Attention please: vigilance in patients with excessive daytime sleepiness

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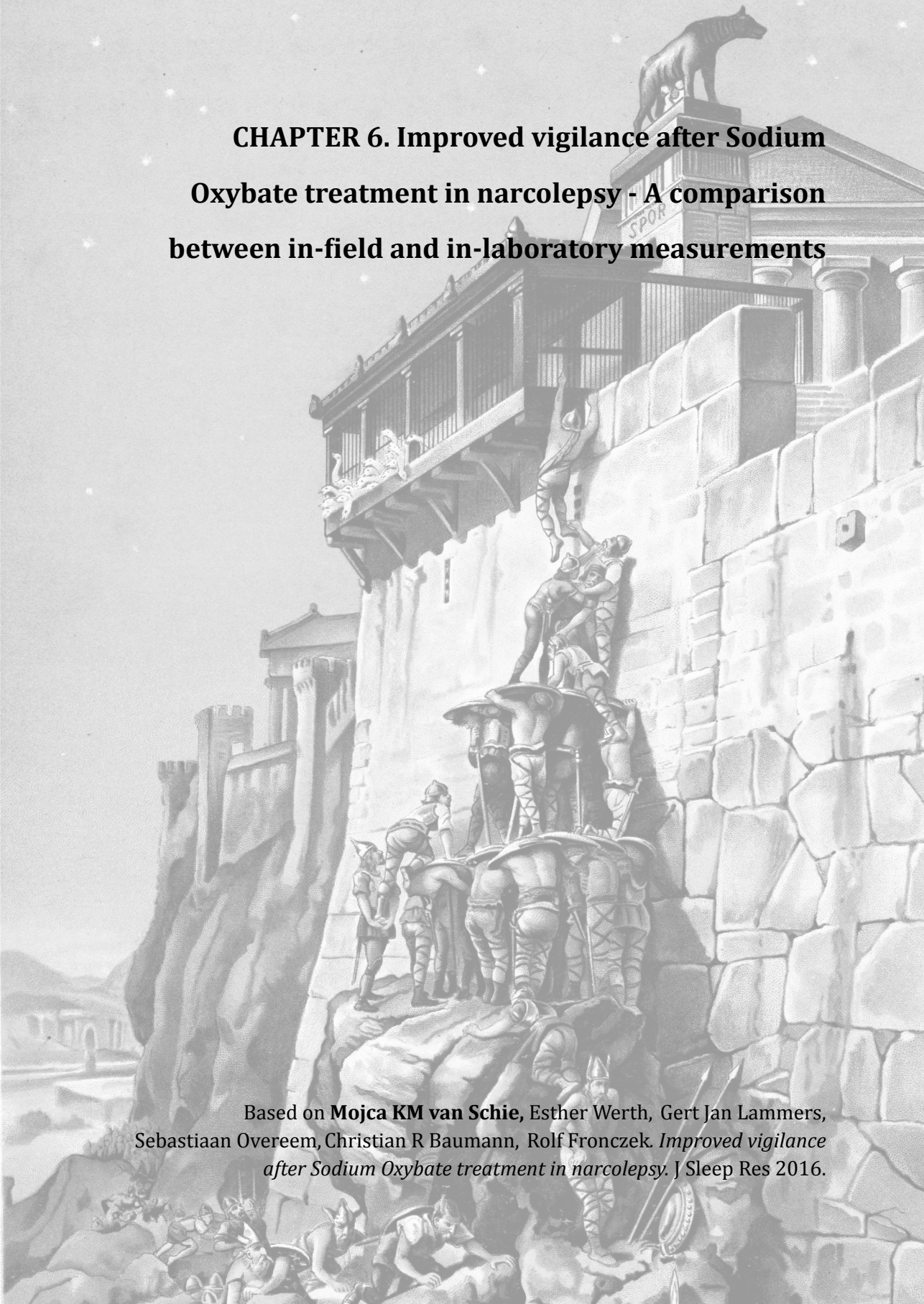

CHAPTER 6. Improved vigilance after Sodium Oxybate treatment in narcolepsy - A comparison between in-field and in-laboratory measurements

Based on **Mojca KM van Schie,** Esther Werth, Gert Jan Lammers, Sebastiaan Overeem, Christian R Baumann, Rolf Fronczek. *Improved vigilance after Sodium Oxybate treatment in narcolepsy.* J Sleep Res 2016.

ABSTRACT

This two-centre observational study of vigilance measurements assessed the feasibility of vigilance measurements on multiple days using the Sustained Attention to Response Task (SART) and the Psychomotor Vigilance Test (PVT) with portable task equipment, and subsequently assessed the effect of Sodium Oxybate (SXB) treatment on vigilance in narcolepsy patients. Twenty-six narcolepsy patients and 15 healthy controls were included. The study comprised two in-laboratory days for Maintenance of Wakefulness Test (MWT) and Oxford Sleep Resistance test (OSLER), followed by seven-day portable vigilance battery measurements. This procedure was repeated for narcolepsy patients after at least three months of stable treatment with SXB. Narcolepsy patients had a higher SART error count, lower PVT reciprocal reaction time, higher OSLER omission error count adjusted for test duration ($OSLER_{OMIS/MIN}$), and lower OSLER and MWT sleep latency compared to controls (all $P < 0.01$). Treatment with SXB was associated with a longer MWT sleep latency ($P < 0.01$), lower $OSLER_{OMIS/MIN}$ ($P = 0.01$), and a lower SART error count ($P = 0.01$) in narcolepsy patients, but not with absolute changes in OSLER sleep latency or PVT reciprocal reaction time. We concluded that portable measurements of sustained attention as well as in-laboratory OSLER and MWT measurements revealed worse performance for narcoleptic patients compared to controls and that SXB was associated with an improvement of sustained attention and a better resistance to sleep.

INTRODUCTION

Type 1 narcolepsy is a sleep-wake disorder characterized by excessive daytime sleepiness (EDS) and cataplexy. Additional symptoms include disturbed nocturnal sleep, and other rapid eye movement sleep associated symptoms, such as hypnagogic hallucinations, and sleep paralysis and cataplexy (American Academy of Sleep Medicine, 2005). The presence of chronic EDS, that is, the subjective and objective appraisal of the tendency to fall asleep and the ability to stay awake, is mandatory for the diagnosis of narcolepsy. Disturbed vigilance, i.e. a disturbed capability to be aware of internal or external stimuli, is an additional largely neglected symptom of narcolepsy that is directly related to impaired daytime performance and quality of life (Fronczek et al., 2006, Valley and Broughton, 1981). The severe vigilance problems experienced by patients with narcolepsy may be reflected by the inability to recall the content of a conversation, not being able to finish a book, or to concentrate on studies or work.

