

Claire E.H.M. Donjacour, Monique A.J. Mets,
Aurora J.A.E. van de Loo, and Joris C. Verster

Introduction

Excessive daytime sleepiness (EDS), cataplexy, hypnagogic hallucinations, sleep paralysis, and nocturnal sleep disturbances are the best known symptoms of narcolepsy. Although less well described, but important in the context of driving, disturbed vigilance is also a very important symptom of narcolepsy [1]. About 4–12 % of general population suffers from EDS. Daytime sleepiness may result in reduced alertness and thus affects driving ability. The 2002 Gallup survey [2] revealed that 37 % of drivers reported

that they have nodded off or fallen asleep at least once in their driving career. The Sleep in America Poll [3] showed that 91 % of respondents acknowledged that less sleep may increase the risk for injuries, but 51 % of them reported that they did drive while sleepy. Powell and colleagues [4] reported that an increase of 1 unit on the Epworth Sleepiness Scale (ESS) was associated with a 4.4 % increase of having at least one accident ($p < 0.0001$). Fulda and Schulz [5] reviewed the literature concerning cognitive functioning of patients with narcolepsy. A total of 14 studies revealed narcolepsy is characterized by reduced alertness, poor performance on divided attention and tracking tasks, and reduced vigilance.

C.E.H.M. Donjacour, MD, MA, PhD
Sleep Centre SEIN Zwolle, Zwolle, The Netherlands

Center for Sleep-Wake Disorders and Epilepsy SEIN,
Zwolle, The Netherlands

Department of Neurology, Leiden University Medical
Centre, Leiden, The Netherlands

M.A.J. Mets, PhD • A. J.A.E. van de Loo, MSc
Division of Pharmacology, Utrecht University,
Universiteitsweg 99, 3584 CG, Utrecht,
The Netherlands

J.C. Verster, PhD (✉)
Division of Pharmacology, Utrecht University,
Universiteitsweg 99, 3584 CG, Utrecht,
The Netherlands

Centre for Human Psychopharmacology,
Swinburne University, Melbourne, Australia
e-mail: j.c.verster@uu.nl

Narcolepsy and Accident Risk

Broughton et al. [6] performed a survey among 180 patients with narcolepsy. When compared to matched controls, patients reported more often falling asleep at the wheel (66 %) and had ever near or actual accidents (67 %). Cataplexy (29 %) and even sleep paralysis (12 %) while driving were reported. These high numbers were gathered by subjective patient reports about their driving behavior. More recent studies also reported a significantly increased traffic accident risk for patients with narcolepsy [7].

Driving Performance of Untreated Narcolepsy Patients

Findley et al. [8] examined driving performance of 10 patients with untreated narcolepsy. In the Steer Clear driving simulator, subjects observe a car driving on a two-lane drawn highway. Now and then during the 30-min task, obstacles (i.e., cartoon bulls) appear on the road. By pressing the space bar, the car changes lane and a collision is avoided. When compared to matched controls, narcolepsy patients hit a higher percentage of obstacles. Poor performance on the Steer Clear was associated with a higher reported traffic accident rate in the patients with narcolepsy.

Using the same computerized simple RT driving simulation task, Findley and colleagues [9] compared performance of 16 patients with narcolepsy with that of 31 untreated sleep apnea patients and 14 healthy controls. The number of collisions was measured in six 4-minute periods of simulated driving. Narcolepsy and sleep apnea patients had significantly more collisions than healthy controls. Interestingly, the inter-subject variability in errors among the narcoleptic patients was fourfold that of the apnea patients, and 100-fold that of the control volunteers, pointing at the great difference in impairment levels among narcoleptic patients.

George and colleagues [10] compared performance of 21 patients with sleep apnea, 16 narcolepsy patients, and 21 healthy controls. Using a simple driving simulator, participants were tested for 20 min. Tracking error was much worse in narcolepsy patients when compared to controls. The relationship between the multiple sleep latency test (MSLT) and tracking in either patient group was weak.

Kotterba and colleagues [11] compared driving simulator performance and neuropsychological test results in narcolepsy patients in order to evaluate their predictive value regarding driving ability. Thirteen patients with narcolepsy and ten healthy control subjects performed a 60-min driving simulator test (Computer-Aided Risk Simulator, CAR), including different weather and daytime conditions. Also, occasionally obstacles were present on the road.

