

Drug-resistant MS spasticity treatment with Sativex[®] add-on and driving ability

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Objective – The aim of the present observational study was to determine the effects of a delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) oromucosal spray (Sativex[®] spray), brand name Sativex[®], indicated for drug-resistant MS spasticity, on the driving ability of treated MS patients. **Methods** – The study was conducted over a period of 4–6 weeks. Thirty-three MS patients with moderate to severe treatment-resistant spasticity and planned to begin add-on treatment with Sativex[®] were enrolled at three specialized MS centres in Germany. A set of five driving test procedures from a validated computerized test battery was used to evaluate the driving ability of eligible patients. Tests were performed by patients at baseline and repeated after 4–6 weeks of treatment with Sativex[®] oromucosal spray. According to German normative data, the test thresholds achieved by the general population served as a reference to allow for a fitness/unfitness to drive classification. **Results** – Patients showed comparable driving test results at baseline and at final visits. Only two patients changed classification shifting from ‘unfit’ to drive to ‘fit’ and vice versa. The mean severity of spasticity, as self-reported by the patients, improved with statistical significance. Sativex[®] was generally well tolerated. **Conclusions** – Treatment of MS patients with Sativex[®] does not negatively impact on driving ability and may improve moderate to severe treatment-resistant MS spasticity.

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Introduction

Multiple sclerosis (MS) is the most common chronic inflammatory disease of the central nervous system (1). A wide range of symptoms appear at onset and during progression (2). MS spasticity (muscle rigidity, spasms) affects up to 80% of patients and is one of the most common and disabling symptom (3). It impacts significantly on patients' quality of life (4). Suffering from moderate to severe spasticity does not only impair mobility, social life and activities of daily living but may also be associated with additional complications such as pain, sleep disorders, depression and skin damage (5).

The number of MS disease-modifying treatment options has expanded in recent years. Nevertheless, for MS spasticity symptomatic treatment, a combined delta-9-tetrahydrocannabinol/cannabidiol

oromucosal spray (Sativex[®]; GW Pharma Ltd., Salisbury, UK) is the only approved drug specifically developed to treat MS spasticity in recent years. Sativex[®] is indicated as an add-on therapy for patients suffering from moderate to severe MS spasticity resistant to previous pharmacological interventions. The drug has recently been recommended in the German Guideline for the treatment of MS spasticity (6).

Several clinical trials have investigated the efficacy and safety of Sativex[®] and demonstrated a clinically relevant benefit for MS patients suffering from spasticity (7–11). These data were confirmed by long-term studies (10, 12–14).

According to the studies mentioned above, Sativex[®] was well tolerated. Treatment-related adverse events with a higher incidence in the active treatment group compared to the placebo group were as follows: dizziness (32% vs10%),

fatigue (23% vs 16%), somnolence (14% vs 4%), nausea (14% vs 5%), vertigo (11% vs 4%) and asthenia (13% vs 6%) (8). The tolerability of Sativex[®] was also analysed in several systematic reviews (10, 15, 16). The adverse events are most often described as mild or moderate (8, 10, 17). The most frequent reported adverse events during a longitudinal/follow-up study in which patients received up to 2 years Sativex[®] were oral pain (20%), dizziness (15%), diarrhoea (12%) and nausea (11%), mostly described as mild or moderate. Only 17/137 patients discontinued the study due to adverse events (10,18). Despite the potential of cannabinoids to negatively impact on cognitive functions of MS patients, the rate of reported motor vehicle accidents has not increased under cannabinoid medication use (17).

Until now, the ongoing GW EU Sativex[®] registry has collected data regarding tolerability and safety of Sativex[®] from more than 680 patients with an average follow-up time of 570 days. In this registry, a questionnaire with specific questions concerning driving ability was applied (19, 20). According to these data, no signs of deterioration of driving ability were reported by any of the patients. Nevertheless, there is great interest to further clarify the putative impact of Sativex[®] on patients driving abilities and to allow physicians to advise their patients regarding any potential risks.

This pilot, prospective, multicentre and non-interventional study was conducted to collect data on driving ability, tolerability and safety from patients starting Sativex[®] treatment under real-life conditions.