The Multiple Sleep Latency Tests (MSLT) (Littner et al., 2005) and the Maintenance of Wakefulness Test (MWT) (Littner et al., 2005) are the most commonly used electrophysiological tests for the diagnosis and the quantification of EDS after the initiation of treatment. The MSLT entails the measurement of sleep latency at 4-5 different times on one day while subjects are lying in bed in a quiet, dark room and try to fall asleep. The MSLT thus assesses sleep propensity. The MWT follows a similar schedule, but subjects are requested to try to stay awake instead of trying to fall asleep. The MWT thus assesses the ability to remain awake / resist sleep.

While reports about quality of sleep in narcolepsy are numerous, treatment-effect studies hardly address the quality of wakefulness, even though the value of vigilance measurements has become gradually more recognized (Fronczek et al., 2006, Moller et al., 2006, Van Schie et al., 2012). A study by Weaver (Weaver and Cuellar, 2006) measured changes in quality of life following the administration of sodium oxybate (SXB) in narcolepsy patients. SXB is a strong hypnotic drug, known to be effective in the treatment of disturbed night sleep, EDS, and cataplexy in narcolepsy (The U.S. Xyrem Multicenter Study Group, 2002) In the study by Weaver et al, the nightly administration of SXB produced significant dose-related improvements in the vigilance subscale of the questionnaire (Weaver et al., 1997) that was used. Thus, nocturnal administration of SXB in patients with narcolepsy was associated with clinically relevant improvements in vigilance, an important component of quality of life. Objective tests to measure vigilance, however, have not been applied. The current study was therefore designed to compare vigilance in daily life of narcolepsy patients before and on treatment with SXB by objective measurements.

Several methods are available for this purpose. The most frequently used vigilance measurements are response tasks assessing sustained attention, such as

the Sustained Attention to Response Task (SART) (Robertson et al., 1997) and the Psychomotor Vigilance Test (PVT) (Wilkinson and Houghton, 1982). Such tests only concern external stimuli, not internal stimuli, and measure whether responses are perceived by whether they are acted upon.

SART measurements have been validated in narcolepsy, i.e. have been demonstrated capable of detecting vigilance impairment in narcolepsy compared to healthy controls (Fronczek et al., 2006), while PVT measurements have not yet been validated in this group. The latter however, are widely used in sleep deprivation studies. In contrast, the PVT has been utilized in a portable test version, while SART has not. As direct comparisons of these tests were not available, we decided to combine both tests in a portable task battery. For that purpose, feasibility of portable testing in narcolepsy patients had to be investigated firstly. Since some authors consider the ability to stay awake an aspect of vigilance (Parasuraman et al., 1998), we chose to measure sleep resistance in addition to sustained attention by means of the MWT. Measurements of sustained attention and sleep resistance are combined in the Oxford Sleep Resistance test (OSLER). We therefore considered this test of additional value to a protocol already measuring these aspects, but by different tests in different conditions, that is daily life versus the laboratory. The basic setting for the OSLER is the same as for the MWT, as is its duration. In contrast to the MWT, which is a polysomnographic test and behaviourally undemanding, the OSLER requires continuous monitoring and responding. It is a computerized, non-assisted method for monitoring quality of wakefulness and detecting sleep onset without polysomnography. The OSLER has been validated in patients with obstructive sleep apnea (Bennett et al., 1997). In short, this study comprises the SART, PVT, MWT, and OSLER as objective measurements to compare vigilance in daily life of narcolepsy patients before and on treatment with SXB.

METHODS

Subjects

Subjects were patients with type 1 narcolepsy, diagnosed according to the ICSD-3 criteria (American Academy of Sleep Medicine, 2005). A control group was included to which baseline measurements of sustained attention and sleep resistance were compared. Healthy controls were matched for age and sex. Patients were treatment-naïve and were scheduled to start with SXB or were already using SXB and were prepared to stop medication at least 14 days prior to the study start. The decision for treatment with SXB was part of their therapeutic plan; i.e. no patients were put on SXB treatment for the purpose of participation in this study. Exclusion criteria for both patients and controls were cognitive impairment due to neurological disorders other than sleep-wake

disorders, the use of hypnotics or sleep-wake active drugs other than SXB, and age below 18 or above 70 years.

Twenty-six patients (16 males) were recruited from the narcolepsy outpatient clinics of Leiden University Medical Centre, The Netherlands and University Hospital Zurich, Switzerland between 2007 and 2012. Fifteen controls (8 males) were recruited using notices in local newspapers. The mean age in the patient group was 34.8 years compared to 34.1 years in the control group. Thirteen narcoleptics were available for the second study part. The average of their scheduled treatment dosages was 5.5 g SXB/day.

The protocol was approved by the medical ethical committees of both institutions and written informed consent was obtained from all subjects prior to the study.

Design

The study comprised a nine-day protocol (Figure 1) consisting of two days of in-laboratory sleep resistance tests and a seven-day in-field, i.e. out-of-hospital period of portable vigilance battery measurements. Controls followed the procedure once. Narcolepsy patients followed this procedure before and three months after stable single-drug treatment with the usual therapeutic dose of SXB (4.5 – 9.0 g/day), prescribed by their treating physician.

