6)	0
Asthenia	2 (3.2)	0
Fatigue	5 (8.1)	1 (1.7)
Pyrexia	0	1 (1.7)
Immune system disorders	0	1 (1.7)
Drug hypersensitivity	0	1 (1.7)
Infections and infestations	12 (19.4)	7 (11.9)
Upper respiratory tract infection bacterial	0	1 (1.7)
Injury, poisoning and procedural complications	5 (8.1)	5 (8.5)
Overdose	1 (1.6)	0
Procedural vomiting	1 (1.6)	0
Investigations	3 (4.8)	2 (3.4)
Weight decreased	2 (3.2)	0
Metabolism and nutrition disorders	2 (3.2)	0
Decreased appetite	1 (1.6)	0
Musculoskeletal and connective tissue disorders	3 (4.8)	0
Pain in extremity	1 (1.6)	0
Nervous system disorders	20 (32.3)	7 (11.9)
Cerebellar ataxia	1 (1.6)	0
Dizziness	5 (8.1)	0
Dysarthria	1 (1.6)	0
Memory impairment	1 (1.6)	0
Muscle spasticity	2 (3.2)	0
Paraesthesia	1 (1.6)	0
Somnolence	0	1 (1.7)
Stupor	1 (1.6)	0
Tremor	1 (1.6)	0
Psychiatric disorders	5 (8.1)	1 (1.7)
Anxiety disorder due to a general medical condition	1 (1.6)	0
Disorientation	1 (1.6)	0
Euphoric mood	2 (3.2)	0
Reproductive system and breast disorders	0	1 (1.7)
Respiratory, thoracic and mediastinal disorders	0	1 (1.7)
Oropharyngeal blistering	0	1 (1.7)
Skin and subcutaneous tissue disorders	1 (1.6)	0
Surgical and medical procedures	1 (1.6)	1 (1.7)

Table 4: Number of patients with at least one all-causality AE by primary system organ class and at least one treatment-related AE by preferred term.

Bold items indicate the total numbers of patients with an all-causality AE by system organ class according to the MedDRA classification of AEs. Non-bold items indicate numbers of patients with treatment-related AEs.

Discussion

This study has shown that there is no evidence of long-term cognitive impairment or significant changes in mood in MS patients taking Sativex compared with those taking placebo. These findings are in agreement with previous placebo-controlled clinical studies, which found no evidence for an effect of Sativex on cognitive function [5,6,23,24] or mood [6,8,23,25]. In addition, although suicidal intent occurs in approximately 30% of MS patients [26], there was only one single case of active suicidal ideation in a patient receiving placebo. As such, no suicidality findings were identified in the current study. Together with the fact that no psychotic disorders were reported, these findings are encouraging when put into a clinical context.

Analysis of each of the three GIC secondary efficacy measures showed statistically significant treatment differences in favour of Sativex. The agreement between all parties (Subject, Physician and Caregiver) that spasticity had improved with Sativex treatment suggests an inherent validity in these results. These findings are consistent with previous studies in MS patients with spasticity, in which various GIC outcome measures improved significantly with Sativex treatment [8, 25], and suggest that alleviation in the severity of spasticity is maintained for at least 12 months with Sativex treatment.

The outcome of the MAS, 10-metre walk time and number of visits to a healthcare professional secondary efficacy endpoints were also consistent with results from previous studies that showed a trend towards improvement in favour of Sativex [7,8,25,27]. Failure to achieve statistical significance may be due to known issues with these methods [28] and/or that the current study was insufficiently powered to detect statistically significant changes for these endpoints. Nonetheless, any improvements in these parameters can only be viewed positively given the potential impacts on the cost-benefit of taking Sativex, as well as from a patient's perspective.

In terms of safety, Sativex was well tolerated with no evidence of tolerance developing. The safety findings in longer-term use of Sativex over 12 months do not raise any concerns with regards to the safety profile, and the benefit-risk assessment remains favourable. There was a notable difference in the numbers of patients with reported AEs between Sativex and placebo groups; the frequency of AEs in the Sativex group matches closely to other clinical studies in patients with MS [9,23,29]. AEs were the most common reason for discontinuation of treatment in the Sativex group, although the severity of AEs that led to withdrawal from the study was mostly mild or moderate. There were only three treatment-related SAEs (all occurring in one patient), all of which were mild in severity and resolved following interruption of study medication. There was one death, caused by a myocardial infarction in a patient randomised to receive Sativex, but this was not considered to be related to the study medication.

The observation that the median (mean [SD]) daily dose reduced from 8 (7.6 [3.1]) sprays to 6 (6.4 [3.1]) sprays over the 12-month period in the Sativex group is consistent with results reported from a post-marketing registry study conducted in the UK [30], and with post-marketing data reported from Germany [31]. The observation that patient, caregiver and physician-reported efficacy was maintained over the 12-month period suggests that the maintenance of efficacy can be achieved at lower drug exposures that are seen in short-term clinical trials, and confirms previous observations that there is no evidence of tolerance with continuing use [10]. It also seems likely to have some implications for the pharmaco-economic evaluation of the cost-benefit of Sativex, which is generally based on a daily dose of eight sprays [32].

Study limitations

The mean duration of MS at study entry was high at 13.9 years (Table 1). The symptom severity was also reflected in a high mean baseline spasticity 0-10 numerical rating scale (NRS) score in this study (6.7 for both Sativex and placebo), with a high number of patients (59%) having "severe" spasticity (spasticity 0-10 NRS score=7-10) despite the best available anti-spasticity treatment. In addition, the mean duration of spasticity was 7.8 years, with the proportion of patients taking anti-spasticity or disease modifying medications being high (anti-spasticity: 82% Sativex, 85% placebo; disease modifying: 81% Sativex, 92% placebo). Over half of the patients were concomitantly taking baclofen, and around one fifth were also taking tizanidine (Table 2), further indicating that this study population had severe spasticity. These demographics may have impacted the ability to observe a statistically significant improvement in some of the secondary efficacy measures in this study, although they are similar to the characteristics of patients included in shorter-term studies of Sativex[7-9]. Among the secondary efficacy endpoints, the Ashworth Scale score in particular was not significantly different between drug and placebo. The Ashworth Scale has previously been described as unsuitable for use as an assessment tool for clinical trials of anti-spasticity agents, and this result would support that conclusion [33]. Although multicentre, the study was conducted in a single country. However, the study's use of specialised MS clinics, with international patterns of care, limits the non-multinational implementation of possible bias.

Conclusions

In conclusion, this study has shown that there is no evidence of long-term cognitive decline or significant changes in mood in MS patients taking Sativex compared with those taking placebo. There were no treatment-related suicidal ideations or behaviours in patients taking Sativex and patients, physicians and carers were all in agreement that the patient's spasticity had improved since starting Sativex treatment. Sativex was well tolerated and no new safety concerns were identified.

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