EFFECTS OF SLEEP DISORDERS AND PHARMACOLOGICAL TREATMENT ON DRIVING ABILITY AND TRAFFIC SAFETY

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EFFECTS OF SLEEP DISORDERS AND PHARMACOLOGICAL TREATMENT ON DRIVING ABILITY AND TRAFFIC SAFETY

Effecten van slaapstoornissen en farmacologische behandeling op

rijvaardigheid en verkeersveiligheid

(met een samenvatting in het Nederlands)

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te Geleen

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TABLE OF CONTENTS

1

GENERAL INTRODUCTION

Road traffic accidents are at the tenth most common causes of death (WHO, 2011). On a global scale, the annual number of traffic fatalities is expected to rise from 1.3 million to 2.4 million by the year 2020, which would rank traffic accidents in the fifth place for causes of death. To take action, governments and organizations around the world have joined forces and launched the Decade of Action for Road Safety 2011-2020 (UN road safety collaboration). A number of risk factors in crash involvement have been identified; among them are two factors that constitute the focus of this dissertation: drugs, and driver fatigue (WHO, 2004).

Driver fatigue or drowsy driving is a condition in which a driver has diminished capability to operate a vehicle due to sleepiness or fatigue. Although the terms sleepiness and fatigue are often used interchangeably, they refer to distinct clinical states. Sleepiness can be described as the propensity to fall asleep and is associated with homeostatic sleep pressure and the circadian rhythm. Fatigue is a more ambiguous term, and is typically explained in terms of physical or mental deteriorations in performance. Moreover, both phenomena may co-exist as well as interact. For example, sleepiness may be enhanced by a decrease in activity, e.g. boredom, and be reduced after physical activity (Hussain et al., 2005; Shahid et al., 2010; Shen et al., 2006). Important factors associated with sleepiness and fatigue behind the wheel are sleep deprivation; sleep disorders, e.g. narcolepsy and sleep apnea; circadian factors, i.e. time of day and disruptions; medication use, monotonous conditions, and time-on-task (Connor et al. 2001; MacLean et al., 2003; Maycock et al., 1996 ; Neutel, 1995; Ohayon et al., 2010; Philip et al., 2010; Thiffault and Bergeron, 2003). Of note, alcohol interacts with sleepiness causing significant impairment in driving performance (Banks et al., 2004; Vakulin et al., 2007).

While it is often not possible to identify the exact cause, these conditions can have similar and pervasive neurobehavioral consequences and affect cognitive performance, alertness, physiological functioning and mood. In turn, these lead to an increase in errors and compromise safety (Banks and Dinges, 2007; Dawson and McCulloch, 2005). One of these impairments is inattention, which is often confused with fatigue. Although inattention can be a result of fatigue, it can also occur in other situations, such as making a phone call while driving. With regard to driving, sleep-related impairment may lead to a

conflict between a need to drive and a diminished inclination to drive (NHTSA, 1998). Consequently, drivers may no longer react adequately to potentially dangerous traffic situations and are at risk of falling asleep behind the wheel.

Over the last decades, the problem of drowsy driving has received increasing attention from researchers, traffic safety organizations, and governments. The best example is the state of New Jersey, where a bill, “Maggie's Law”, named after a vehicle accident victim killed by a sleepy driver, was passed that makes it illegal to knowingly drive a vehicle while sleep-deprived. However, in contrast to alcohol or drug testing alongside the road, there is as yet no method to determine if a driver is fatigued or sleepy. To date, biological markers are inaccurate and in-vehicle devices are still under development. Similarly, sleep-related crashes are often underreported in police documents, because drivers are often alone in the vehicle, are reluctant to admit or are unaware of the cause, and will generally be aroused by the impact (Stutts et al., 2005; Van Schagen, 2003). The exact magnitude of the problem is therefore unknown. Estimates are often made based on surveys and crash reports, while thorough analyses of crashes arrive at higher numbers.

In several surveys, 7 to 37% of drivers reported having fallen asleep while driving in the preceding year (McCartt et al., 1996; National Sleep Foundation, 2007; Vanlaar et al., 2008) and 0.27-1 % of respondents indicated having had a sleep-related crash in the year prior to the studies (National Sleep Foundation, 2009; Sagaspe et al., 2010; Vanlaar, 2008). A recent survey in The Netherlands shows that 55% of the drivers indicated that they has been fatigued while driving at least once in the preceding year; 25% declared that they were so tired they had problems keeping their eyes open, and 4% had fallen asleep behind the wheel, while 20% acknowledged they had been driving while they knew it was no longer responsible. 0.5% had had at least one crash due to falling asleep (Goldenbeld et al., 2011).

Overall, between 2 and 25% of car crashes have been attributed to sleep-related causes (Brown, 1994; Goldenbeld et al., 2011). When looking at professional drivers, a study by the National Transportation Safety Board in the USA indicated that fatigue was the most likely cause of accidents (31%; NTSB, 1990), preceding alcohol and drugs (29%). Importantly, sleep-related

traffic accidents seem to occur more often on highways (Maycock 1995, Sagaspe et al., 2010).

Psychoactive substances play a pivotal role in the context of drowsy driving. On the one hand, drug treatment of the underlying disorders may improve performance, but on the other hand, these drugs can compromise safety even further by causing residual effects. Two main classes can be identified: the sedatives, most importantly hypnotic drugs, and psychostimulants. In order to advise drivers and health care providers about the benefits and risks of these substances, it is of importance to assess their respective effects on driving ability.

DRIVING RESEARCH CONCEPTS AND METHODOLOGY

Operating a vehicle is an example of complex, skilled behaviour, which requires the simultaneous execution of several functions. This complexity is reflected by the wide availability of theories and models of driver behavior, which in turn can be categorized according to different criteria. One can distinguish not only between behavior, including input-output relations and psychology, referring to internal states, but also between functional and taxonomic, or descriptive models. Functional models can be divided into motivational and processing models.

Michon (1985) aimed at combining different models of driver behavior by using cognitive process models, and his Hierarchical Control Model (Figure 1) has become a widely applied model in driving research. This model distinguishes 3 hierarchical levels, which require increasing levels of controlled processing:

- The highest level is the **strategic (planning, or navigational) level**. This level is characterized by controlled processing and is memory- or knowledge driven, i.e. top-down controlled. It is oriented towards planning and determination of goals. An example is navigating in an unfamiliar city.
- The **tactical (or maneuvering) level**, also characterized by controlled processing, is data-driven, or bottom-up controlled. This level concerns actual behaviour in traffic in terms of interacting with the traffic system. An example is overtaking maneuvers.

- The **operational (or control) level** is characterized by automatic processing, is data-driven, and concerns basic vehicle control, such as operating the controls.

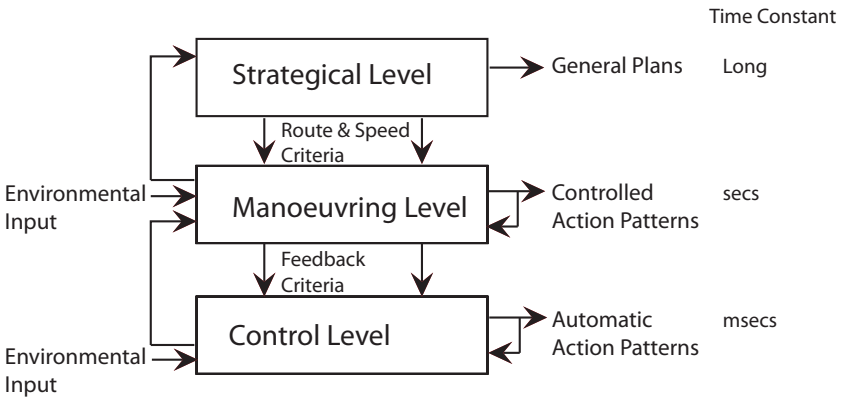

Figure 1. Michon's Hierarchical Control Model (adapted from Michon, 1985, in Giannopoulos et al., 2006)

Thus, higher order decisions exert their influence on lower order levels, and require longer processing time. Why and how these decisions are made is a subject of interest in motivational models. Examples of subjects that are described in these models are emotions and beliefs of the driver, as well as risk-taking.