Figure 1 Overview of study design

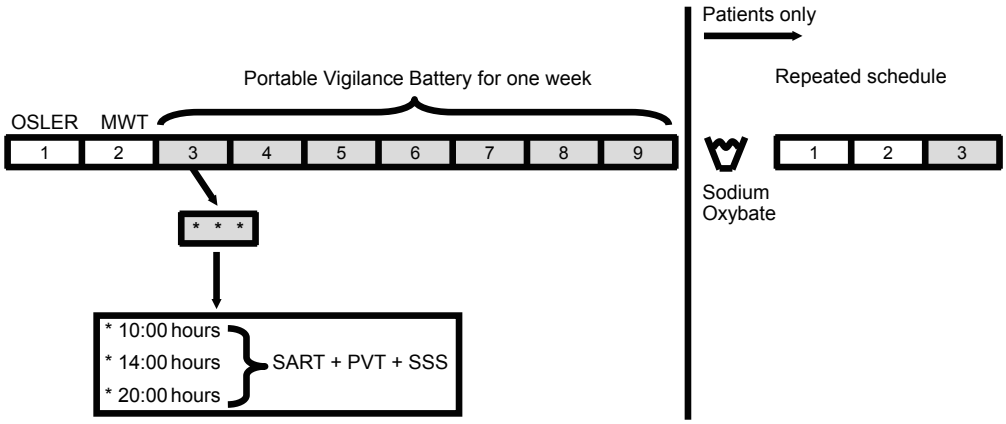

Figure 1: The nine-day protocol consisted of two days of in-laboratory sleep resistance tests and a seven-day in-field, i.e. out-of-hospital period of portable vigilance battery measurements. Controls followed the procedure once. Narcolepsy patients followed this procedure before and three months after stable single-drug treatment with the usual therapeutic dose of SXB, prescribed by their treating physician. SART: Sustained Attention to Response Task; PVT: Psychomotor Vigilance Test; SSS: Stanford Sleepiness Scale; OSLER: Oxford Sleep Resistance; MWT: Maintenance of Wakefulness Test.

Measurements

Vigilance test battery

SART

A number from 1 to 9 was presented 225 times in white on a black computer screen over a 4-minute 19-second period as described previously (Fronczek et al., 2006). Each of the 9 numbers was presented 25 times in a predetermined and quasi-random way so that identical numbers were not clustered. Subjects had to respond to the appearance of each number by pressing a small button, except when the number was a 3. Subjects had to press the button before the next number appeared and were instructed to give equal importance to accuracy and speed in performing the task. The SART error score consisted of the total number of errors, expressed as the sum of the times a key was pressed when no key should have been pressed (i.e. after a '3', the so-called commission errors), and the times when no key was pressed when it should have been (i.e. after anything but a '3', the so-called omission errors).

PVT

Subjects were instructed to press a button as quickly as possible to stop a digital millisecond counter, which started to scroll at variable intervals ranging from 2-10 seconds. Each PVT trial lasted for 10 minutes. We considered the average of the reciprocal RTs (1/RT) the main outcome parameter (Basner and Dinges, 2011), and analyzed the percentage of lapses as secondary outcome parameter.

Subjects received a pocketsize personal digital assistant (PDA) computer to perform SART, PVT and administer the Stanford Sleepiness Scale (SSS) (Hoddes et al., 1973), a seven-point visual-analogue scale to assess momentary EDS, in a 15-minute task battery. Subjects had to take this PDA with them wherever they went during the next seven days. The device could only be turned on during 1-hour-intervals around 10:00 hrs, 14:00 hrs and 20:00 hrs, and gave an acoustic signal at the start of each period. When turned on, instructions appeared on the screen, followed by the SSS. This was followed by a single session of the SART and PVT in random order. Subjects practiced the portable vigilance test battery in the sleep laboratory to assure their familiarity with the device for the start of the ambulatory study part.

MWT

The MWT consisted of four 40-minute sessions in a quiet and dimly lit room according to the AASM recommendations (Littner et al., 2005). The first session started between 1.5 and 3 hours after a participant's usual wake-up time. Consecutive sessions were performed

at two-hour intervals. Subjects were instructed to stay awake while comfortably seated in a semi-supine position. Movements or vocalizations were not allowed. The session was terminated either when sleep onset occurred, defined as three consecutive epochs of stage 1 sleep, or one epoch of any other stage of sleep, or after 40 minutes of being awake. We assessed the mean of the four sleep-onset latencies.

OSLER

The OSLER follows the schedule of the MWT and subjects were similarly positioned. In addition, the participant's dominant hand was placed on a box held in the lap. The index finger was placed on a non-recoil proximity sensor with a sensing distance of 1–2 mm, which transmitted signals of finger contact to a computer. A light-emitting diode was positioned four to six feet away at eye level in the frontal visual field. The light flashed regularly for 1 second every 3 seconds. Subjects were instructed to keep their finger in contact with the button, and to remove the finger for 1 second when the red light flashed. Sleep onset was defined as seven consecutive omissions, i.e. non-responding to flashes for ≥ 18 seconds. The session was terminated when sleep-onset occurred or after 40 minutes of being awake. The mean of the four sleep-onset latencies, a measure of sleep resistance, was considered the primary outcome measure.

By the registration of correct and missed responses before the occurrence of sleep onset, the OSLER may also be interpreted as a measure of sustained attention. We included the following sustained attention outcome measures: the number of omissions per session ($OSLER_{OMIS}$), and the number of omissions per minute test duration ($OSLER_{OMIS/MIN}$).

Actigraphy

Actigraphic data were acquired using wrist actigraphy (on the non-dominant wrist; light sensor data included, Actiwatch, Neurotechnology) (Ancoli-Israel et al., 2003). Determination of the estimated "time in bed" relied on a software algorithm using the activity data recorded by the Actiwatch (Actiwatch Sleep Analysis Version 5, Neurotechnology). The validity of the estimated time in bed detection was improved by using light information and sleep dairy information additionally to set "bed time" and "get-up time". Actigraphic data have been recorded during the week before and week of the in-field study part.

Statistical Analysis

Statistical analysis comprised comparisons of outcome measures between baseline measurements for patients and controls, and before and after treatment with SXB for patients. Data were analyzed using IBM® SPSS® Statistics version 20.

PDA data handling

The in-field nature of the PDA measurements allowed for test sessions being started, but not actually performed due to conflicting demands or technical difficulties at the time of registration. Since the results of all started tests were automatically saved without the possibility of objective verification of their reliability (there was a subjective assessment in the form of a question about having been disturbed while performing the test), unreliable test results had to be filtered out in retrospect before starting the analyses to reduce the type I error in the data obtained from the PDA (Matthias R. Mehl, 2012). The following criteria were defined based on in-laboratory obtained 95th percentile or maximum values for various SART and PVT measurements (Loh et al., 2004, Van Schie et al., 2012) (partially based on unpublished data): SART sessions were regarded unreliable if (1) 50% of RTs were < 200 ms or > 600 ms, (2) if the number of omission errors exceeded 100 for patients or 15 for controls, or (3) if the number of omissions errors was between 40-100 for patients or 10-15 for controls *and* responses to the questions were missing. PVT sessions were filtered out if (1) < 30 responses were recorded (maximum ~ 70-100), (2) if > 50 errors of commission were recorded, or (3) if 50% of responses was > 1000 ms, or 90% of responses > 500 ms. In addition, SART and PVT sessions were regarded unreliable if they concerned abundant sessions (i.e. performed at day 8 or later).