The number of accidents (crashes with other cars, pedestrians, or obstacles on the road) was recorded. Concentration lapses (e.g., disregarding traffic lights or speed limit, driving at night with switched off headlights) were counted manually. Patients with narcolepsy had significantly more accidents than healthy controls. No differences were found on the number of concentration lapses.

Philip et al. [12] examined performance of nine narcoleptic patients and ten idiopathic hypersomnia patients in a 40-min driving simulator test. Outcome measure was the number of inappropriate line crossings. Patients were either treated or untreated. Unfortunately, patients were grouped according to their sleep latencies on the MWT, and the data was not analyzed by patient group. The results were compared to 14 healthy controls and revealed that patients with pathological MWT scores, defined as having a sleep latency between 0 and 19 min, showed significantly more inappropriate line crossings than the other groups.

Treatment Effects on Driving Performance

Currently, gamma-hydroxybutyrate (sodium oxybate) is the first-line treatment option for narcolepsy patients who suffer from both EDS and cataplexy. However, up to now, the effects of sodium oxybate on driving performance of narcolepsy patients have not been examined.

Modafinil and methamphetamine are also often used to improve symptoms of EDS. The effect on driving of the stimulant drug methamphetamine has been studied in narcolepsy patients [13]. Methamphetamine was administered daily to eight narcoleptic patients (0, 20, or 40–60 mg) and eight healthy controls (0, 5, or 10 mg) for 4 days for each dosage, separated by 3 days of washout (drug-free). A test in the Steer Clear driving simulator was performed on the last day of each treatment condition. In addition, the MSLT was performed to determine sleep tendency. Sleep latency increased from 4.3 min (placebo) to 9.3 min (highest dose) in narcoleptic patients.

In healthy controls sleep latency increased from 10.4 (placebo) to 17.1 min (highest dose). In line with this, error rate on the driving task decreased from 2.53 % (placebo) to 0.33 % (highest dose) for narcoleptic patients. In healthy controls, the error rate decreased from 0.22 % (placebo) to 0.16 % (highest dose). When taking a high dose of methamphetamine, the performance of narcoleptic patients did not differ significantly from healthy controls receiving placebo. This study illustrates that stimulant drugs cause a dose-dependent decrease in daytime sleep tendency and improvement in performance.

Two healthy volunteer studies confirm improvement of driving performance after stimulant drug use. Ramaekers and colleagues [14] examined the effects of 3-4-methylenedioxy methamphetamine (MDMA) (75 mg), methylphenidate (20 mg), and placebo on driving performance in 18 recreational MDMA users. On-the-road driving tests were performed 3–5 h after drug use and the next day (27–29 h after intake) to examine possible withdrawal effects. The first driving test measured the weaving of the car while participants tried to maintain a steady lateral position within the right traffic lane and a constant speed. Primary parameter of the test is the standard deviation of lateral position (SDLP), i.e., the weaving of the car. A second driving task, also performed on a public highway in normal traffic, comprised of following a lead car. Main parameters in this task were time to speed adaptation (TSA) and break reaction time (BRT). Both MDMA and methylphenidate significantly improved driving performance as indicated by reduced weaving. However, MDMA affected performance negatively in the car following test, whereas performance after using methylphenidate did not differ significantly from placebo. During withdrawal, no significant differences from placebo were found.

Verster and colleagues [15] examined the effects of methylphenidate on driving performance in adults with attention deficit hyperactivity disorder (ADHD). After a training session and withdrawal of methylphenidate for at least 4 days, patients participated in a double-blind trial and performed an on-the-road driving test

after intake of placebo or their regular dose of methylphenidate. In line with Ramaekers' findings, driving performance after using methylphenidate was significantly improved when compared to placebo. Given these findings, it can be expected that stimulant drugs will also improve driving in patients with narcolepsy.