Similar to Michon, Rasmussen (1987) distinguishes between *automatic*, i.e. fast and effortless, and *controlled* processing, i.e. slow and effortful. He divides operative behavior into three levels:

- **Knowledge-based behavior** entails conscious problem-solving, and is mostly relevant in unfamiliar environments;
- **Rule-based behavior** involves conscious control and attention and applying learned rules;
- **Skill-based behavior** is without conscious control and refers to automatic behaviors, making it immediate and efficient.

The more experience a driver gains, the more automated the processes become. However, in new or unexpected environments, the driver will

perform at knowledge -or rule-based level until the situation is mastered and behavior returns to rule- or skill-based level.
The relationship between the models of Michon and Rasmussen, as developed by Ranney (1994), is depicted in figure 2. Skill-based behaviour will occur in most driving situations, while rule-based-behavior is displayed by experienced drivers when interacting with traffic, and at the operational level when driving an unfamiliar car. Knowledge-based behavior is displayed by novice drivers at the control level, and by more experienced drivers at the tactical or strategic level when confronted with demanding or unfamiliar situations.

	Strategic/Planning	**Tactical/Maneuvering**	**Operational/Control**
Knowledge	Navigating in an unfamiliar area	Controlling skid	Novice on first lesson
Rule	Choice between familiar routes	Passing other vehicles	Driving an unfamiliar vehicle
Skill	Route used for daily commute	Negotiating a familiar intersection	Vehicle handling on curves

Figure 2. Classification of selected driving tasks by Michon's control hierarchy and Rasmussen's skill-rule-knowledge framework (adapted from A. R. Hale et al. 1990, Figure 1, p. 1383, in Ranney, 1994)

The studies in this dissertation examine driving performance at the operational/control level. The main objective measure is lane keeping, as expressed by the Standard Deviation of the Lateral Position (SDLP). This parameter is employed in the-on-the road driving test in normal traffic, which was developed by James O'Hanlon in the eighties of the last century (O'Hanlon et al., 1982; O'Hanlon, 1984). Details of this test method are provided in chapter 2.

The on-the-road driving test using SDLP as a primary outcome measure is a standard method to examine the effect of psychoactive drugs on driving ability (Verster and Roth, 2011) and as such has been used in numerous studies over the last decades. Additionally, apart from its applicability in pharmacological studies, the SDLP was also proven to be sensitive to sleepiness-related performance reduction while driving long distances (Verster et al., 2011).

OUTLINE OF THIS DISSERTATION

This first part of this dissertation discusses the currently available medicinal treatment options for insomnia. In addition, the results of a study into the effects of ramelteon, a novel type of hypnotic, on driving performance and driving-related skills are presented. The second part of this dissertation reports on the development and calibration of a method to examine the effect of psychoactive substances in the STISIM driving simulator. Applying a sleepy driver paradigm, effects on driving after consumption of coffee and Red Bull® Energy Drink, i.e. common countermeasures of driver sleepiness, were examined.

Part I. Sleep disorders, hypnotics and daytime functioning: an overview

The first part provides an outline of the problem of drowsy driving in the context of sleep disturbances and pharmacological treatment.

Chapter 2 gives an overview of currently used psychoactive medication and the effect on driving ability, with an emphasis on hypnotic drugs. This chapter shows that most currently prescribed hypnotics, which belong to the class of the benzodiazepine receptor agonists (BZRAs) affect driving ability the morning after intake. Additionally, they have a potential for other side effects, such as abuse, tolerance, and memory and psychomotor impairments. One such effect is a disturbance of postural balance.

Chapter 3 summarizes the most commonly used BZRAs used in insomnia treatment and their respective effects on postural equilibrium.

In *Chapter 4* the sleep disorder narcolepsy and its treatment in relation to driving ability are discussed.

Chapter 5 discusses a specific type of circadian rhythm disorder as seen in shift work and its effect on traffic safety. While the first chapters provided scientific evidence on these themes, *Chapter 6* explores how some of these subjects are interpreted by clinical experts. The results of a survey on fitness to drive, held among sleep specialists, will be presented.

Part II. Ramelteon

A novel drug that was regarded as promising with regards to the absence of the before-mentioned side effects is ramelteon. *Chapter 7* describes the characteristics of this drug. In *Chapter 8*, the results of a study on the effects of

ramelteon on driving performance, memory, psychomotor functioning, mood, and body balance is presented.

Part III. Driving Research Methodology

Part three presents a methodological study. The on-the-road driving test was used as a basis for developing a similar driving test in the STISIM driving simulator. On-the-road driving is regarded as most reliable, because it is more naturalistic. However, simulators have a number of advantages regarding costs, safety and standardization (e.g. no influences of weather and changes in traffic). Because of advancements in methodology, simulators are increasingly used in scientific studies. However, the highway driving test such as conducted on-the-road has not been standardized and calibrated in a driving simulator thus far. It is of importance to know the sensitivity of this test for future use in psychopharmacological research. This study is discussed in *Chapter 9*.

Part IV. Drowsy driving countermeasures

Chapter 9 describes the highway driving test in the STISIM driving simulator. Following this study, a "sleepy driver paradigm" was developed in which subjects drive for two hours, have a fifteen minute break, and then continue driving for two additional hours. The duration of the test was based on advice from traffic safety organizations which recommend drivers to take a break after every two hours of driving. Subsequently, this paradigm was used to assess the effectiveness of coffee and Red Bull® Energy Drink, two freely available sleepiness countermeasures, which are regularly used by drivers.

In *chapter 10*, the effects of one cup of caffeinated coffee (80 mg) were compared to decaffeinated coffee. C*hapter 11* describes a study into the effects of Red Bull® Energy Drink.

This dissertation concludes with a general discussion of the studies presented and suggestions for future research in *chapter 12*.

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2

PSYCHOACTIVE MEDICATION & TRAFFIC SAFETY

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and

Verster JC, Mets MA. 2009. Psychoactive medication & traffic safety. *International Journal of Environmental Research and Public Health* **6**:1041–1054.

ABSTRACT

Driving a car is important to maintain independence and participate in society. Many of those who use psychoactive medication are outpatients and are thus likely to drive a car. Most common adverse effects that impair driving are reduced alertness, affected psychomotor functioning and impaired vision. This review discusses the effects of most commonly prescribed psychoactive drugs on driving ability including hypnotics, antidepressants, antihistamines, analgesics and stimulant drugs. Within these categories of medicines significant differences concerning their impact on driving ability are evident. The ICADTS categorization can help physicians to make a choice between treatments when patients want to drive a car.

Keywords: driving; drugs; psychoactive medication; traffic safety, ICADTS.

INTRODUCTION

Psychoactive drugs, i.e. drugs that exert their activity on the central nervous system, and drugs that affect motor function are of concern when it comes to traffic safety. Since the vast majority of those who use psychoactive medication are outpatients it is reasonable to assume that they also participate in traffic. Roadside surveys estimate the incidence of drivers who are under the influence of psychoactive drugs between 5% and 35% [1]. Given the worldwide increase in prescribing psychoactive medication [2], traffic safety is an issue that's becoming increasingly relevant. Yearly, increasing numbers of traffic deaths are reported. Although in the U.S.A. and Europe a significant reduction in traffic accidents is evident, in other parts of the world (e.g. Africa and Southeast Asia) number of traffic accidents dramatically increase. In this context, the World Health Organization dedicated the 2004 World Health Day to road safety [3]. This review updates on the effects on driving performance of the most commonly prescribed psychoactive drugs.

