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Maintenance of Wakefulness Test, real and simulated driving in narcolepsy/hypersomnia patients

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Abstract

Study Objectives: To assess the relationship between real and simulated driving performance and the objective level of alertness as measured by the Maintenance of Wakefulness Test (MWT) in patients suffering from narcolepsy or idiopathic hypersomnia.

Methods: 27 patients (10 patients with narcolepsy, type 1 (n=7) and type 2 (n=3), and 17 patients with idiopathic hypersomnia, mean age=33.8 ± 11.1 years, range=18-65 y; 4 males) were recruited in a randomized, crossover, double-blind placebo-controlled trial and compared to 27 matched healthy controls. Patients were randomly assigned to receive modafinil (400 mg) or placebo before the driving test (2 hours of real and 2 hours of simulated highway driving for each patient). Standard Deviation of Lateral Position (SDLP) of the vehicle in real and simulated driving and mean sleep latency in a 4 x 40min MWT were assessed.

Results: Untreated patients presented shorter sleep latencies on the MWT (20.8 (IQ range 16.1-32.9) vs. 34.9 min (IQ range 28.1-40.0)) and worse simulated driving performance ($P<0.001$) than treated patients. Nevertheless, treated patients still exhibited shorter mean sleep latencies on the MWT than controls (34.9 (IQ range 28.1-40.0) vs. 40 min (IQ range 37.1-40.0), $P<0.05$) but driving performance was identical in both groups. The SDLP of the vehicle in real driving conditions and the MWT score correlated with the SDLP in simulated driving (respectively, $r=0.34$, $P<0.05$ and $r=-0.56$, $P<0.001$).

Conclusions: In patients with narcolepsy/idiopathic hypersomnia, simulated driving and MWT explore different dimensions of fitness-to-drive and could be used complementarily to better evaluate sleep-related driving impairment.

Keywords: Driving simulator, Maintenance of Wakefulness Test, Central Hypersomnia.

Introduction

Sleepiness at the wheel is a major risk factor for highway traffic accidents [1]. Narcolepsy and idiopathic hypersomnia (IH) are rare central disorders that induce severe daytime sleepiness [2, 3]. While less studied for driving risk than OSAS, narcolepsy and idiopathic hypersomnia have been shown to increase the risk of sleep-related accidents [4-12]. The Maintenance of Wakefulness Test (MWT) is a consensus clinical objective test for evaluating excessive daytime sleepiness and is part of the guidelines for driving license legislation for professional drivers in France [13]. In a previous study, we showed that the MWT can be used to predict driving ability in untreated sleep apnea patients [14].

Another concern is the driving ability of both untreated and treated patients with central hypersomnia. Modafinil is the reference drug used to treat excessive daytime sleepiness in patients with narcolepsy and hypersomnia [15, 16]. We demonstrated in real road conditions [10] that modafinil improves driving performance in patients with narcolepsy and idiopathic hypersomnia. Another study [11] showed that patients affected with central disorders of hypersomnolence had an increased risk of car accidents, a finding potentially reversed by long-term treatment.

A question remains regarding the predictability of actual driving performance in untreated and treated patients with central hypersomnia. Driving simulation is an attractive and safe method for assessing driving behavior. A study [17] demonstrated that untreated patients with narcolepsy and sleep apnea had impaired driving performance on a simulated driving task compared to healthy controls. Another [18] compared MWT scores with simulated driving performance in healthy sleep-deprived volunteers and provided evidence that an objective measure of sleepiness predicted simulated performance. Finally, a driving simulator was found to predict driving ability in patients with untreated narcolepsy [7]. Nevertheless, the

driving simulators used in all these studies were not designed specifically to be compared with real driving performance. Our group developed a research program sponsored by the French Ministry of Transport to design and test a simple driving simulator reproducing very precisely the driving scenario of a real freeway located near our sleep laboratory. We published a validation study of this driving simulator in sleep-deprived subjects [19] and have now used it to measure the driving performance of narcoleptic/hypersomniac patients.