As the number of reliable sessions could differ between subjects from 0 to 21, the outcome measures were separately grouped for time of day within a subject. This resulted in three average values (morning, afternoon, evening) per outcome measure (SART error count, PVT 1/RT) for each subject. To further enhance reliability, only average values with a weight ≥ two original sessions were used in the analyses. 'Average' values consisting of one original session were artificially made missing.

Due to these restrictions, the number of participants with available, reliable PDA data is slightly lower than the total number of participants for certain study parts. Table 1 presents these numbers, as well as the exact number of sessions used in the analyses of the PDA study part. Table 2 illustrates the proportion of PDA sessions available for patients and controls in more detail: firstly irrespective of their reliability, secondly as the proportion of reliable sessions available. The proportions did not differ significantly between patients and controls or before and after treatment with SXB in narcoleptics.

Comparison of narcoleptic patients and controls

Differences between the patient and control groups were primarily analyzed by means of linear mixed effect models (LMMs) of the outcome parameters. The analyses were adjusted for age, time of day and centre, as well as for all two- and three-way interactions between group, time of day and centre. For the PDA measurements, time of day comprised a variable indicating whether the average value was derived from morning, afternoon of evening sessions. "Time of day" for the OSLER and MWT measurements was different

from the PDA measurements and was therefore called differently: since the four sessions were separately analyzed (instead of averaged) to take into account possible fluctuations of sleepiness and vigilance across the day, this variable was called "session".

Table 1 – Group sizes

	Controls	**Narcolepsy patients at baseline**	**Narcolepsy patients on SXB**
SART error count	N = 14 (k = 183)	N = 23 (k = 346)	N = 13 (k = 174)
PVT 1/RT	N = 14 (k = 181)	N = 22 (k = 329)	N = 12 (k = 144)
OSLER	N = 10	N = 22	N = 13
MWT	N = 15	N = 24	N = 13

Legend: SXB: sodium oxybate; N: number of subjects; k: number of sessions; 1/RT: average of reciprocal reaction times. Because of time restraints, 5 controls and 2 narcolepsy patients did not participate in the OSLER study part.

Table 2 – Proportion of PDA sessions performed

	SART at baseline	**SART on SXB**	**PVT at baseline**	**PVT on SXB**
	Proportion of sessions performed: number of sessions performed / 21			
Controls	0.72 (0.60-0.92)	N.A.	0.71 (0.60–0.95)	N.A.
Patients	0.81 (0.67-0.95)	0.62 (0.38-0.90)	0.81 (0.67-0.95)	0.62 (0.38-0.90)
	Proportion of reliable sessions: number of reliable sessions performed / number of sessions performed			
Controls	0.94 (0.84-1.00)	N.A.	0.98 (0.70-1.00)	N.A.
Patients	1.00 (0.89-1.00)	1.00 (0.90-1.00)	1.00 (0.95-1.00)	1.00 (0.85-1.00)

Data are presented as median with 25^{th}–75^{th} percentiles. No significant differences were found between patients and controls or between baseline and post-treatment conditions for patients.
Legend: SXB: Sodium oxybate; NA: not applicable. The number 21 reflects the maximum number of sessions that subjects could have performed, i.e. three sessions per day for seven days.

Thanks to the LMM approach, it was possible to analyze data of subjects with missing values for certain outcome values or time points. Multiple comparisons, inherent to the LMM approach, were accounted for by Bonferroni-Holm adjusted significance levels (adjusted from 0.05) (Holm, 1979). To facilitate the interpretation of *P* values in the context of varying significance levels resulting from this correction, all significant values are marked with an asterisk (*).

Secondarily to the LMMs, the non-parametrical Mann-Whitney U test was used for two-group comparisons in case the assumption of normality had to be dropped, even after data transformation.