METHODOLOGY

There are various methods to examine driving ability and assess the effects of psychoactive medication on traffic safety. Epidemiological studies provide evidence about the (increased) risk of becoming involved in traffic accidents when using psychoactive medication. Although this is important information, it is gathered after accidents have happened. Ideally, one would like to have this information beforehand in order to prevent driving under the influence of these drugs. A limitation of most epidemiological studies is that the statistical analysis is based on groups of drugs instead of individual drugs. This is unfortunate, because within drug groups the effects of individual drugs on driving ability can differ significantly. Many researchers use laboratory tests to examine driving related skills and abilities such as reaction speed, working memory and psychomotor functioning. Although these skills and abilities are all of great importance to operating a vehicle it has been proven that it is very difficult to predict actual driving performance from these tests [4]. This is caused by the fact that these skills and abilities are tested in isolation, whereas in real driving they are integrated and performed simultaneously. Also, the extent of impairment of individual skills and abilities differs greatly after

administration of a psychoactive drug [5]. This is illustrated by Figure 1, showing the blood alcohol concentrations (BAC) at which different skills and abilities become impaired.

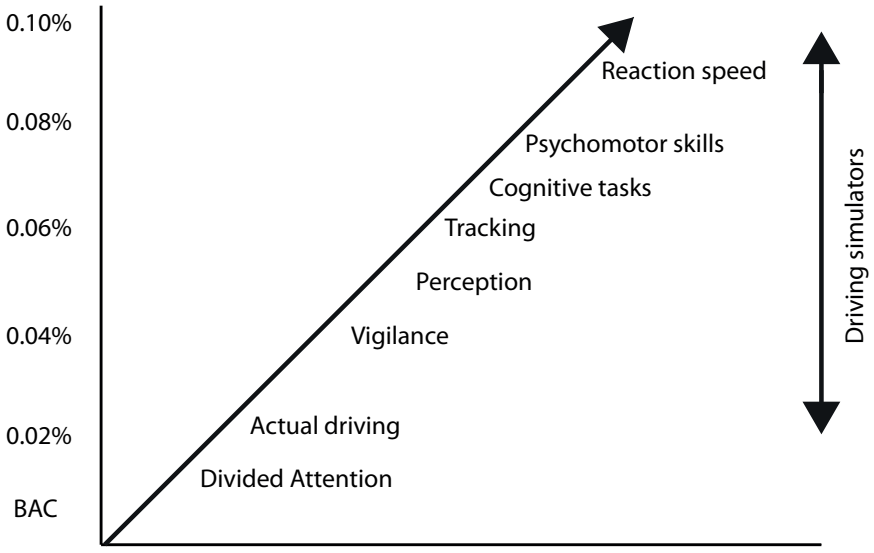

Figure 1. Skills and abilities related to driving and corresponding blood alcohol concentrations at which more than half of behavioural tests show significant impairment [5].

Driving simulators are popular to test driving skills. They are safe because no real traffic is involved and tests can be performed in a controlled environment. Traditional driving simulators were often very simple divided attention tasks. Equipment regularly consisted of a steering wheel and a computer screen. Subjects had to perform a tracking task and reaction speed task simultaneously, mimicking two important driving skills. Unfortunately, no other traffic was involved and often no road scenery was depicted on the computer screen. Therefore, these driving simulators had little predictive validity for actual driving [6]. The vital lacking element of other traffic has been introduced in most current driving simulators. Equipment of these sophisticated driving simulators often comprises a real car, a wide screen, and road scenery involving other traffic that interacts with the subject. This set-up is a great improvement when compared to the first generation of driving simulators. Nevertheless, it remains to be determined to what extent driving

simulators predict actual driving in real traffic. Subjects who perform a driving simulator test are aware of the artificial environment and this may have a significant impact on their driving style and performance.

Given legislative restrictions of most countries, relatively few studies have been performed in real traffic. Methods to determine driving performance were often limited to subjective ratings of driving instructors or researchers and self reports by patients. The subjective nature of these measurements makes it difficult to compare different drugs or dosages. To establish this, objective measurement of the magnitude of impairment is essential. One test that does measure driving performance objectively is the standardized on-the-road driving test in real traffic. Over the past 30 years, many psychoactive drugs have been examined using this test. The methodology of the driving test, applied only in The Netherlands to examine psychoactive medication, will be described below and results from studies applying this test are summarized in this review.

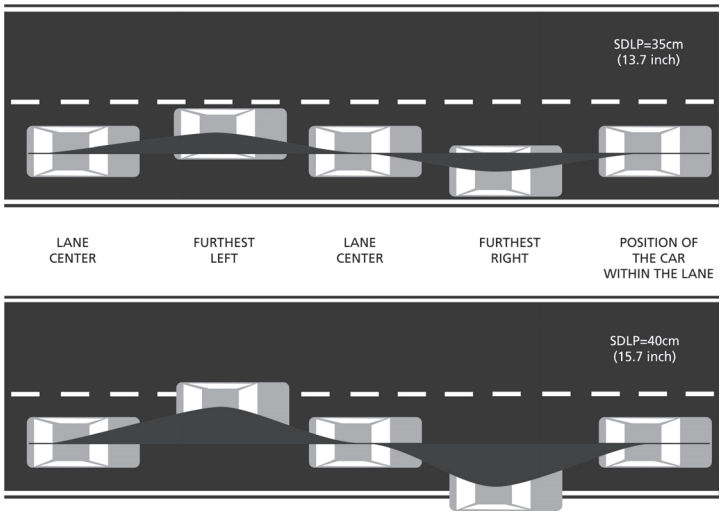

Figure 2. Standard Deviation of the Lateral Position, SDLP. Increased weaving of the car (higher SDLP values) represents reduced vehicle control and may result in excursions out of lane.

The on-the-road driving test

The on-the-road driving test in real traffic was developed in the 1980s [7] and has been applied in over 50 studies to determine the effects of psychoactive drugs on driving ability. The test has been highly standardized and has shown

to be sensitive to dose-dependent impairment after administration a variety of psychoactive drugs including hypnotics, anxiolytics, antidepressants, analgesics, stimulants, and antihistamines. In the standardized driving test, subjects are instructed to drive a car over a 100-km (61 miles) highway while maintaining a constant speed (58 miles/h) and a steady lateral position within the right (slower) traffic lane. The primary parameter of the test is the Standard Deviation of Lateral Position (SDLP, cm): the weaving of the car. This is shown in Figure 2.

It is evident from Figure 2 that SDLP represents the amount of vehicle control. Higher SDLP values represent increased weaving of the car.

A camera, mounted on the roof of the car, continuously records the position of the car within the right traffic lane, by tracking the relative distance of the car from the delineation in the middle of the road. This is illustrated in Figure 3 and Figure 4. In the right front seat, a licensed driving instructor accompanies the subject. His main responsibility is to guard safety during the driving test, and he is equipped with a brake and clutch system. If the subject or the driving instructor judges that it is unsafe to continue driving, the test is terminated before completion and the driving instructor transports the subject back to the Institute.

Figure 3. The instrumented car.

Note that the camera for lateral position measurements is equipped with two infrared lights, to enable recording during the night and dark weather circumstances. Adapted with permission from reference [12].