Philip et al. [16] studied the effects of modafinil (400 mg) in 27 patients with central hypersomnia. Of them, 13 had narcolepsy and 14 suffered from idiopathic hypersomnia. In this study, patients performed a driving test on a public highway in normal traffic. Outcome measures were SDLP and the number of inappropriate line crossings. The outcomes did not differ significantly between patients with narcolepsy and idiopathic hypersomnia. For both groups combined, relative to placebo treatment, modafinil improved driving performance: it reduced SDLP ($p=0.06$) and the number of inappropriate line crossings ($p<0.05$). However, when treated with modafinil, the number of inappropriate line crossings in patients remained significantly higher when compared to healthy controls.

Interpretation of Driving Simulator Results

Various studies have shown that untreated narcolepsy patients have impaired cognitive functioning, especially on domains of attention and vigilance [5]. Excessive daytime sleepiness impairs performance and successful treatment should diminish these symptoms. Besides the fact that the number of driving studies examining narcolepsy treatment is limited, there are some methodological issues that should be taken into account when interpreting the results and conclusions of these studies.

First, although a relationship between daytime sleepiness and driving performance has been reported [16], the simple fact that successful treatment reduces daytime sleepiness does not automatically imply that driving is safe. Second, predicting actual driving from laboratory tests measuring attention, vigilance, and other isolated psychological skills and abilities

is often inaccurate [17]. Driving is an example of skilled but complex behavior in which various skills and abilities are integrated. These can be tested in isolation, but the results do not sum up in a predictive score of actual driving performance. Third, various driving simulators were used in the studies discussed in this chapter. Especially the older driving simulators such as the Steer Clear are in fact divided attention tasks. Subjects are seated behind a computer screen and use the computer keyboard to control a drawn car on the computer screen. These tests do not differ from other divided attention tests when it comes to predicting actual driving.

The aim of the study by Kotterba and colleagues [11] was to see whether performance on a neuropsychological test battery correlates significantly with driving simulator performance in patient with narcolepsy. If this was the case, the extensive testing methods could be replaced by a simple and shorter driving simulator test. Unfortunately, there was no correlation between driving performance and neuropsychological test results. Also, there was no significant correlation between driving simulator performance and excessive daytime sleepiness. Surprisingly, Kotterba and colleagues conclude that the driving simulator is suitable to assess fitness for driving and state that “On-road evaluation may be unnecessary especially in cases with ambiguous neuropsychological test results.”

The obviously artificial environment of simple driving simulators is evident to participants of experiments, and this will affect their performance accordingly. In contrast to driving in actual traffic, the tests are often experienced as a game. For example, in real life accidents may have serious consequences while this is not the case in a driving simulator. Subjects may therefore differ in risk-taking behavior in the simulator when compared to actual driving. Newer more advanced driving simulators such as the STISIM are more promising and try to make the driving test more realistic. Subjects are seated in a real car and a driving scene can be presented on a curved screen surrounding the front of the car. These newer driving simulators also include other traffic—an essential prerequisite to test driving

performance in a more realistic manner. Up to now, the on-the-road driving test is the gold standard to examine driving performance [18]. Performing the test on a public highway in real traffic ensures its ecological validity.

Taken together, although often claimed, there is little direct scientific evidence that treatment of narcolepsy improves driving performance. Future studies should be executed to examine driving performance of patients with narcolepsy, preferably using the on-the-road driving test during normal traffic.

Decisions on Fitness to Drive

There is no standard list of criteria or assessment scale to assess fitness to drive in people with narcolepsy. Commonly, physician and psychiatrists rely on their own clinical experience and base their decision on the presence and severity of narcolepsy symptoms. Unfortunately, decisions whether a narcolepsy patient is suitable to drive a car are not always uniform, given differences between physicians in interpretation of the assessment criteria. Ingravallo [19] reported that agreement on driving license decision ranged from 73 to 100 %. The decision correlated significantly with age, number of daytime naps, sleepiness, cataplexy, and quality of life. A survey among sleep specialists who attended the 2007 WorldSleep conference confirmed that there is disagreement whether or not narcolepsy patients should drive a car and that this depends greatly on the amount of daytime sleepiness experienced by patients [20] (see Fig. 20.1).

Currently, most European countries do not include EDS among the specific medical conditions to be considered when judging whether or not a person is fit to drive. A unified European Directive seems desirable [21]. In addition, there is a need for a social awareness program to educate the public about the potential consequences of narcolepsy and EDS in order to reduce impaired driving and the number of traffic accidents [22].