Figure 2 Vigilance study parameters from patients vs. controls

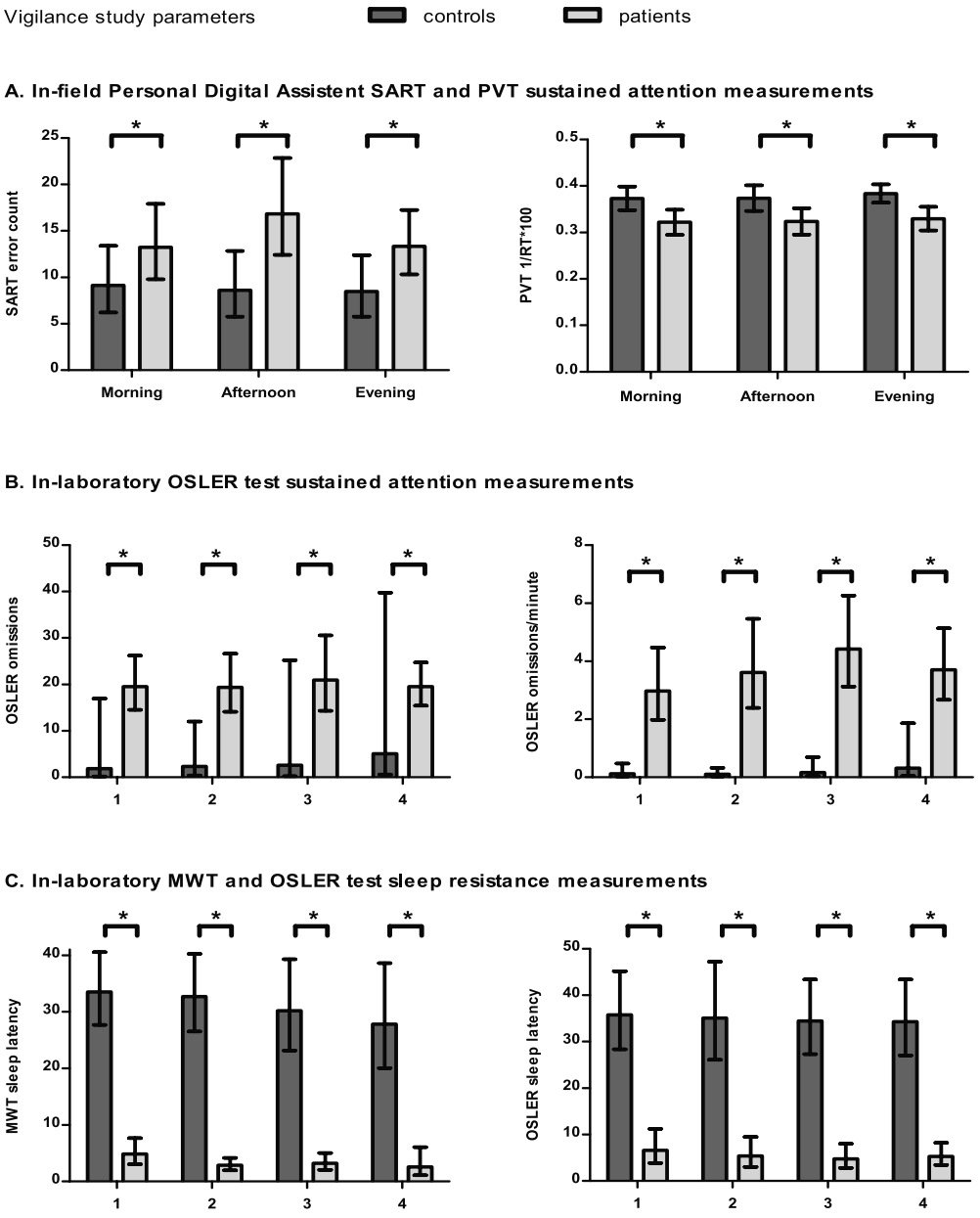

Figure 2: A. Comparisons of seven-day in-field SART and PVT measurements. **B.** Comparisons of one-day in-laboratory MWT and OSLER measurements. Data are presented as geometrical means with 95% confidence intervals. Asterisks (*) flag significant differences between patients and controls. SART: Sustained Attention to Response Task; PVT: Psychomotor Vigilance Test; RT: reaction time; OSLER: Oxford Sleep Resistance; MWT: Maintenance of Wakefulness Test.

Figure 3 Vigilance study parameters before vs. on SXB treatment

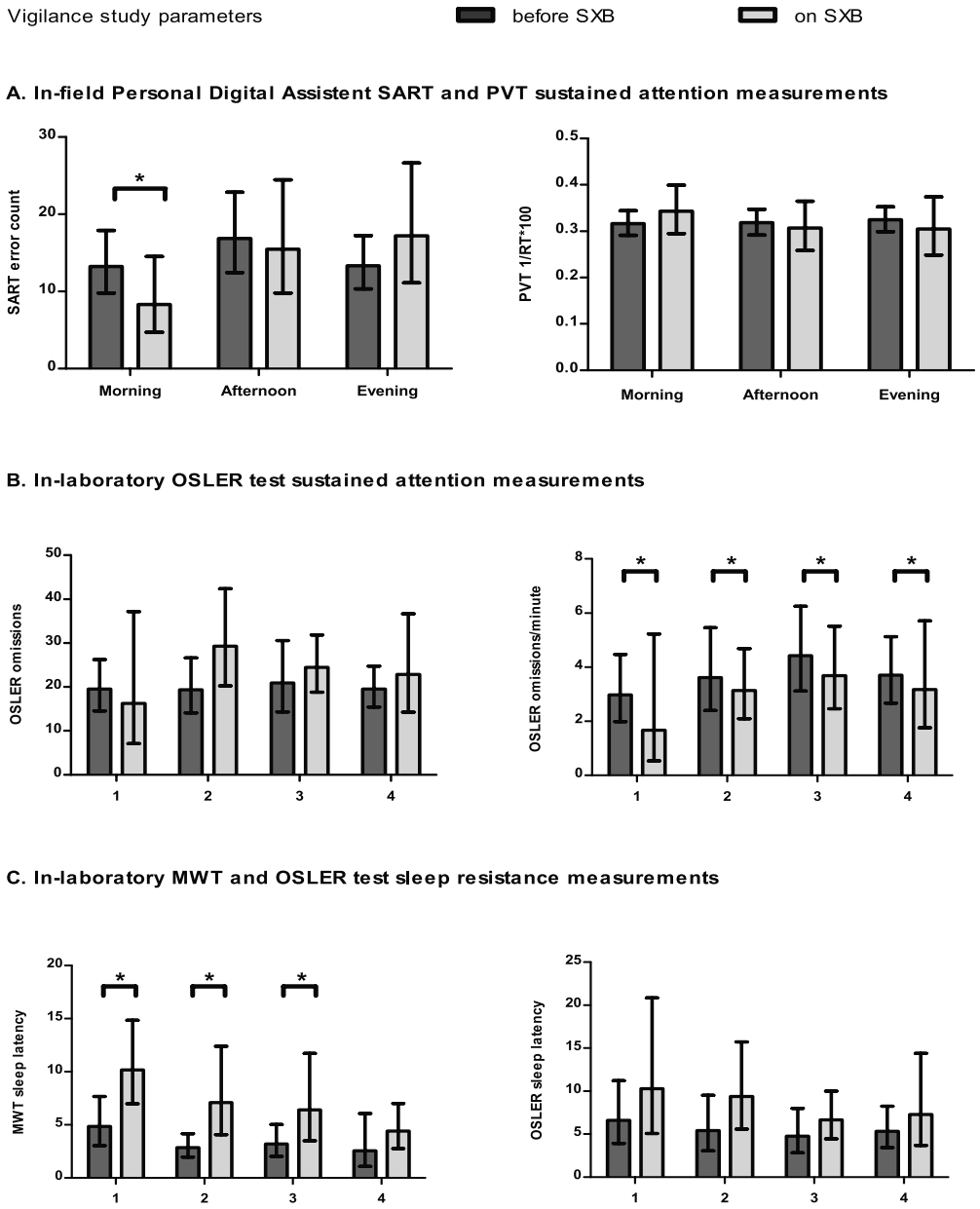

Figure 3: A. Comparisons of seven-day in-field SART and PVT measurements. **B.** Comparisons of one-day in-laboratory MWT and OSLER measurements. Data are presented as geometrical means with 95% confidence intervals. Asterisks (*) flag significant differences between pre-treatment and post-treatment conditions. SART: Sustained Attention to Response Task; PVT: Psychomotor Vigilance Test; RT: reaction time; OSLER: Oxford Sleep Resistance; MWT: Maintenance of Wakefulness Test.