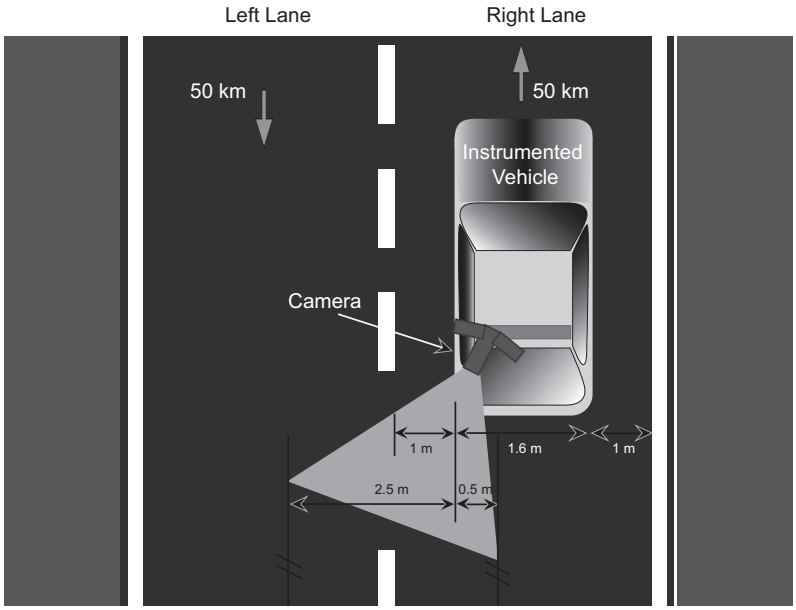

Figure 4. Schematic representation of the on-the-road driving test.

ICADTS categorization

The categorization system of the International Council on Alcohol, Drugs and Traffic Safety (ICADTS) will be used to indicate whether or not it is safe to drive a car when using a specific psychoactive drug [8]. Drugs are allocated to one of the following categories:

1. Presumed to be safe or unlikely to produce an effect
2. Likely to produce minor or moderate adverse effects
3. Likely to produce severe effects or presumed to be potentially dangerous.

To make the categories understandable, a comparison with blood alcohol concentration (BAC) is made. Driving impairment for the categories I, II and III are equivalent to BAC < 0.5 g/l (<0.05%), BAC 0.5-0.8 g/l (0.05-0.08%), and BAC > 0.8 g/l (>0.08%), respectively.

Description and interpretation of the categories is summarized in Box 1.

Box 1. Description of ICADTS category Interpretation and practical use.

Category I: Presumed to be safe or unlikely to produce an effect

In various experimental circumstances negligible or no impairment of driving performance or performance related to driving is repeatedly demonstrated. Also for medicinal drugs that are presumed not to be dangerous based on their pharmacological profile, even though there are no experimental studies that support this presumption. For the most frequently used drugs in this category the effect has been assessed in over-the-road driving tests as equivalent to blood alcohol concentrations < 0.5 g/l (<0.05%).

Advice for the patient: Be careful not to drive before having read the warnings in the package insert.

Category II: Likely to produce minor or moderate adverse effects

Some impairment of driving performance or performance related to driving is seen in various experimental laboratory circumstances. Also for drugs that will not produce severely adverse effects, but because of a lack of sufficient experimental studies it can not be established if the effect is moderate, light or absent. For the most frequently used drugs in this category the effect has been assessed in over-the-road driving tests as equivalent to blood alcohol concentrations 0.5- 0.8 g/l (0.05-0.08%).

Advice for the patient: Do not drive without consulting a healthcare professional about the possible impairing effects.

Category III: Likely to produce severe effects or presumed to be potentially dangerous

In various experimental circumstances gross impairment of driving performance, or performance related to driving, is repeatedly seen. Also for drugs presumed to be potentially dangerous based upon their pharmacological profile, but there are not sufficient experimental studies to support this presumption. For the most frequently used drugs in this category the effect has been assessed in over-the-road driving tests as equivalent to blood alcohol concentrations > 0.8 g/l (>0.08%).

Advice for the patient: Do not drive when this drug is taken and consult a healthcare professional when to start driving again after evaluation of the treatment outcomes.

The effect of different BAC levels on driving performance was determined in 24 social drinkers [9]. A dose-dependent impairment was observed. SDLP increments after alcohol consumption corresponding to the most common legal limits for driving were +2.4 cm (0.05%), +4.1 cm (0.08%), and +5.3 cm (0.10%) and are often used as reference values to illustrate driving safety when using psychoactive drugs. The study revealed a steady correlation between BAC and SDLP.

CNS DRUGS AND TRAFFIC SAFETY

The following sections discuss the effects on driving ability of the most commonly used psychoactive drugs, including hypnotics, anxiolytics, antidepressants, antihistamines, analgesics and stimulant drugs.

Hypnotics / Sleep medication

Insomnia is the inability to fall asleep or to maintain sleep during the night. People who suffer from insomnia may, therefore, have fewer hours of sleep during the night and often fragmented sleep, characterized by several awakenings during the night. As a result, people with insomnia often are sleepy during the day. Sleepiness may result in reduced attention and affect daily activities such as driving a car.

Surveys show that insomnia is a common disease affecting approximately one-third of the general population [10]. Insomnia is often a co-morbid disorder accompanying other diseases such as depression or anxiety [11].

Although non-pharmacological strategies, such as cognitive behavioral therapy, are increasingly being implemented in the treatment of insomnia, pharmacotherapy is still the most frequently used treatment for insomnia [12]. The primary choice of sleep-enhancing medication is sedative hypnotics, such as benzodiazepines and the newer benzodiazepine receptor agonists zopiclone, zolpidem and zaleplon [13]. However, prescription of antidepressants for the treatment of insomnia has increased over the last decade, which may be the result of frequent reports of adverse effects and drug dependence of benzodiazepines [14].

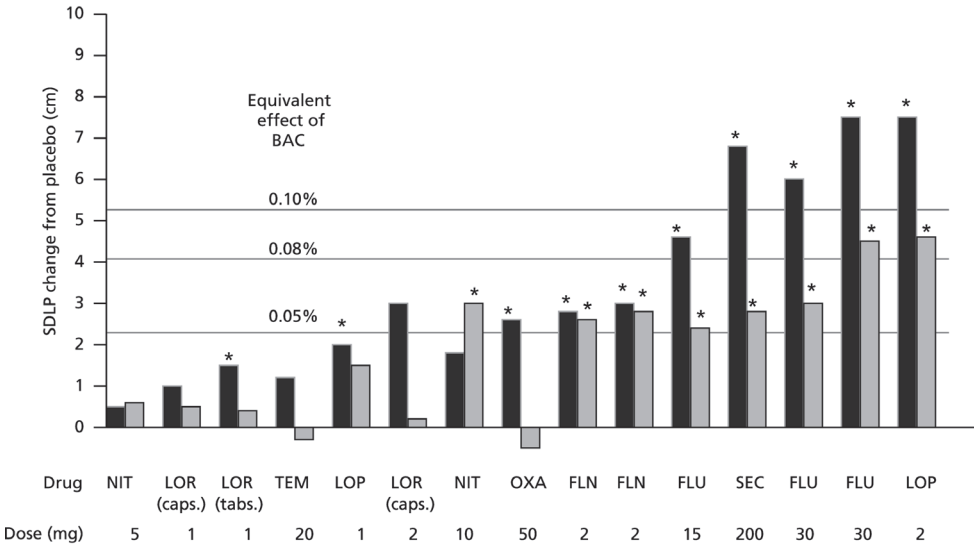

Figure 5. Benzodiazepine hypnotics and driving performance. Standard Deviation of Lateral Position (SDLP) increments relative to placebo are shown. Driving tests were performed in the morning (dark blue bars) and afternoon (light blue bars) (10–11 and 16–17 h after bedtime administration, respectively). Significant differences from placebo are indicated by an asterisk, orange lines indicate levels of SDLP increment observed with most common legal blood alcohol limits for driving a car. NIT, Nitrazepam; LOR, lormetazepam; TEM, temazepam; LOP, loprazolam; FLN, flunitrazepam; FLU, flurazepam, SEC = secobarbital, caps = capsules, tabs = tablets, BAC = blood alcohol concentration.