Methods

Patient population

It was intended to recruit at least 30 MS patients suffering from moderate to severe treatment-resistant spasticity over a period of 6 months by three ambulant German MS specialist centres. Main selection criteria

Inclusion:

1. MS patients ≥ 18 years, suffering from moderate to severe MS spasticity and who did not respond adequately to other antispasticity medication.
2. Patients who drive a vehicle at least once a week.
3. Signed informed consent.
4. Decision to start Sativex[®] treatment made prior to study enrolment.

Exclusion:

1. Any condition or shortcomings in their knowledge of national language, suggesting that the driving ability tests were not to be fully understood, and/or patient questionnaires could not be completed.

Due to the nature of a non-interventional study, there were no other specific selection criteria regarding restrictions on concomitant medication. Contraindications and warnings were followed as stated by the approved Sativex[®] Summary of Product Characteristics (SmPC).

Investigational product and dosing

The investigational product is a cannabinoid-based oromucosal spray medication distributed under the brand name Sativex[®], which contains the active substances delta-9-tetrahydrocannabinol and cannabidiol at an approximate ratio of 1:1 and is applied directly to the mucosa of the oral cavity. Importantly, the drug is licensed as add-on therapy to patients' current antispasticity medication. As recommended by the SmPC, patients follow a 2-week dose titration phase during which the most active and tolerable dose is determined through gradual titration. The maximum daily dose of Sativex[®] allowed was 12 sprays/day.

Study design

The study was designed as a pilot, prospective and post-marketing surveillance study over a period of 4–6 weeks.

Besides anamnestic data, the results from baseline and final visit driving ability tests, as well as data concerning the efficacy and safety of the Sativex[®] treatment, have been documented.

Driving ability tests were performed at the start of the treatment and at a follow-up visit 4–6 weeks later, when physicians examined whether the patient had responded to the new antispasticity treatment.

At baseline sociodemographic data and information about patients' MS, such as MS type, symptoms, MS spasticity, treatment with antispastic and/or other concomitant drugs, were documented. Expanded Disability Status Scale (EDSS) (20) scores at baseline were compared to a reference score 12 months earlier to monitor MS disease progression. In addition, the number of MS relapses 12 months prior to the study were determined. Information regarding severity of MS spasticity was collected through a validated and

patient-rated outcome measure, a 0–10 numeric rating scale (NRS), at baseline and final visit (21). In addition, results from specific driving ability tests and the Epworth 8-item Daytime Sleepiness Scale (ESS) (22) were also collected at baseline and final visit. Adverse events were reported throughout the study.

An ethics approval for this study was obtained by the Freiburg Ethics Commission International (FEKI), feci code: 012/1343.

Data management and statistical analysis were performed by ANFOMED GmbH (Möhrendorf, Germany).

Driving tests

Following German guidelines (23), a computerized and validated test battery Schuhfried-Wiener Testsystem was used to assess driving ability. The test battery offered by Schuhfried GmbH (24) consists of five different test categories, each of which measures a different dimension including reaction speed, concentration, orientation, stress tolerance and attention. With test duration of 6–14 min per category, an entire test session lasted about 45 min. The individual reaction time was measured by the motor speed reaction test (RT), which assesses basic attention (vigilance) and response (reaction time defined as the time that elapses between a signal and the start of a tested person's mechanical response movement).

Concentration was tested by the concentration cognitrone test (COG), which measures the mean reaction time between a complex (bimodal) signal (simultaneous appearance of yellow light and tone) and the response by mechanical movement. Besides time measurement (reactions times), tasks need to be solved as a decisive criterion of this test (85% of the requested tasks are normally solved).

The visual pursuit test (LVT) measures visual orientation facing simple structures in a complex environment.

The stress tolerance determination test (DT) measures attention and individual reaction time in situations requiring continuous, swift and varying responses to rapidly changing visual and acoustic stimuli.

Finally, the adaptive tachistoscopic traffic perception test (ATAVT) assesses visual observational ability and skill in obtaining an overview as well as perceptual capacity to react in specific situations.