To our knowledge, no study to date has compared the relationships between real driving performance, simulated driving performance and objective sleepiness in patients suffering from central hypersomnia, yet these are important questions to be able to provide a complementary means of evaluating fitness-to-drive in addition to the classical MWT in this at-risk patient population.

Methods

Twenty-seven patients with narcolepsy (narcolepsy type 1 (NT1) or type 2 (NT2)) or idiopathic hypersomnia (IH) were recruited in a randomized double-blind placebo-controlled crossover study (modafinil versus placebo). **Patients were diagnosed according to the criteria of the current International Classification of Sleep Disorders (ICSD-3, 2014) [20].** Anti-cataplectic medication was maintained for NT1 patients. Twenty-seven healthy control participants matched by age and gender with patients were recruited outside of the sleep clinic.

Design

Patients recruited in the sleep clinic were randomly assigned to receive modafinil (400 mg/day) or placebo for 5 days prior to the driving test. Treatment was administered at 08:00 (modafinil 2×100 mg) and 12:30 (modafinil 2×100 mg). In each condition, a period of 3 days at home with actigraphy recordings and a sleep diary was followed by 2 days to perform a 4 ×

40-min MWT (10H, 12H, 14H and 16H) and a 2-h on-road and simulator driving session. Simulated driving tests were performed either at 10H or 14H in a counterbalanced order while real driving tests were performed at 17H for logistic reasons. Nocturnal sleep was controlled by polysomnography (PSG) (time in bed from 23H to 7H). Each condition was separated by at least 3 weeks of washout.

Each of the 27 control participants underwent a clinical interview and examination by a sleep medicine specialist. We excluded participants with any complaint of sleep disorders as reported on the Basic Nordic Sleep Questionnaire [BNSQ] [21] and subjective EDS based upon the ESS (score > 10) [22]. The presence of nocturnal sleep-disordered breathing (apnea–hypopnea index [AHI] > 5/hr) and periodic limb movements (PLM index > 5/hr) were ruled out through polysomnography recording in the laboratory. Control participants were paid 150 euros for their involvement in the study.

All participants provided written informed consent and the local ethical committee (consultative committee for the protection of persons participating in biomedical research, Comité de Protection des Personnes [CPP] Sud-Ouest et Outre Mer III) approved the study.

Driving evaluation

Our team developed a specific simulator called INRETS-MSIS SIM2 to determine whether it could identify the same impact of sleepiness (i.e., extended wakefulness) and fatigue (i.e., 2-, 4- and 8-h prolonged nocturnal driving) as that obtained in real-life driving used as a gold standard [19]. It was specially equipped with the reconstructed scenario of the real-life highway experiments. The simulator [19] has been shown in healthy subjects to measure nocturnal driving impairment appropriately compared to real driving conditions [23] in a dose-response design of extended wakefulness and duration of driving. It comprises a computer and a video-game steering wheel with no force feedback applied. The participant's

head was situated 60 cm in front of the screen. The resolution of the visual scene was 1024 × 768 pixels and the update rate was 60 Hz. The simulator displayed a highway driving scene on a 19-in screen. The simulated road surface was colored and the scene visibility corresponded to clear daytime conditions with no traffic. The highway geometry depicted in the simulation was a reconstruction, in virtual reality, of a real highway (A62 between Agen and Langon, France). This reconstruction was based on the topographic layout which consists of a 2-lane highway. Lane widths and road marks were incorporated into the simulation in order to obtain similar road perceptions to those in real driving. The car's speed was set by the experimenter at 130 km/h and participants were instructed to drive in the center of the right-hand lane. Environmental lighting at eye level was about 150 lux.

Real world driving performance was identified by a Continental Automotive (Toulouse, France) video system, recording the lateral position (cm) of the car (10 times/sec) from the right lateral lane marker of the road.

The mean standard deviation of lateral position (SDLP) of the vehicle in real and simulated driving was measured to assess the weaving of the car during the driving session [24-26].