Benzodiazepines

Figure 5 summarizes the results of six studies [6,15-18] that examined the effects of benzodiazepine hypnotics on driving ability. Most studies were performed in healthy female subjects with a history of insomnia and benzodiazepine use. In these studies, hypnotic drugs were taken at bedtime for 1 or 2 nights. The driving tests were performed the following morning (10-11 hours after intake) and in the afternoon (16-17 hours after intake), corresponding to the times one drives to work in the morning and from work in the afternoon. Figure 5 also shows levels of impairment that were observed with 3 blood alcohol concentrations (BAC), corresponding to the most common legal limits for driving a car [9].

Flurazepam

Three studies were performed to examine the residual effects of flurazepam on driving ability [15,18,19]. In 24 female subjects, both 15 mg and 30 mg flurazepam severely impaired driving performance the morning following bedtime administration [15,19]. In the afternoon, 16-17 hours after intake, driving performance was also significantly impaired [15]. Four subjects used the 30 mg treatment for one week. After eight nights, driving was still impaired in the morning session. The latter finding was confirmed in a larger sample (16 females): driving was impaired the morning following two, four and seven nights of treatment with flurazepam 30 mg [18]. Impairment, relative to placebo, with flurazepam 15 mg equaled that observed with blood alcohol concentration above 0.08%.

Flunitrazepam

Two studies showed that flunitrazepam (2 mg) significantly impaired driving performance in the morning and afternoon after two treatment nights [15-16]. On both sessions, driving impairment was comparable to that observed with a BAC of 0.05%. Surprisingly, another study failed to find significant effects of flunitrazepam 2 mg after a single night of treatment [20]. Nevertheless, results of driving simulator and closed road studies support that performance is impaired the morning following intake of 1 or 2 mg flunitrazepam [21-22].

Nitrazepam

Two studies examined the effects of nitrazepam on driving ability. The 5 mg dose did not affect driving performance in 16 female subjects [16]. The second study showed that the 10 mg dose of nitrazepam significantly impaired driving after two nights of treatment [17]. Interestingly, impairment in the afternoon was more pronounced than in the morning session. This illustrated the impact of active metabolites; in hypnotics without active metabolites impairment is more pronounced in the morning session. After four and seven nights of treatment, 10 mg nitrazepam did not significantly impair driving, suggesting that tolerance develops after repeated treatment.

Lormetazepam

Lormetazepam is available as a tablet and soft gelatine capsule. Both formulations have been tested on the road. In 16 females, 1 mg lormetazepam (soft gelatine capsule) did not significantly impair driving performance the morning following two, four and seven treatment nights [18]. The 2 mg dose did cause significant impairment. A study in 18 healthy men showed significant impairment after treatment with a 1 mg lormetazepam tablet after one or two treatment nights [6]. Impairment was relatively slight (comparable to that observed with a BAC less than 0.05%) and not found in a driving simulator. A more recent driving simulator study in 12 healthy volunteers also found no significant effects the morning following bedtime administration of 1 mg lormetazepam [23].

Oxazepam

Oxazepam (50 mg) significantly impaired driving performance in 18 healthy men after one and two treatment nights [6]. Impairment was comparable to that observed with a blood alcohol concentration of 0.05%. In the afternoon, driving was not affected. Subjects also performed a driving simulator test, but no significant effects were found.

Loprazolam

Loprazolam (1 mg) significantly impaired driving performance in the morning, but not in the afternoon [15]. Twice the recommended dose (2 mg) also showed significant impairment in the afternoon driving session. Impairment in the afternoon session was comparable to that observed with a BAC greater than 0.10%.

Temazepam

Temazepam (20 mg) did not affect driving performance after 2, 4 and 7 nights of treatment [17]. Another on-the-road study [22] reported that driving performance after one and seven nights of treatment improved in patients with insomnia. A closed road study did show impairment 12 hours after intake of temazepam (20 mg): healthy female subjects had more collisions when maneuvering passable and non-passable gaps on the circuit. No effects were reported on a waving test between bollards [24].

Other benzodiazepine hypnotics

Triazolam and brotizolam are relatively short acting benzodiazepines. Triazolam at a recommended dosage of 0.25 mg taken at night, has not been examined using the on-the-road driving test. In a driving simulator and a closed road circuit, triazolam (0.25 mg) did not significantly impair performance [25]. Also, on a monotonous driving simulator test, brotizolam (0.25 mg) did not impair performance [26].

Non-benzodiazepine hypnotics: the z-drugs

Given the adverse effects of benzodiazepine hypnotics the search for new hypnotics continued and resulted in the development of the so-called z-drugs: zopiclone, zolpidem and zaleplon. Although these drugs also act at the GABA receptor, they do so in a much more specific way than the benzodiazepines. In addition, they have a relatively short half-life.

Zopiclone

Three studies have been performed to examine the effects of zopiclone 7.5 mg on driving performance. Significant driving impairment was reported by all studies [16,19,27]. The magnitude of impairment (3 to 8 cm increment of SDLP relative to placebo) was comparable to that observed after intake of benzodiazepines and higher than that what is regarded as acceptable after intake of alcohol (2.4 cm with a BAC of 0.05%). Epidemiological research showed that zopiclone was significantly associated with traffic accidents [28]. In terms of traffic safety, zopiclone is no improvement.

Zolpidem

Research showed that zolpidem (10 mg) when taken as recommended did not affect driving performance [20]. However, when taken in the middle of the night, or at a higher dosage than recommended (i.e. 10 or 20 mg, 4 hours before driving), performance on the driving test was significantly impaired [29]. Recent reports on misuse of zolpidem are also a reason for concern: an increasing number of traffic accidents have been related to the misuse of zolpidem [30].

Zaleplon

Zaleplon (10 and 20 mg) does not significantly impair driving performance 10-11 hours after intake [19,27]. Even when administered during the night and at higher dosages than recommended (i.e. 20 mg, 4 hours before driving) no significant impairment was found [29].

Summarizing the data: results of a meta-analysis

Results from a recent meta-analysis [13] confirm that benzodiazepine hypnotics and zopiclone significantly impair driving performance the day following bedtime administration whereas zolpidem and zaleplon do not (see Figure 6).

Six studies, published from 1984 to 2002, were included in the meta-analyses [6,15-18]. The morning following bedtime administration, i.e. 10-11 hours after dosing, significant driving impairment was found for the recommended dose of various benzodiazepine hypnotics (ES=0.42; 95% Confidence Interval (CI)=0.14 to 0.71). Twice the recommended dose of benzodiazepine hypnotics impaired driving both in the morning (ES=0.68; CI=0.39 to 0.97) and afternoon, i.e. 16-17 hours after dosing (ES=0.57; CI=0.26 to 0.88). Most benzodiazepine hypnotics were categorized in ICADTS category II or III (see Table 1).