To be classified as 'fit for driving', official test thresholds require an individual to score a

minimum percentile rank of 16% in each of the five different categories of the driving ability test.

A test score lower than 16% means that a subject performs below the bottom sixth of the common population, independently of age.

Importantly, in real-life conditions, German driving guidelines are flexible within the classification 'fit' for driving if:

1. Values below 16% are situation specific (situational),
2. Values below 16% in one test are compensated by stable performances in other tests,
3. There are other procedures which indicate (allow for) reasonable compensation of deficits (anticipation, risk awareness and caution),
4. The driver gains credit for having already proven herself/himself in practice.

The participants' driving fitness in this study was defined by use of two different approaches. The first approach required patients to score a minimum percentile rank of 16% in each of the five tests in order to be classified as 'fit to drive'. The second approach followed the German normative flexibility frame and allowed for 'fit to drive' classification of patients scoring below 16% in one or more test when low performance was compensated by a minimum score of 50% in another test.

MS spasticity rating scales

The severity of MS spasticity was assessed by the patient through the validated 0–10 NRS (22). Patients were asked to indicate their current level of spasticity ranging from 'no spasticity (NRS = 0)' to the 'worst spasticity imaginable (NRS = 10)'. In addition, the physician rated the level of spasticity, by selecting one of the following categories: mild (occasional impact on activities), moderate (frequently affects activities) or severe (patient is forced daily to modify activities) (3).

Adverse events

Adverse events were documented at the final visit.

Statistical analysis

Computation of mean values and standard deviation, median, lower and upper quartiles and listing of minimum and maximum values was performed for quantitative variables, as well as calculation of frequencies for nominal and ordinal

variables. Tests for significance (signed rank test) were computed for driving tests and level of spasticity severity, but should only be interpreted in a descriptive exploratory way. *P*-values reported are two-tailed, and an alpha level of 0.05 was used to assess statistical significance. No correction for multiple testing was performed.

The five tests procedures (LVT, COG, DT, RT and ATAVT) were analysed as percentile ranks. The percentile rank of a particular test allows to ascribe the percentage of examinees in the norm group who scored below threshold score (24).

Results

Demography and baseline characteristics

Thirty-three patients were enrolled in the study, which started in June 2012 and was completed in April 2013. Patients' ages ranged from 33 to 68 years, implying a mean age of 48.1 years. More female (60.6%) than male (39.3%) subjects were recruited, reflecting the epidemiology of MS in the general population.

Most patients (63.6%) suffered from secondary progressive MS and, on average (\pm SD), patients were diagnosed with MS 11.5 (\pm 6.8) years prior to enrolment into the study. More than 90% of all patients presented with additional MS symptoms such as fatigue, depression and bladder disorders being among the most common symptoms. On average, spasticity had been present for 6.7 (\pm 5.4) years. EDSS scores were collected from all patients at baseline with an average score of 4.6.

Multiple sclerosis was treated with immune modulators in 22 participants (66.7%). Twenty-six patients (78.8%) received physiotherapy and 13 (39.4%) received pharmacological therapy for

their spasticity at baseline, including baclofen (nine patients), tolperisone (nine patients), gabapentin (five patients) and tizanidine (three patients) (multiple prescription possible). Concomitant diseases were documented in 11 patients (33.3%), the majority with epilepsy (9.1%), followed by hypertension, pain, migraine, osteoarthritis and restless legs syndrome (all at 6.1%). Seven of these patients (21.2%) received additional medication for these treatment of these diseases (for example, pramipexol, tramadol and/or non-steroidal anti-inflammatory drugs).

Exposure to study medication

The mean duration of the observational period was 5.3 weeks. Two patients (6.1%) stopped treatment prematurely; one non-responder and one due to intolerance. Thirty-one subjects (93.9%) completed the study according to schedule. The mean dose of Sativex[®] at the end of the study was 5.1 sprays per day.

Driving tests results

A total of 31 patients completed all five driving tests at both baseline and final visit. Compared to baseline, none of the driving tests indicated a statistically significant deterioration of patients' performance at final visit. Interestingly, stress tolerance (DT) improved considerably and was statistically significant ($P = 0.026$; Fig. 1).