Objective sleepiness evaluation

Mean sleep latency was assessed by the MWT to evaluate the ability of patients to fight against sleepiness in a soporific condition during a longer duration. Objective sleepiness was assessed with four 40-min MWT trials performed at 10H, 12H, 14H, and 16H, as recommended by the American Academy of Sleep Medicine (AASM) [27]. Electroencephalograms (F3/A2, C3/A2, O1/A2), electromyograms and electro-oculograms

were recorded according to the recommendations of the AASM [28]. Data were recorded and manually analyzed in 30-sec epochs. Sleep onset was defined as the first epoch of greater than 15 sec of cumulative sleep in a 30-sec epoch. The test was ended after three continuous epochs of stage N1 or one epoch of any other sleep stage to avoid interfering with sleep homeostasis [27]. Patients who did not sleep during a trial were assigned a value of 40 min. Patients were video-monitored during the whole test. The mean sleep latency of the four MWT trials was then calculated. Patients were not allowed to sleep between the tests.

Statistical Analysis

Demographic and clinical characteristics were expressed as mean ± standard deviation (SD). Quantitative variables were expressed as median and interquartile (IQ) range.

The Mann-Whitney *U* test was used to identify whether subjective and objective sleepiness scores differed between the two independent groups (idiopathic hypersomnia vs. narcolepsy). The Wilcoxon matched-pairs signed-rank test was used to identify whether MWT scores and real and simulated driving performance differed between the treatment conditions in patients (placebo vs. modafinil). The Mann-Whitney *U* test was used to identify whether MWT scores and real and simulated driving performance differed between the two independent groups (treated patients vs. controls). Rho Spearman correlations were computed to measure the association between simulated driving performance and real driving performance**, objective sleepiness (MWT and MSLT scores) and subjective ESS score.** The data for the real-driving condition used for these analyses were published in a previous study [10]. The alpha risk threshold was set at $P = .05$. All analyses were performed using the SPSS statistical software package (v18.0.0, SPSS Inc., Chicago, USA).

Results

Participants

Twenty-seven patients (7 with narcolepsy type 1 (NT1), 3 with narcolepsy type 2 (NT2) and 17 with idiopathic hypersomnia (IH); mean age = 33.9 ± 10.9 years, range = 21-59 y; 4 males), were evaluated. The mean Epworth Sleepiness Scale score was 16.6 ± 3.8 (range, 11-23). The mean MWT score was 23.2 min ± 9.9 (range, 8.5-40). The mean IAH was 2.2 events/hr ± 3.3 (range, 0-15) and the mean PLM index was 1.1 events/hr ± 2.1 (range, 0-8.5). The mean sleep latency in the Multiple Sleep Latency Test (MSLT) was 7.1 min ± 2.8.

No difference in sleepiness appears between untreated idiopathic hypersomnia and narcolepsy groups on ESS score (Mann-Whitney *U* test, Z = 1.683, NS), mean sleep latency on the MSLT (Mann-Whitney *U* test, Z = -0.956, NS) nor on sleep latency on MWT (Mann-Whitney *U* test, Z = 0.485, NS). Table 1 present clinical characteristics of patients with narcolepsy or idiopathic hypersomnia.

Twenty-seven healthy control participants (age = 33.3 ± 10.4 years, range = 21-62 y, 4 males) matched by age and gender with patients were evaluated. One control participant stopped owing to discomfort and sickness during the simulated driving experiment.

Driving performance versus mean sleep latency on MSLT and ESS score

In untreated patients, the SDLP in real and simulated driving does not correlate with the ESS score (respectively, r = 0.06, NS and r = -0.11, NS) nor with the MSLT sleep latencies (r = -0.05, NS and r = -0.00, NS). Moreover, no correlation was observed between mean sleep latencies in the MSLT and MWT (r = -0.21, NS).

MWT scores and simulated driving performance of hypersomniac/narcoleptic patients versus controls

Table 2 present MWT scores and simulated driving performance in untreated and treated patients suffering from narcolepsy/hypersomnia and in matched controls. Treated patients improved their MWT scores and driving performance (compared to untreated condition) but did not recover MWT scores comparable to that of control subjects.