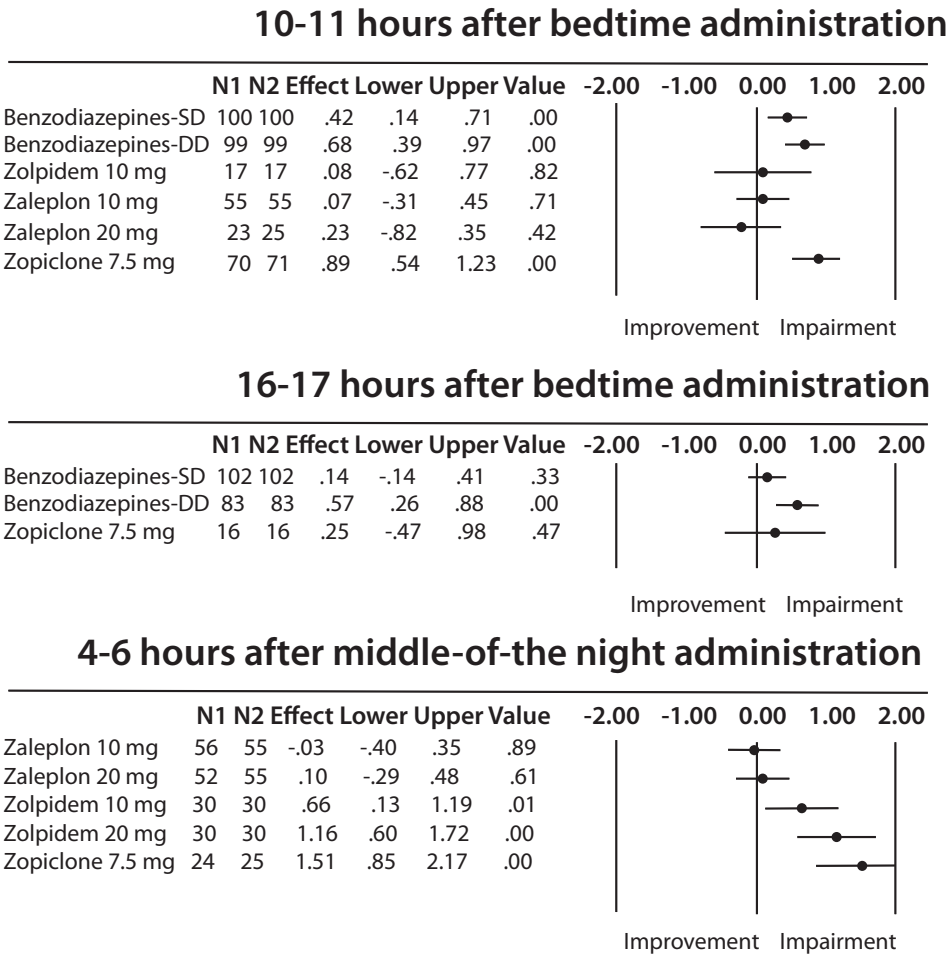

Figure 6. Results from the meta-analysis. The effects are significant ($p < 0.05$) if the 95 % Confidence Interval is greater or smaller than 0. Abbreviations: SD = single dose, DD = double dose, N1 = treatment, N2 = placebo. Lower = lower limit of the 95 % CI, Upper = upper limit of the 95 % CI. Adapted with permission from reference (13).

Table 1. ICADTS classification of commonly prescribed hypnotics and sedative drugs [8].

Substance name	Category
Barbiturates	
Secobarbital	III
Benzodiazepine derivatives	
Flurazepam	III
Nitrazepam	III
Flunitrazepam	III
Estazolam	III
Triazolam	III
Lormetazepam	III
Temazepam	III
Midazolam	III
Brotizolam	III
Quazepam	III
Loprazolam	III
Benzodiazepine related drugs	
Zopiclon	III
Zolpidem	II

Anxiolytics

Up to 50% of the patients visiting their physician suffer from anxiety disorders, including generalized anxiety disorder, panic disorder, post-traumatic stress disorder, obsessive-compulsive disorder, social anxiety disorder, or phobias. A substantial number of those patients use anxiolytics including benzodiazepines, tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), or buspirone. Their effects on driving ability have been extensively studied and results supported by epidemiological evidence [31].

Both benzodiazepines and TCAs significantly impaired driving performance after single dose administration. Impairment of benzodiazepines when used as anxiolytic is much more pronounced when compared to impairment when used as hypnotic drug. This difference is caused by the fact that the time between drug intake and the driving test is much greater for

hypnotics (10-11 hours) when compared to anxiolytics (1 hour). The different time intervals were chosen to reflect normal use of anxiolytics (during the day, for example after awaking) and hypnotics (at bedtime).

Table 2. ICADTS classification of anxiolytic drugs [8].

Substance name	Category
Benzodiazepine derivatives	
Diazepam	III
Chlordiazepoxide	III
Medazepam	II
Oxazepam	III
Lorazepam	III
Bromazepam	III
Clobazam	II
Ketazolam	III
Alprazolam	III
Azaspirodecandione derivatives	
Buspirone	I

Tolerance develops slowly and after a week of daily treatment with benzodiazepine anxiolytics driving remained significantly impaired [31]. This effect was less pronounced for TCAs. In contrast, SSRIs, 5HT-antagonists and buspirone produced no significant impairment on the driving test after both acute and repeated administration. Corresponding ICADTS categories of most commonly prescribed anxiolytics are summarized in Tables 2 and 3.

Tables 2 and 3 clearly show that benzodiazepine anxiolytics and TCAs (listed as category II and III drugs) are regarded as more dangerous than SSRIs and related compounds (listed as category I drugs).

Antidepressants

The effects of most commonly used antidepressants on driving ability have been investigated applying the on-the-road test [32]. Driving after intake of TCAs (including amitriptyline, doxepine and imipramine), mianserin and

mirtazapin was significantly impaired after treatment initiation. Tolerance developed gradually, and after 1 week of treatment driving impairment was absent or much less pronounced. Nocturnal treatment with these antidepressants did not affect next day driving performance. In contrast to the TCAs, SSRIs (including fluoxetine, paroxetine and escitalopram), related antidepressants (venlafaxine and nefazodone), and moclobemide showed no significant effect on driving performance. The ICADTS categorization of most commonly used antidepressant drugs is summarized in Table 3.

Table 3. ICADTS classification of commonly prescribed antidepressants [8].

Substance name	Category
Non-selective monoamine reuptake inhibitors	
Desipramine	II
Imipramine	II
Clomipramine	II
Amitriptyline	III
Nortriptyline	II
Doxepin	III
Selective serotonin reuptake inhibitors	
Fluoxetine	I
Citalopram	II
Paroxetine	I
Sertraline	II
Fluvoxamine	II
Escitalopram	II
Monoamine oxidase A inhibitors	
Moclobemide	II
Other antidepressants	
Mianserin	III
Trazodone	III
Nefazodone	II
Mirtazapine	III
Venlafaxine	I
Reboxetine	I

Antihistamines

All antihistamines are capable of crossing the blood-brain barrier and thus may cause sedation. Most commonly used antihistamines have been examined using the on-the-road test [33]. Over the past decades 3 generations of antihistamines have been developed, each improving his proceeding generation in terms of less sedation and adverse effects.

Table 4. ICADTS classification of commonly prescribed antihistamines [8].

Substance name	Category
Aminoalkyl ethers	
Diphenhydramine	III
Clemastine	III
Substituted alkylamines	
Dexchlorpheniramine	II
Chlorphenamine	II
Pheniramine	II
Phenothiazine derivatives	
Promethazine	III
Mequitazine	II
Piperazine derivatives	
Meclozine	II
Cetirizine	II
Levocetirizine	I
Other antihistamines for systemic use	
Triprolidine	III
Terfenadine	I
Loratadine	I
Azelastine	I
Ebastine	I
Mizolastine	II
Fexofenadine	I
Desloratadine	I

The oldest (first-generation) antihistamines (diphenhydramine, triprolidine, terfenadine, dexchlorpheniramine, clemastine) significantly impair driving performance after both one-time and repeated (daily) administration. Second-generation antihistamines (cetirizine, loratadine, ebastine, mizolastine, acrivastine, emedastine, mequitazine) may also impair driving performance, but this differs greatly among individuals. The magnitude and extent of impairment depends on the administered dose, sex, and time between driving and treatment administration. Tolerance develops after 4 to 5 days of administration, but impairment is not always absent. In contrast, third-generation antihistamines (fexofenadine, desloratadine, and levocetirizine) produce no driving impairment after both one-time and repeated administration. The ICADTS categorization of most commonly used antihistamines is summarized in Table 4.