Comparison of narcolepsy patients before and on treatment with SXB

On-treatment data were compared to pre-treatment data of all subjects by LMM analyses similar to those described above. Instead of "group", which was used in the previous comparison, "visit" was analyzed as a factor, which indicated whether measurements were derived from a baseline visit or a post-treatment visit.

Unless specified otherwise, data are presented as median with 25^{th}–75^{th} percentiles in this paper, because most values did not follow a standard normal distribution. Data transformations are indicated in table legends if applicable.

RESULTS

Comparison of narcolepsy patients and controls

Geometrical group means of SART, PVT, OSLER and MWT data are presented in Figure 2. Asterisks flag significant differences resulting from the analyses described below.

Measurements of sustained attention

SART error count was significantly higher in patients than in controls ($P < 0.01$) according to the LMM presented in Table 3. The reciprocal average RT of the PVT was significantly lower in patients compared to controls, i.e. their RT was significantly higher ($P < 0.01$). The proportion of lapses on the PVT was significantly higher in narcolepsy patients (0.10, 0.04-0.19) than in controls (0.02, 0.01-0.05, $P < 0.01$). The average number of omissions on the OSLER was significantly higher in narcoleptics (23.0, 16.0-31.6) than in controls (4.7, 3.4-26.8, $P = 0.01$), which was the same for the number of omissions per minute test duration (4.1, 3.2-6.2 compared to 0.1, 0.1-1.1, $P < 0.01$). Age was inversely correlated with SART error count ($P < 0.01$), but not with PVT or OSLER sustained attention measures.

Measurements of sleep resistance

The MWT sleep latency was 38.5 minutes (23.5-40.0) for controls compared to 4.1 (2.4-5.9) for narcoleptics at baseline ($P < 0.01$). A similar pattern was observed for the OSLER sleep latency, which was 40.0 minutes (33.0-40.0) for controls compared to 8.0 (4.0-15.3) for narcoleptics ($P < 0.01$).

Comparison of narcolepsy patients before and on treatment with SXB

Geometrical group means of SART, PVT, OSLER and MWT data are presented in Figure 3. Asterisks flag significant differences resulting from the analyses described below.

Table 3 – Linear Mixed Models (LMM) of PDA data compared between patients and controls

	SART error count°		**PVT 1/RT*100**	
Cov. matrix	*CS*		*AR1*	
Model parameters				
Basis	***Beta / S.E. / P***			
Intercept	1.04/0.11/0.00	*	0.39/0.02/0.00	*
Target factors	***Beta / S.E. / P***			
Group (G)	0.42/0.11/0.00	*	-0.10/0.02/0.00	*
Time (T)	N.A.		N.A.	
Centre (C)	0.40/0.11/0.00	*	-0.02/0.02/0.36	
Interactions	***Beta / S.E. / P***			
G*C	-0.31/0.14/0.04	*	0.09/0.03/0.00	*
Covariates	***Beta / S.E. / P***			
Age	-0.01/0.00/0.00	*	N.A.	

Asterisks flag significant LMM coefficients. Patients made more errors on the SART and responded slower on the PVT compared to controls.
Legend: Beta: regression coefficient derived from the LMM; S.E: standard error of the regression coefficient; N.A: not available, i.e. no significant contribution to the final model; °: log-transformed parameter; Cov: covariance; CS: compound symmetry; AR1: first-order autoregressive.

Model building strategy: The model of the mean was created from a saturated model including all target factors and possible interactions between them, followed by removing non-significant parameters as long as the model fit was not significantly impaired. The interactions G*T, T*C and G*T*C did not contribute significantly to any of the tested models and were therefore omitted from this table. Target factor coding: Group: 0=controls, 1=patients; Centre: 0=Zurich, 1=Leiden.

Measurements of sustained attention

SXB treatment decreased SART error count according to the LMM presented in Table 4 (P = 0.01). Furthermore, there was a trend towards an interaction of treatment with time of day (P = 0.03), indicating that the significantly lower error count was most pronounced in the morning SART sessions on SXB treatment, but less in the afternoon and evening sessions. PVT 1/RT *per se* was not changed after treatment with SXB, but was significantly lower in the afternoon and evening PVT sessions compared to the morning session on treatment (P = 0.01). The PVT proportion of lapses was not significantly different before (0.10, 0.04-0.19) and on SXB (0.09, 0.03-0.28, P = 0.90). No effect of SXB or any of the other model parameters was found in a LMM analysis of $OSLER_{OMIS}$, as presented in Table 5. In contrast, the number of $OSLER_{OMIS/MIN}$ was significantly decreased on treatment with SXB (P = 0.01). We observed a positive main effect of sessions, indicating that the number of $OSLER_{OMIS/MIN}$ increased during the day. Age was again inversely correlated with SART error count (P < 0.01), as well as $OSLER_{OMIS/MIN}$ and PVT proportion of lapses (R_S -0.323, P < 0.01), but not with PVT 1/RT or $OSLER_{OMIS}$.

Table 4 – Linear Mixed Models (LMM) of baseline versus post-treatment comparisons of PDA data

	SART error count°		**PVT 1/RT*100°**	
Cov matrix	*CS*		*UN*	
Model parameters				
Basis	***Beta / S.E. / P***			
Intercept	1.55/0.13/0.00	*	0.108/0.00/0.00	*
Target factors	***Beta / S.E. / P***			
Visit (V)	-0.18/0.07/0.01	*	0.001/0.00/0.75	
Time (T)	0.01/0.03/0.65		-0.001/0.00/0.32	
Centre (C)	N.A.		0.013/0.01/0.02	
Interactions	***Beta / S.E. / P***			
V*T	0.11/0.05/0.03		-0.005/0.00/0.01	*
V*C	N.A.		N.A.	
T*C	N.A.		0.007/0.00/0.00	*
Covariates	***Beta / S.E. / P***			
Age	-0.01/0.00/0.00	*	N.A.	

Asterisks flag significant LMM coefficients. SXB treatment decreased the number of errors on the SART, but did not alter PVT reciprocal RTs.
Legend: Beta: regression coefficient derived from the LMM; S.E: standard error of the regression coefficient; N.A: not available, i.e. no significant contribution to the final model; °: log-transformed parameter; Cov: covariance; CS: Compound Symmetry; UN: Unstructured.