The International Council on Alcohol, Drugs and Traffic Safety (ICADTS) states that the decision

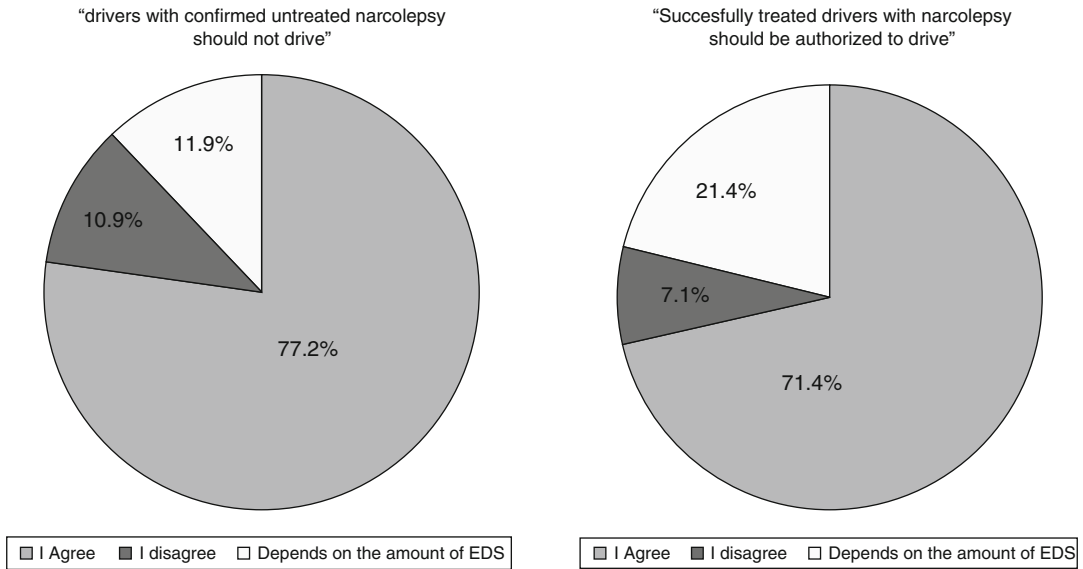


Fig. 20.1 Results from a survey conducted among attendants of the 2007 WorldSleep conference in Cairns, Australia ($N=125$) [20]

whether or not it is safe to drive (irrespective of the condition or treatment) should be based on the results of driving tests performed in actual traffic, preferably combined with additional evidence from driving simulators and laboratory test results that examine driving-related skills and ability in isolation.

From this chapter it is evident that untreated narcolepsy may significantly impair driving ability and may increase the risk of becoming involved in traffic accidents.

More systematic epidemiological studies are needed to calculate the traffic accident risk of both treated and untreated patients with narcolepsy. Given the great variability in symptom severity between narcolepsy patients (e.g., the presence and severity of daytime sleepiness), this should be taken into account when determining whether narcolepsy patients are fit to drive or not.

References

1. Fronczek R, Raymann RJEM, Romeijn N, Overeem S, Fischer M, van Dijk JG, Lammers GJ, van Someren EJW. Manipulation of core body and skin temperature improves vigilance and maintenance of wakefulness in narcolepsy. *Sleep*. 2008;31:233–40.
2. Gallup Organization. National survey of distracted and drowsy driving attitudes and behaviors. Washington: National Highway Traffic Safety Administration; 2003.
3. National Sleep Foundation. 2002 Sleep in America Poll. Washington: National Sleep Foundation; 2002.
4. Powell NB, Schechtman KB, Riley RW, Guilleminault C, Chiang RP, Weaver EM. Sleepy driver near-misses may predict accident risks. *Sleep*. 2007;30:331–42.
5. Fulda S, Schulz H. Cognitive dysfunction in sleep disorders. *Sleep Med Rev*. 2001;5:423–45.
6. Broughton R, Ghanem Q, Hishikawa Y, Sugita Y, Nevsimalova S, Roth B. Life effects of narcolepsy in 180 patients from North America, Asia and Europe compared to matched controls. *Can J Neurol Sci*. 1981;8:299–304.
7. León-Muñoz L, de la Calzada MD, Guitart M. Accidents prevalence in a group of patients with the narcolepsy-cataplexy syndrome. *Rev Neurol*. 2000;30:596–8.
8. Findley L, Unverzagt M, Guchu R, Fabrizio M, Buckner J, Suratt P. Vigilance and automobile accidents in patients with sleep apnea or narcolepsy. *Chest*. 1995;108:619–24.
9. Findley LJ, Suratt PM, Dinges DF. Time-on-task decrements in “steer clear” performance of patients with sleep apnea and narcolepsy. *Sleep*. 1999;22:804–9.
10. George CF, Boudreau AC, Smiley A. Comparison of simulated driving performance in narcolepsy and sleep apnea patients. *Sleep*. 1996;19:711–7.
11. Kotterba S, Mueller N, Leidag M, Widdig W, Rasche K, Malin JP, Schultze-Werninghaus G, Orth M. Comparison of driving simulator performance and neuropsychological testing in narcolepsy. *Clin Neurol Neurosurg*. 2004;106:275–9.