Analgesics

Pain itself can significantly impair driving performance [34]. Effective treatment with Non steroid anti-inflammatory drugs (NSAIDs) or opioids may (partially) relieve the pain. Up to now, only few driving studies have been performed with analgesics. Laboratory tests of cognitive functioning and psychomotor skills generally do not show significant performance impairment in patients using NSAIDs or acetaminophen. Therefore they are listed in ICADTS category I. One driving study [35] examined the effects on driving of bromfenac. This NSAID which is no longer marketed did not affect driving or related skills. The same study also examined the opioid oxycodone. No significant differences from placebo were found, but subjects indicated that much more effort was needed to perform the driving test. Laboratory studies failed to find consistent results when testing opioids [36]. Nevertheless, ICADTS categorizes many opioid analgesics in class II (e.g., oxycodone, and codeine) or III (e.g. morphine, tramadol and fentanyl). Opioids show a strong dose-dependent impairing effect on performance and after treatment initiation dosages are often gradually increased. This may interfere with developing tolerance to their impairing effects, and thus these drugs are often grouped in category II or III.

Chronic pain patients are often treated with antidepressants such as amitriptyline instead of opioids and NSAIDs. 13 hours after treatment

administration, amitriptyline (25 mg) significantly impaired on-the-road driving performance in chronic neuropathic pain patients [37]. After 2 weeks of daily use, tolerance developed to the impairing effects of amitriptyline.

Stimulant drugs

Stimulant drugs are used in the treatment of attention deficit hyperactivity disorder (ADHD) and narcolepsy. Purpose of using these drugs is to improve attention and daytime alertness. Two studies showed improvement of driving performance after stimulant drug use.

Ramaekers and colleagues [38] examined the effects of 3-4-methylendioxymethamphetamine (MDMA) (75 mg), methylphenidate (20 mg) and placebo on driving performance in 18 recreational MDMA users. The on-the-road driving test and a car following test were performed 3 to 5 hours after drug use, and the next day (27 to 29 hours after intake) to examine possible withdrawal effects. Both MDMA and methylphenidate significantly improved driving performance as indicated by reduced weaving. However, MDMA negatively affected performance 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 [39] examined the effects of methylphenidate on driving performance in adults with 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.

CONCLUSIONS

Various psychoactive drugs affect driving performance. These effects are most prominent after treatment initiation and tolerance develops after chronic use. Impairment further depends on dose and half-life of a drug, time after administration, gender and age.

Limitations of current driving research include the fact that they have not examined driving in patients who chronically use psychoactive medication. Epidemiological data show that after long-term use of psychoactive

medication tolerance develops to the impairing effects of these drugs. Patients get used to the adverse effects of drugs, and gradually they wear off as do the risks of traffic accidents [40]. Tolerance develops slowly and is much less likely to develop after intermittent (as-needed) use. For example, increased traffic accident risks for users of benzodiazepine hypnotics have been reported after 1 year of chronic use [10-11]. Unfortunately, on-the-road studies have focused primarily on short term use (i.e. 1 day to 2 weeks). One study did examine the effects of 4 weeks daily treatment with diazepam [41] and confirmed that tolerance develops slowly. After 4 weeks of treatment with diazepam SDLP increment was still significantly increased. Nevertheless, epidemiological studies have shown no significant increase in traffic accident risk after chronic use (> 1 year) of other psychoactive drugs such as opioids [42].

A second limitation is that individual differences between patients are often not taken into account. Most drugs are supplied in a standardized dose, not taking into account age, gender and metabolism of individual users. However, these factors are important in determining the presence and magnitude of adverse effects. In some driving studies – but not in general, it has been shown that SDLP increment in women is significantly greater than in men [43]. Also, elderly often perform worse when compared to healthy young adults [44]. In this context, it is unfortunate that most experimental studies have been conducted in healthy male young adults, whereas patients using psychoactive medication are often female elderly.

Future pharmaceutical research should focus on developing new psychoactive medication that produces less sedation and adverse effects. These new drugs should be tested preferably in healthy volunteers followed by studies in patients who actually need the medication. Effects on driving ability after long-term use should be examined as well.

Finally, for many diseases a number of different treatment options are available. In terms of traffic safety, physicians should choose medication that has shown to be devoid of impairing effects on driving ability. The ICADTS categorization can help them in making this decision.

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3

EFFECT OF HYPNOTIC DRUGS ON BODY BALANCE AND STANDING STEADINESS

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ABSTRACT

Background: Disturbed body balance and standing steadiness are problematic for those who wake up at night or in the morning after using hypnotic drugs. As a result, falls and hip fractures are frequently reported in patients using sleep medication.

Methods: A literature search was performed to identify double-blind, placebo-controlled clinical trials that examined body balance and standing steadiness. Drugs that were searched were nitrazepam, triazolam, lorazepam, temazepam, loprazolam, flunitrazepam, flurazepam, and the Z-drugs zopiclone, zolpidem and zaleplon.

Results: A total of 57 studies were eligible for inclusion. Results showed that both benzodiazepine hypnotics and the Z-drugs significantly impair body balance and standing steadiness after single dose administration. Impairments correlate significantly with blood plasma levels and are greatest at peak plasma concentrations, but are sometimes still present upon awakening. Balance problems were dose-related and most pronounced in elderly. Co-administration of alcohol aggravated the impairment. After repeated daily use of hypnotic drugs partial tolerance develops to the impairing effects on standing steadiness.

Conclusion: Single dose administration of benzodiazepine hypnotics and z-drugs significantly impair body balance in a dose-dependent manner. Zolpidem and zopiclone produced similar significant impairment as benzodiazepine hypnotics. Zaleplon significantly impaired balance up to 2 hours after intake. Partial tolerance develops after repeated daily use. In conclusion, patients should be warned about the possible risk of imbalance and falls due to the use of sleep medication.

Keywords: hypnotics, balance, body sway, postural sway, standing steadiness

INTRODUCTION

Most falls occur during daytime and are related to imbalance and postural instability. Slippery sidewalks, irregular surfaces (e.g., a bobbling carpet) and bad luck account for the majority of falls.[1-2] Approximately 20% of falls occur at night. Falls are most common among elderly; about 30% of elderly experience at least one fall yearly. The majority of these falls have no serious consequences, but 20-30% of falls result in injury, hip-factures or even death. For example, in 2001, over 15,000 deaths from falls were reported in the USA. In contrast to young adults, elderly recover much slower from injury, if at all. Indeed, increased mortality rates have been reported in elderly who have been involved in falling accidents resulting in hip fracture.[3-5]

The economic burden of non-fatal falls is significant. For the USA, it has been estimated that over 20 billion dollars yearly are spend on medical costs related to falls.[6,7] Various studies have associated the use of hypnotic drugs, including benzodiazepines and zopiclone, with postural instability and an increased risk of falls and hip fractures.[8,9] Hypnotic drugs can have an effect on functions that are not related to sleep. Some of these may be of importance in postural control, which is governed by a number of processes such as sensory, cognitive and motor processes.[2] This review discusses the clinical trials that examined the effects of hypnotics on body balance and postural stability.

MEASUREMENT OF BALANCE AND BODY SWAY

Ability to stand upright on one foot

A method to measure body balance that does not require special equipment, is recording the time a person is able to maintain balance on one foot. This method has been very popular in the first experiments that wanted to measure effects of hypnotics on body balance. In the test, subjects are instructed to stand on one foot, with hands held horizontally and with eyes closed.[10-18] Subsequently, the time until the second foot touches the ground is used as a measure of body balance. Tests are generally performed for 30- 60 s, and for each foot. Unfortunately, this test gives a rather crude measure of body balance. In modern research, it is therefore largely replaced by electronic measurements of body balance.