Model building strategy: The model of the mean was created from a saturated model including all target factors and possible interactions between them, followed by removing non-significant parameters as long as the model fit was not significantly impaired. The interaction V*C did not contribute significantly to any of the tested models and was therefore omitted from this table. Target factor coding: Visit: 0=baseline, 1=post-SXB; Time of day: 0=morning, 1=afternoon, 2=evening; Centre: 0=Zurich, 1=Leiden.

Measurements of sleep resistance

While MWT sleep latency was significantly increased on treatment with SXB ($P < 0.01$), we found no significant effect of treatment on the OSLER sleep latency. However, OSLER sleep latency appeared to decrease across sessions during the day ($P < 0.01$) irrespective of visit (before/after treatment), as no treatment*session interaction was observed. No significant time-of-day effect was found for the MWT sleep latency.

Covariates

Measurements of momentary sleepiness by the SSS did not contribute to any of the tested models and were therefore omitted from all tables.

Age was associated with a minimally higher omission error rate per minute on the OSLER, as well as minimally lower numbers of errors on the SART. Age was not linked to MWT or OSLER sleep latency or to PVT 1/RT.

Table 5 – Linear Mixed Models (LMM) of baseline versus post-treatment comparisons of OSLER and MWT

	OSLER omissions°	**OSLER om/min°**	**OSLER latency°**	**MWT latency°**
Covariance matrix Model parameters	*ARH1*	*UN*	*UN*	*CS*[1]
Basis	***Beta / S.E. / P***			
Intercept	1.36/0.03/ 0.00 *	0.54/0.06/0.00 *	0.88/0.08/0.00 *	0.73/0.09/0.00 *
Target factors	***Beta / S.E. / P***			
Visit (V)	N.A.	-0.11/0.03/0.01 *	N.A.	0.39/0.09/0.00 *
Centre (C)	N.A.	-0.18/0.04/0.00 *	0.07/0.10/0.47	0.05/0.12/0.67
Session (S)	N.A.	0.05/0.01/0.00 *	-0.07/0.01/0.00 *	-0.02/0.02/0.28
Interactions	***Beta / S.E. / P***			
V*C	N.A.	-0.24/0.03/0.00 *	N.A.	N.A.
S*C	N.A.	N.A.	0.06/0.01/0.00 *	-0.04/0.02/0.05
Covariates	***Beta / S.E. / P***			
Age		0.00/0.00/0.05 *	N.A.	N.A.

Asterisks flag significant LMM coefficients. SXB treatment increased MWT but not OSLER sleep latency and decreased the number of OSLER omissions per minute.
Legend: om: omissions; min: minute; Beta: regression coefficient derived from the linear mixed model; S.E: standard error of the regression coefficient; N.A: not available, i.e. no significant contribution to the final model; N.T: not tested in the model; °: log-transformed parameter; [1]: no convergence was reached with any other covariance matrix; ARH1: heterogeneous first-order autoregressive; UN: unstructured; CS: compound symmetry.

Model building strategy: The model of the mean was created from a saturated model including all target factors and possible interactions between them, followed by removing non-significant parameters as long as the model fit was not significantly impaired. The interactions V*S and V*S*C did not contribute significantly to any of the tested models and were therefore omitted from this table. Target factor coding: Visit: 0=baseline, 1=post-SXB; Centre: 0=Zurich, 1=Leiden; Session: 0-3 for the first-fourth session.

SART error counts were higher in Leiden compared to Zurich ($P < 0.01$), especially for controls ($P = 0.04$). Controls in Leiden also had higher PVT reaction times ($P < 0.01$).

There were no site differences for the comparison of SART error count before and after SXB treatment, nor were there main effects of center for PVT 1/RT. On the opposite, a centre*time-of-day interaction effect was observed for PVT 1/RT in narcolepsy patients, i.e. there was a time-of-day effect on PVT 1/RT in Leiden, irrespective of the administration of treatment ($P = 0.01$). Patient versus control comparisons of OSLER and MWT measures did not differ across study sites. The same was found for pre- and on-treatment comparisons of $OSLER_{OMIS}$ and OSLER and MWT sleep latency in narcoleptics. However, there was a significant main effect of centre ($P < 0.01$), as well as a

centre*visit interaction ($P < 0.01$) for $OSLER_{OMIS/MIN}$ in narcolepsy patients, which means that the number of omissions per minute test duration was lower in Leiden, especially on treatment with SXB. The described time-of-day effect on OSLER sleep latency in narcolepsy was less pronounced in Leiden, as indicated by a session*centre interaction ($P < 0.01$).

There was no significant difference in time in bed (night) between controls and narcolepsy at baseline and there was no significant difference in time in bed (night) between narcolepsy patients at baseline and narcolepsy patients during SXB treatment.

DISCUSSION

We investigated sustained attention and sleep resistance in type 1-narcolepsy patients before and during SXB treatment. Sustained attention was measured in normal daily life using the PVT and the SART; and in the sleep laboratory using the $OSLER_{OMIS/MIN}$. Sleep resistance was measured in the sleep laboratory using the MWT and the OSLER sleep latency. Pre-treatment data of narcolepsy patients were compared to data from a matched group of healthy controls. The investigated measurements consistently indicated lower sustained attention and decreased sleep resistance in patients compared to controls. SXB treatment was associated with a better resistance to sleep and a small improvement of sustained attention, i.e. improved wakefulness.

Feasibility of a portable vigilance task battery

Narcolepsy patients and healthy control subjects performed on average 70% of portable SART and PVT sessions in this study, which required subjects to pay attention to three test sessions per day for seven consecutive days and to simultaneously ignore competitive obligations. Narcolepsy patients did not significantly differ from controls in the proportion of sessions performed, indicating the feasibility for these patients to comply with such a demanding protocol. Moreover, over 95% of tests were considered reliable. A shorter protocol is likely to enhance compliance even more.

Quantifying sustained attention and sleep resistance in narcolepsy

Narcolepsy patients had a lower level of sustained attention compared to controls on SART and PVT measurements, as well as on the respective aspects of the OSLER. In other words, both in-field and in-laboratory measurements consistently indicated impaired sustained attention in patients compared to controls.

Compared to previous in-laboratory data, portable SART error count data were approximately 3-4 points higher (Fronczek et al., 2006) and portable PVT RTs were approximately 40-50 ms faster (Dimitrova et al., 2011) for both narcolepsy patients and

controls.