Simulated driving performance versus real driving performance

In patients suffering from narcolepsy or IH, the SDLP in real driving correlated significantly with the SDLP in simulated driving ($r = 0.34$, $P < 0.05$) (See Figure 1).

Simulated driving performance versus mean sleep latency on MWT

The SDLP correlated significantly with the mean sleep latency on the MWT in patients suffering from narcolepsy or IH ($r = -0.56$, $P<0.001$) (See Figure 2).

Discussion

This study shows that simulated driving performance in addition to mean sleep latency on the MWT are correlated with real driving performance in narcoleptic/hypersomniac patients. We previously showed that modafinil improves real driving in both patients with narcolepsy and idiopathic hypersomnia [10]. Here, we confirm this finding in simulated driving performance introducing a new and easily implementable task to quantify sleep-related driving risk.

Our findings show that the MWT and the driving simulation task are both complementary indicators of real driving performance. Interestingly, MWT and simulated driving provided different values in treated patients and control subjects; MWT performance was lower in treated patients than in controls while simulated driving performance was

identical in both groups. Both tests involve an identical process reflecting the difficulty in remaining awake during a monotonous situation. However, driving involves factors other than the level of alertness. The driving impairment experienced by patients very likely stems from a difficulty not only in remaining alert but also attentive. The MWT is an indicator of the ability to stay awake and could be complemented by the driving simulator task, which is closer to real driving and probably more appropriate for assessing cognitive processes including vigilance and lane control.

Driving performance does not correlate with sleep latency on the MSLT but significantly correlate with the mean MWT score. Therefore, this result corroborates the idea that MWT and MSLT measure different abilities or kinds of sleepiness [29, 30]. The ability to stay awake seems inherently different from the ability to fall asleep. The MWT measures sleep tendency plus several arousal components while the MSLT is a relatively pure measure of sleep propensity. An activity requiring safety such as driving is closer to the measurement of the ability to maintain alertness than to the proneness to fall asleep [2].

In narcoleptic/hypersomniac patients, driving simulation could be used as a first-line test to evaluate driving performance before measuring objective measure of alertness. Efficient performance on the driving simulator could be complemented by an MWT to confirm a patient's ability to drive if he reports feeling sleepy at the wheel.

If patients perform poorly on the simulator, they could be clinically reevaluated and have their treatment readjusted. Sleepiness could therefore be tested by MWT as well as by a new driving test. In addition, some patients who have to perform the MWT for legal reasons remain moderately sleepy during the test but still have good simulated driving performance. Therefore, simulated driving performance could complement MWT results in such patients to evaluate their fitness to drive. We recommend that simulated driving performance resulting in

an SDLP > 40, a value which represents the median in untreated patients and the last quartile in treated patients and in controls, should be considered as a pathological threshold defining driving risk.

A limitation of our study concerns the lack of statistical power due to our sample size so we were unable to perform sub-analyses in treated and untreated patients. Nevertheless, our results are still valid overall because a global measure of driving impairment is required in clinical practice. A recent study [11] showed that patients suffering from central disorders of hypersomnolence had an increased risk of recent car crashes, a finding potentially reversed by long-term treatment. Treatment duration in terms of stable treatment is an important factor for studying the beneficial effect of modafinil on real driving performance. If simulated driving performance could be re-evaluated after 6 months or one year of treatment, it could confirm its predictive value in the long term.

In summary, our results highlight the complementary value of a simulated driving test in addition to the MWT when assessing driving risk. The use of validated simulators among the sleep community would be a reasonable goal to harmonize evaluation of the ability to drive in patients suffering from central hypersomnia. **The best way to standardize driving simulator approach is to use a common simulated driving task and to implement it in a single protocol with a fixed timing. Indeed, a study [29] found a reproducibility of simulated driving performance across time. A 1-hour unique session of simulated driving seems relevant.** Larger data sets are also needed to obtain normative values and cut-off points for simulated driving tests in other types of patients and to identify the period when simulated driving is the most predictive.