According to the strict criterion for evaluating driving ability, a person was only considered 'fit' for driving if a percentile rank of at least 16% was achieved in each of the five subscores (tested areas). According to this analysis, only 14 of the 31 patients analysed (45.2%) proved fit for driving at baseline (Table 1a).

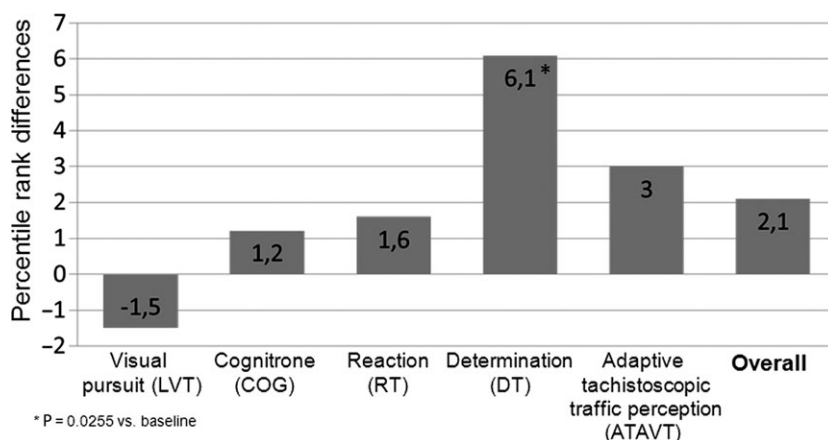


Figure 1. Driving ability tests, differences baseline/final visit.

Table 1 Fitness for driving at baseline and final visit, number and percentage of patients classified 'fit' or 'unfit' for driving (a) according to the strict criterion (surpassing 16% threshold in all tests) and (b) using modified criterion

Baseline visit	Final visit				Total	
	fit		unfit			
	<i>n</i>	Percent	<i>n</i>	Percent	<i>n</i>	Percent
(a)						
fit	10	32.3	4	12.9	14	45.2
unfit	1	3.2	16	51.6	17	54.8
Total	11	35.5	20	64.5	31	100.0
(b)						
fit	22	71.0	2	6.5	24	77.4
unfit	2	6.5	5	16.1	7	22.6
Total	24	77.4	7	22.6	31	100.0

n, number of patients; grey area: test results with no change from fit to unfit (and vice versa) at final visit in comparison to the beginning of study; stripes horizontal: test results with change from unfit to fit at final visit in comparison to the beginning of study; stripes vertical: test results with change from fit to unfit at final visit in comparison to the beginning of study.

The second flexible approach allowed for a 'fit to drive' classification of patients that scored below 16% in one or more tests when low performance was compensated by a minimum score of 50% in another test. When this approach was applied, 24 tested subjects (77.4%) proved fit for driving at baseline, while seven (22.6%) did not (Table 1b).

Upon treatment with Sativex[®], two patients (6.5%) changed categories from 'fit' at baseline to 'unfit' at final visit, and vice versa (Table 1b). Therefore, frequencies of patients classified as 'fit' or 'unfit' did not change during the study. In summary, treatment of patients with Sativex[®] did not show deterioration of patients' ability to drive.

NRS and effectiveness on MS spasticity

Severity of spasticity within the past 24 h was self-rated by patients using the 0–10 NRS. The average score decreased, and therefore spasticity improved, by 2.4 points from 6.0 points at baseline to 3.6 points at final visit (Fig. 2). This change was highly statistically significant ($P < 0.0001$) and clinically relevant (21).

Comparison of severity of spasticity levels showed that spasticity improved during the study. At baseline seven (21.1%) patients suffered from severe spasticity, and at the end of the study, only one patient (3%) was severely affected (Fig. 3).