The large difference in MWT sleep latencies between patients and controls is consistent with previous research (Arand et al., 2005, Doghramji et al., 1997). This study indicated that the OSLER was capable of measuring similarly large differences in sleep latency between narcolepsy patients and controls as the MWT.

Sodium oxybate for the treatment of impaired sustained attention and sleep resistance

In line with previous research (The U.S. Xyrem Multicenter Study Group, 2002), we found longer MWT sleep latencies during SXB treatment. On the contrary, OSLER sleep latency was not significantly longer after SXB treatment.

Both in-field (SART) and in-laboratory ($OSLER_{OMIS/MIN}$) error counts were lower during SXB treatment compared to the baseline measurements, whereas PVT reciprocal RT or proportion of lapses was not associated with SXB treatment. Interestingly, the SART and OSLER error counts exhibited a time-of-day variation with the highest performance measured in the morning, i.e. following a night with SXB administration, whereafter performance decreased during the day. As such, this pattern differs from the effect of SXB on cataplexy, which comprises a longer period of time before effects occur. As SXB acts at night to improve sleep duration and has an elimination half-life of 0.5-1.0 hour (The U.S. Xyrem Multicenter Study Group, 2002), the observed improvement of sustained attention in the morning might result from the improved nocturnal sleep duration and stability, for an alerting effect of SXB itself is not expected. This would also clarify why the improvements did not last longer than a few hours: the decreasing sustained attention paralleled the decreasing sleep resistance as the day advanced. An alternative explanation for the observed time-of-day variation might reside in the suppression of dopaminergic neurotransmission by SXB (Maitre, 1997). While SXB has largely disappeared from our body upon awakening, its suppression of dopamine has ended (Donjacour et al., 2011). Hence, from a speculative point of view, it could allow for dopamine to be released in initially high quantities, which positively affects wakefulness.

Partly due to the observed time-of-day variation, the size of the overall differences between treatment conditions for SART and $OSLER_{OMIS/MIN}$ measurements was fairly low (both measurements < 1 error difference), as was the size of the difference for MWT sleep latency (3 minutes). The relatively low mean dosage of SXB used by the study participants might as well have contributed to the low size of differences between treatment conditions. Another explanation may reside in the duration of exposure to SXB treatment. The three months of stable treatment required in this study should suffice to assess a clinical meaningful improvement, but a longer period might be necessary to reach the maximum response (Bogan et al., 2015). Nevertheless, the observed differences in this study may reflect an important clinical effect, similar to observations in modafinil

treatment effect studies: in these studies, differences in MWT sleep latency and Epworth sleepiness scale were also small, but associated with significant clinical improvements measured by clinical global impression scales (The U.S. Xyrem Multicenter Study Group, 1998, 2000). Unfortunately, we did not administer patient-rated clinical effect scales.

Covariates

The covariate age contributed significantly to the models of SART and OSLER sustained attention measurements, but the observed size of this contribution was very small.

This study included populations from Zurich and Leiden, and cultural characteristics could have influenced behavioral measurements. The main differences between the study sites were a worse PDA performance in both patients and controls in Leiden opposed to a better OSLER sustained attention performance of Leiden patients; and a clearer time-of-day effect on the PVT opposed to a less clear time-of-day effect on OSLER sleep resistance in narcolepsy patients at the Leiden site. However, the main findings of the study, i.e. the differences between patients and controls on the one hand and before and on SXB treatment on the other hand were present in both populations.

Limitations

Since actigraphic data of time in bed did not differ between the investigated study groups, the duration of time in bed is unlikely to have confounded our results. It might be considered a shortcoming that we did not assess the chronotypes of our participants, since the possibility of a selection bias between patients and controls in case of different chronotypes between these groups cannot be excluded. However, we did account for the possibility of different chronotypes among our participants by adapting the start of the first session of MWT and OSLER test measurements to a person's regular wake time, as well as by the careful chosen times of the portable vigilance tests, starting not too early (10:00 hours) and finishing not too late (20:00 hours) during the day. Moreover, the comparison between narcolepsy patients at baseline with those during SXB treatment is made within subject, excluding bias due to chronotype differences. Differences in daytime naps, use of caffeinated drinks, and participants' jobs (sedentary/active) might have influenced our results, as we did not register these as covariates during the in-field study phase. This was because we aimed at assessing differences between patients and controls and patients before and during therapy, while living their lives as they normally would do, without restrictions on life style habits or influencing them by asking questions about those habits. In other words, we improved external validity of our data at the expense of internal validity.

The OSLER as a sustained attention task

While the OSLER has been designed as a behavioural and cost-effective alternative to MWT measuring sleep resistance (Bennett et al., 1997), we additionally investigated two behavioural outcome measures: $OSLER_{OMIS}$ and $OSLER_{OMIS/MIN}$. Both measures reflect the behavioural level of vigilance before falling asleep, turning the OSLER into a sustained attention task. In fact, both OSLER and PVT can be considered simple RT tasks, i.e. tasks in which every stimulus requires an active response. While the timing of the stimulus varies from 2-10 seconds in the PVT, it comes at fixed times in the OSLER, creating a monotonous situation.

The number of $OSLER_{OMIS}$ was less sensitive to differences in sustained attention following SXB therapy than the number of $OSLER_{OMIS/MIN}$. This resulted from the simultaneous occurrence of a higher error count and consequently, shorter test duration, as the time to occurrence of seven consecutive errors was shortened. Subjects who could sustain attention for a longer period made a similar number of errors compared to less vigilant subjects (post-hoc analyses), since the duration of their OSLER sessions was longer. Therefore, correcting for test duration would provide a more sensitive measure of sustained attention. This was indeed demonstrated in this study. The sustained attention aspect of the OSLER, reflected by the $OSLER_{OMIS/MIN}$, was even more sensitive to the effects of SXB than the aspect of sleep resistance.

Conclusion

Ambulatory administration of SART and PVT on a PDA was feasible in both narcolepsy patients and controls. PDA SART and PVT measurements as well as in-laboratory OSLER and MWT measurements revealed worse performance for narcolepsy patients compared to controls. In line with previous research, SXB treatment was associated with a better resistance to sleep, measured by the MWT. Moreover, SXB treatment was associated with a small improvement in sustained attention, which was quantified by both OSLER and SART but not PVT. The SART and OSLER offer solutions for a less time- and manpower-consuming evaluation of treatment effects in patients with narcolepsy than PVT and MWT.

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