Author contributions:

1) Conception and design of the study: PS, OC, SE, DD, PP, 2) acquisition and analysis of data: PS, JAMF, PP or 3) drafting a significant portion of the manuscript or figures: PS, JAMF, OC, DL, SE, DD, RL, YD, PP.

Disclosure Statement:

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Figure Legends

Figure 1. Association of stability of trajectory in real driving conditions with stability of trajectory in simulated driving conditions.

Figure 2. Association of stability of trajectory in simulated driving conditions with objective sleepiness (i.e., mean sleep latency on MWT).

Table 1. Clinical features of patients with narcolepsy or idiopathic hypersomnia (Mean ± Standard deviation).

	Narcoleptic patients (n=10)	**Hypersomniac patients** (n=17)
Age (years)	37.2 ± 13.8	31.9 ± 8.7
Gender (% females)	70.0%	94.1%
BMI (kg/m^2)	23.5 ± 5.5	22.3 ± 3.8
ESS score	18.1 ± 3.9	15.6 ± 3.5
MSLT		
Mean Sleep Latency (min)	6.3 ± 2.6	7.5 ± 2.9
Number of SOREMPs ≥2	2 ± 1.3	0.6 ± 0.8
Cataplexy (%)	70	Na
CSF Hypocretin-1 Level (pg/mL)	246.5 ± 27.6	286.6 ± 71.4
Duration of illness (years)	17.7 ± 14.6	13.2 ± 5.1
Established Diagnosis (years)	8.7 ± 6.4	5.8 ± 4.2
AHI	3.5 ± 5.1	1.5 ± 1.7
PLM Index	1.8 ± 2.9	0.7 ± 1.6

Abbreviations. Na = not applicable; BMI = Body Mass Index; ESS = Epworth Sleepiness Scale; MSLT = Multiple Sleep Latency Test; SOREMP = number of Sleep Onset REM Periods in 5 naps; CSF = Cerebrospinal Fluid; AHI = Apnea/Hypopnea Index; PLM = Periodic Limb Movements.

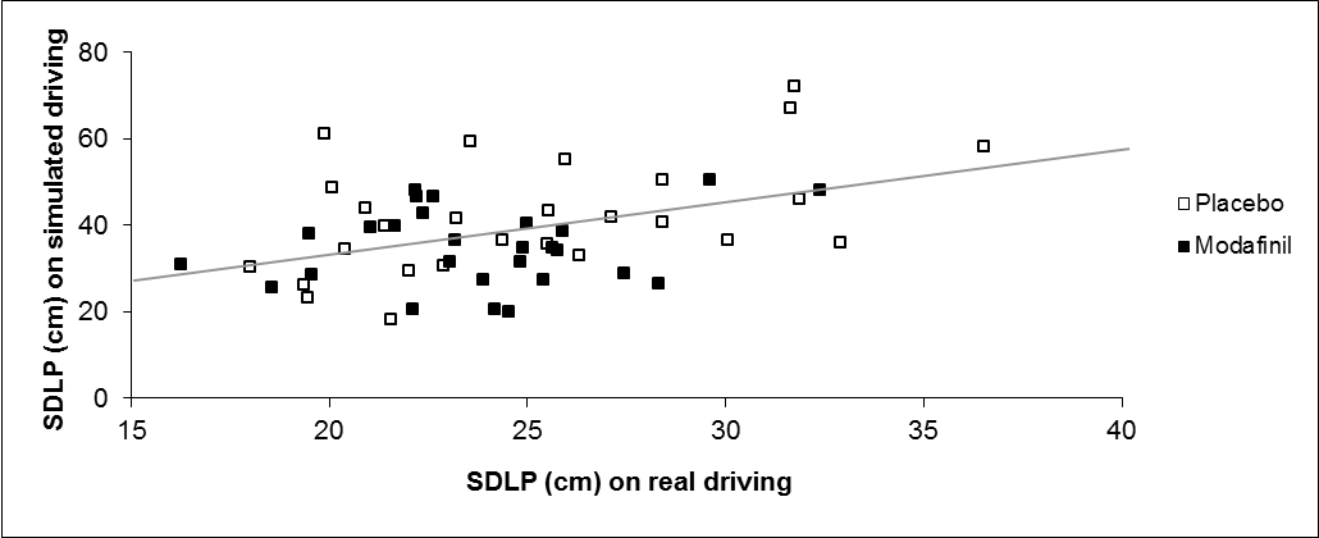
Table 2. Median and interquartile (IQ) in untreated and treated patients suffering from narcolepsy/hypersomnia and in matched controls. Wilcoxon matched-pairs signed-rank test and Mann-Whitney *U* test comparisons.