Safety

In total, five non-serious adverse events occurred in four patients. These were dizziness in two patients (6.1%), and ligament sprain, thrombosis and a vertigo episode in one patient (3.0%), respectively. All of these events were considered mild or moderate. Three events were considered drug related (dizziness and vertigo). All patients had recovered by the end of the study. One patient discontinued prematurely due to adverse events (dizziness and vertigo). Moreover, the dose of Sativex[®] therapy was reduced in one case due to dizziness.

Discussion

Currently, profound knowledge concerning the effects of delta-9-tetrahydrocannabinol/cannabidiol therapy on individuals' driving ability is still lacking. Therefore, patients experiencing side effects such as dizziness and somnolence upon

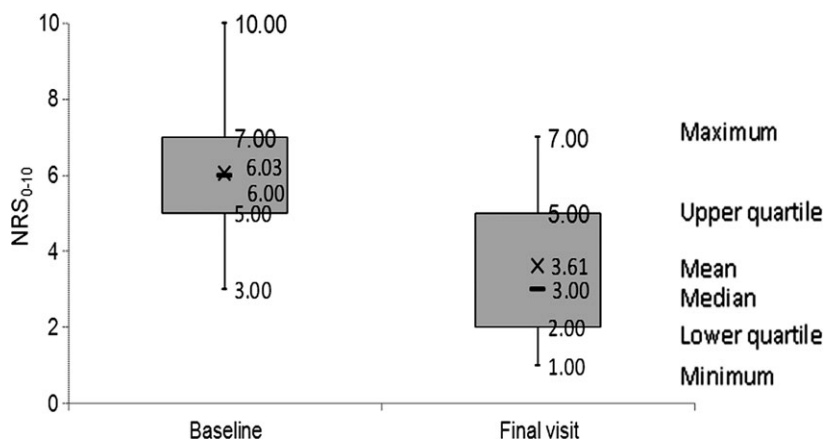


Figure 2. Level of spasticity at baseline and final visit that patients ($n = 33$) have experienced over the past 24 h (0 = no spasticity, 10 = worst spasticity imaginable; X = mean, – = median, [] = interquartile, - = minimum and maximum).

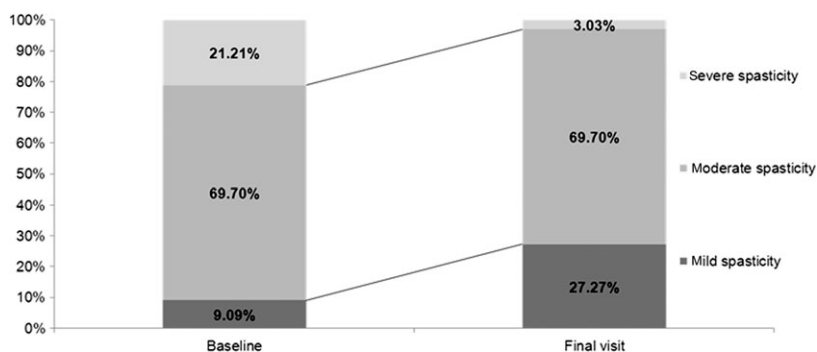


Figure 3. Percentage of patients with mild, moderate and severe spasticity at baseline and final visit.

treatment initiation are often advised not to drive or operate machinery, as physicians are required by duty of care to provide driving advice to patients with certain conditions (25). However, a survey revealed that patients with neurological conditions receive inconsistent advice on driving from their doctors. Moreover, only 61% of MS patients received advice (25).

A possible reason may be the fact that specific evidence from clinical trials on driving ability is currently lacking. This holds also true for the effects of delta-9-tetrahydrocannabinol/cannabidiol therapy on individuals' driving skills. There are only a few general studies investigating the driving ability of MS patients. A previous computer-test based study on 15 MS patients suffering from mild to moderate symptoms of MS showed no differences between healthy controls (17 persons) and patients with MS on all measures of the primary driving task, but MS patients performed worse in the divided response time and accuracy tests (26). Another study showed that MS-associated cognitive and physical impairments might increase the risk for car accidents (27).

Driving is not contraindicated for other approved medications with similar pharmacology and safety profiles to Sativex[®] (such as Nabilone or Dronabinol), but a warning is given to avoid driving or operate machinery if somnolence, dizziness or related adverse events are perceived.