12. Philip P, Chauffon C, Taillard J, Sagaspe P, Leger D, Raimondi M, Vakulin A, Capelli A. Maintenance of wakefulness test scores and driving performance in sleep disorder patients and controls. *Int J Psychophysiol.* 2013;89:195–202.
13. Miller MM, Hajdukovic R, Erman MK. Treatment of narcolepsy with methamphetamine. *Sleep.* 1993;16:306–17.
14. Ramaekers JG, Kuypers KPC, Samyn N. Stimulant effects of 3-4-methylenedioxymethamphetamine (MDMA) 75 mg and methylphenidate 20 mg on actual driving during intoxication and withdrawal. *Addiction.* 2006;101:1614–21.
15. Verster JC, Bekker EM, De Roos M, Minova A, Eijken EJE, Kooij JJS, Buitelaar JK, Kenemans JL, Verbaten MN, Olivier B, Volkerts ER. Methylphenidate and driving ability of adults with attention-deficit hyperactivity disorder: a randomized crossover trial. *J Psychopharmacol.* 2008;22:230–9.
16. Philip P, Chauffon C, Taillard J, Capelli A, Coste O, Leger D, Moore N, Sagaspe P. Modafinil improves real driving performance in patients with hypersomnia: a randomized double-blind placebo-controlled crossover clinical trial. *Sleep.* 2014;37:483–7.
17. Ramaekers JG. Antidepressants and driving impairment: empirical evidence from a standard on-the-road test. *J Clin Psychiatry.* 2003;64:20–9.
18. Verster JC, Roth T. Predicting psychopharmacological drug effects on actual driving (SDLP) from psychometric tests measuring driving-related skills. *Psychopharmacology.* 2012;220:293–301.
19. Mets MAJ, Alford C, Verster JC. Sleep specialists' opinion on sleep disorders and fitness to drive a car: the necessity of continued education. *Ind Health.* 2012;50:499–508.
20. Ingravallo F, Vignatelli L, Brini M, Brugaletta C, Franceschini C, Lugaresi F, Manca MC, Garbarino S, Montagna P, Cicognani A, Plazzi G. Medico-legal assessment of disability in narcolepsy: an interobserver reliability study. *J Sleep Res.* 2008;17:111–9.
21. Alonderis A, Barbé F, Bonsignore M, Calverley P, De Backer W, Diefenbach K, Donic V, Fanfulla F, Fietze I, Franklin K, Grote L, Hedner J, Jennum P, Krieger J, Levy P, McNicholas W, Montserrat J, Parati G, Pascu M, Penzel T, Riha R, Rodenstein D, Sanna A, Schulz R, Sforza E, Sliwinski P, Tomori Z, Tonnesen P, Varoneckas G, Zielinski J, Kostelidou K, COST Action B-26. Medico-legal implications of sleep apnoea syndrome: driving license regulations in Europe. *Sleep Med.* 2008;9:362–75.
22. Pandi-Perumal SR, Verster JC, Kayumov L, Lowe AD, Santana MG, Pires ML, Tufik S, Mello MT. Sleep disorders, sleepiness and traffic safety: a public health menace. *Braz J Med Biol Res.* 2006;39:863–71.