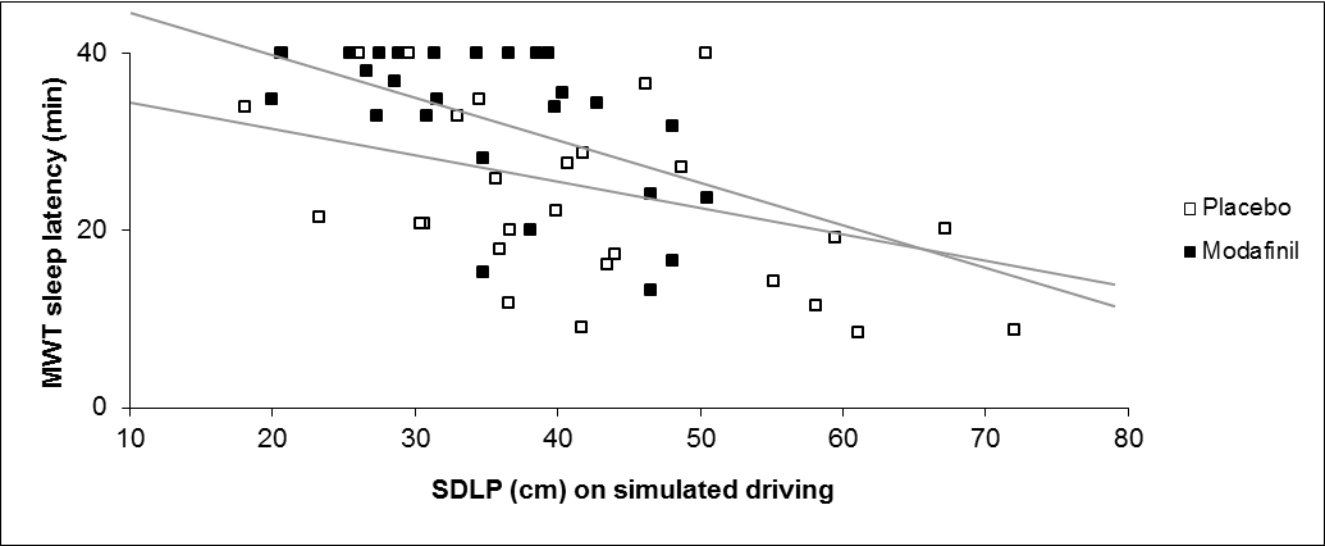
	Median (IQ range)	Median (IQ range)	Wilcoxon test, *P*	Median (IQ range)	Mann-Whitney *U* test, *P*
	Untreated patients	Treated patients	Untreated vs. treated patients	Controls	Treated patients vs. controls
Mean Sleep Latency MWT (min)	20.8 (16.1-32.9)	34.9 (28.1-40.0)	Z = 4.085 ***	40.0 (37.1-40.0)	Z = -2.482 *
Simulated driving					
SDLP	40.7 (33.0-50.4)	34.8 (27.5-40.3)	Z = 3.291 ***	36.0 (27.8-40.6)	Z = 0.001, NS

Note. MWT = Maintenance of Wakefulness Test; SDLP = Standard Deviation of Lateral Position.

* P<.05

*** P<.001


SDLP (cm) on simulated driving
80
60
40
20
0
15
20
25
30
35
40
SDLP (cm) on real driving
Placebo
Modafinil


MWT sleep latency (min)
40
20
0
10
20
30
40
50
60
70
80
SDLP (cm) on simulated driving
Placebo
Modafinil