Importantly, various RCTs have proven that MS patients benefit from cannabinoid therapy (2, 7–9, 12, 15). These trials reported a reduction in the severity of spasticity and associated symptoms, which result in an improved ability to perform daily activities (2, 4). Furthermore, patients who had been resistant to other therapies did benefit from treatment with Sativex[®] (2, 4).

The present pilot study aimed to examine whether Sativex[®] may impair driving ability of MS patients. From a general view, there was no

difference in the number of patients considered fit or unfit to drive before and after Sativex[®] use, which suggests that Sativex[®] does not impair driving ability. Also according to the individual driving tests used for our study, Sativex[®] treatment does not impair patients' ability to drive.

Naturally, no practical on-road test was performed for our study as the use of the modern computerized test systems have previously been proven to be a standardized, accurate and comprehensive tool (28–30). These studies demonstrated an excellent correlation between test results and patients' on-road performance, with more than 80% accuracy for the stroke driver screening assessment and more than 90% accuracy for the useful field of view test (28).

Interim data of safety registries in UK and Spain, which contain data on driving ability, have not reported any new safety/tolerability concerns after 1 or more years of treatment with Sativex[®] (17). Moreover, there was no evidence indicative of impaired driving ability as well as no relevant incidence cases or other aspects of concern such as psychiatric or nervous system events (18).

Importantly, the rate of reported motor vehicle accidents has not increased on Sativex[®] exposition, and no obvious incidents have occurred in the post-marketing experience so far (31).

Within the current legal framework, an expert decides about patients' ability to drive on an individual basis. This potentially allows some people to legally drive although they might fail a driving ability test. This situation is reflected by the results of our study. When patients were assessed according to the strict driving criteria – referring to the requirement to meet the 16% percentile rank threshold at baseline in all subtests – only 45.2% of enrolled MS patients were classified 'fit for driving' at the beginning of the study, whereas 54.8% were classified 'unfit' for driving. When patients were assessed according to the operative modified flexible criterion, 77.4% of the

patients were classified fit for driving, which would still leave more than one-fifth of the evaluated patients officially unable to drive. This suggests that a certain percentage of active drivers among MS patients seem to be in fact unfit for driving. It cannot be excluded that possible changes in the concomitant diseases and/or concomitant medications such as tramadol, pramipexol or β -blockers could have had an influence on driving ability.

In sum, the present study suggests that driving skills are not impaired by treatment with Sativex[®]. The present study has some limitations that should be considered in interpreting the data. The sample size was quite small to generalize the data. Further, long-term studies including more patients, such as specific cohort studies, are required to fully define the aspect of road safety under treatment with Sativex[®].

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Conflict of interest

M. Freidel has received personal compensation for activities with Almirall, Bayer Schering, Teva, Merck Serono, Biogen Idec, Novartis, Sanofi Aventis, Genzyme, Mundipharma and Medtronic. U. Essner received consultancy fees from Almirall Hermal GmbH, Carem GmbH, O. MEANY DM&PM GmbH and Teva GmbH. K. Tiel-Wilck received honoraria for lectures, studies and consultancy from Almirall Hermal GmbH, Bayer-Schering Pharma, Biogen Idec, Genzyme, Ipsen Pharma, Merck-Serono Pharma, Merz Pharma, Novartis AG, Roche Pharma, Sanofi Aventis and TEVA. A. Prechtel is Director of Medical affairs of Almirall Hermal GmbH. H. Schreiber has received research grants from Bayer AG, Biogen Idec and Teva; has received travel grants and honoraria for serving as a speaker at scientific meetings and as a member of scientific advisory boards for Almirall, Bayer AG, Biogen Idec, Merck, Novartis & Teva. M. Lang received compensation for talks and funding for studies from Biogen-Idec, Bayer, Novartis, Serono, Teva, and Genzyme.

Source of funding

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Ethical standard

All patients provided informed consent. The study was approved by the ethical committee in Germany (Freiburg Ethics Commission International (FEKI), under the feci code:

012/1343) and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

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