The ataxiameter and other swaymeters

The ataxiameter is a simple electronic device introduced to measure body sway.[19] Subjects are instructed to stand upright on two feet, placed apart. A cord from the recording device is attached to the subject. Body sway is measured by determining the angular movement of the body around the ankle joint. In other versions of this test such as the swaymeter, the cord is attached to the subject's waist and displacements of the body are measured.[20]

Force platforms

Measurements using electronic force platforms are based on changes of the Center of Pressure (COP), which is the point where the resultant of all ground reaction forces act, e.g., the center of mass and the torque on the surface. Subjects are placed on the platform and are instructed to stand steady. Duration of the test usually varies from 20 s to 3 min.

Figure 1. Balance test using an electronic platform. Subjects are instructed to stand right up (see panel left) for 1 min with eyes closed and one minute with eyes open, focusing on a target point (see right panel). Reprinted with permission from QinetiQ.

Often, tests are carried out with eyes closed and with eyes open. In the latter case, having the subject fixate at a target positioned 2-3 m in front of the subject controls head position. This is illustrated in Fig.1.

Two types of platforms are used: static and dynamic platforms. On dynamic platforms such as the stabilometer, the platform is unstable. Hence, subjects need to adapt posture to attain balance. In addition, situations can be created in which movement of the platform or the environment compromises the use of sensory information to control balance.[21] Static platforms are fixed in a horizontal plane. Subjects are instructed to maintain a steady postural balance. The force platform is connected to a computer and records small movements made by the subject. The three most commonly used statistics of sway are: 1) path length of the COP; 2) the circular area encompassing 100% of data points (Area Circ) and 3) the area of the ellipse encompassing 95% of the data points (if normally distributed; Area95). A typical example of results from a test using the Area95 to measure balance after administration of placebo (Figure 2A) and zopiclone (Figure 2B) is shown in Fig. 2.

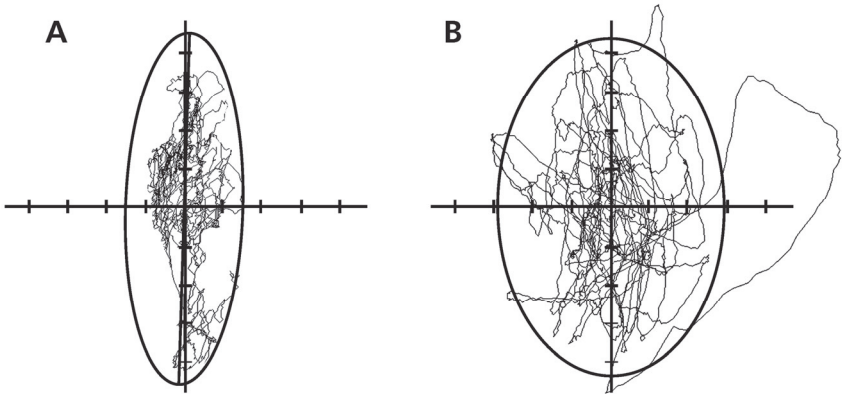

Figure 2. Results from a balance test after administration of placebo (A) and zopiclone (B). The thin line represents the changing Center of Pressure (COP) over time. The oval indicates the Area95.

METHODS

A literature search was performed using Medline (from 1966), Embase (from 1974) and the Cochrane clinical trials database (searched May 15th, 2009), to collect clinical trials that examined body balance or postural sway. Keywords were 'balance', 'body sway', 'coordination', 'body equilibrium', 'postural sway', 'musculoskeletal equilibrium', and 'imbalance'. Hypnotic drugs that were searched were nitrazepam, triazolam, lorazepam, temazepam, loprazolam, flunitrazepam, flurazepam, zopiclone, zolpidem, and zaleplon. Fig. 3 gives an overview of the search process.

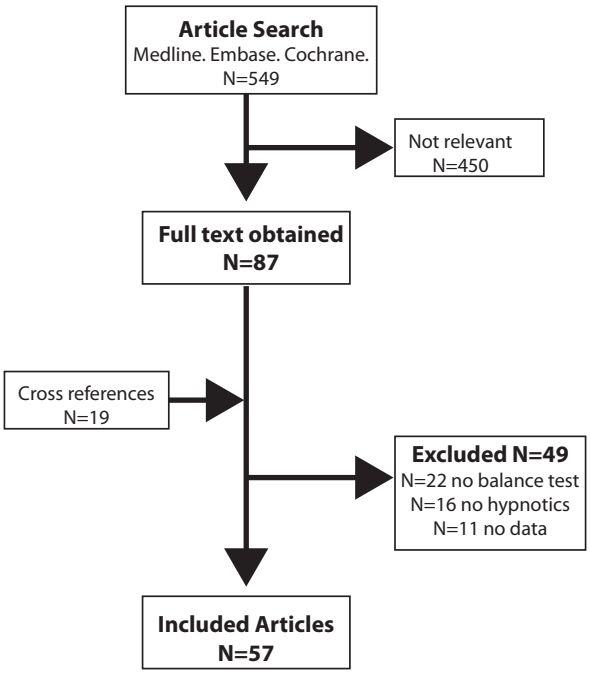

Figure 3. Flow chart of the data search.

For 549 articles the abstract was examined. Since only clinical trials were included, most papers were not relevant for this review (*N* = 459). Of 87 papers, the full text was obtained. Cross-references yielded an additional 19 papers. After reviewing these 106 papers, 49 were excluded. The excluded papers included no balance test (*N*=22), did not test hypnotics or specify which drugs were tested (*N*=16), or were review articles (*N*=11). Results from 57 papers were included and are discussed in this review. The Jadad score (0 = poor quality, 5 = excellent quality) was computed to illustrate the average quality of the included articles.[22] The average Jadad score equaled 3.2. We carefully inspected the data from each clinical trial in order to see whether it was possible to conduct a meta-analysis. Unfortunately, in most papers vital data were lacking. In general, balance test results were poorly reported, presumably because the test was not regarded as the most important measurement of the clinical trial. The data therefore do not allow conducting a meta-analysis.

RESULTS

Single dose in young healthy volunteers

The results from studies testing the effects of a single dose on body balance in healthy young volunteers are summarized in Fig. 4.

Not all studies report the exact timing of the effects. In addition to the results shown in Fig. 4, area under the curve effects were reported for triazolam (0.25, 0.375 and 0.75 mg) from 0 to 4 hours after intake,[17,39-41] and for lorazepam (2 mg) between 0 and 6-8 h after intake.[42-43] In addition, one study reported an unspecified effect of temazepam 20 mg.[44] The maximum duration of effect was generally 7 hours, except for nitrazepam (5 mg), for which a next-morning effect was reported[45] and lorazepam which also affected balance 18 hours after intake[33] (not shown in figure).

The magnitude of balance impairment often correlates significantly with the blood plasma concentration. Dose-dependent impairment was found for triazolam,[16,17,26,40] temazepam,[16] and zolpidem.[16] At higher dosages, impairment is much more pronounced and lasts longer.

For example, impairment for triazolam was significant up to 2 h after intake of 0.25 mg[25,29] and 6 hours after intake of 1 mg.[31] It also matters if subjects are tested with eyes open or eyes closed. Because vision provides information about the body's location in space,[46] the eyes closed condition is experienced as more difficult and accordingly, balance impairment is more pronounced. However, the eyes open condition often shows prolonged impairment in drug conditions compared with placebo than the eyes closed condition.[28,29,47,48] In contrast, some studies only show impairments in the eyes closed condition.[24,49] A study by Allain et al.[50] showed longer durations of balance impairments in the eyes closed condition after the intake of zolpidem, and in the eyes open condition after intake of zopiclone.

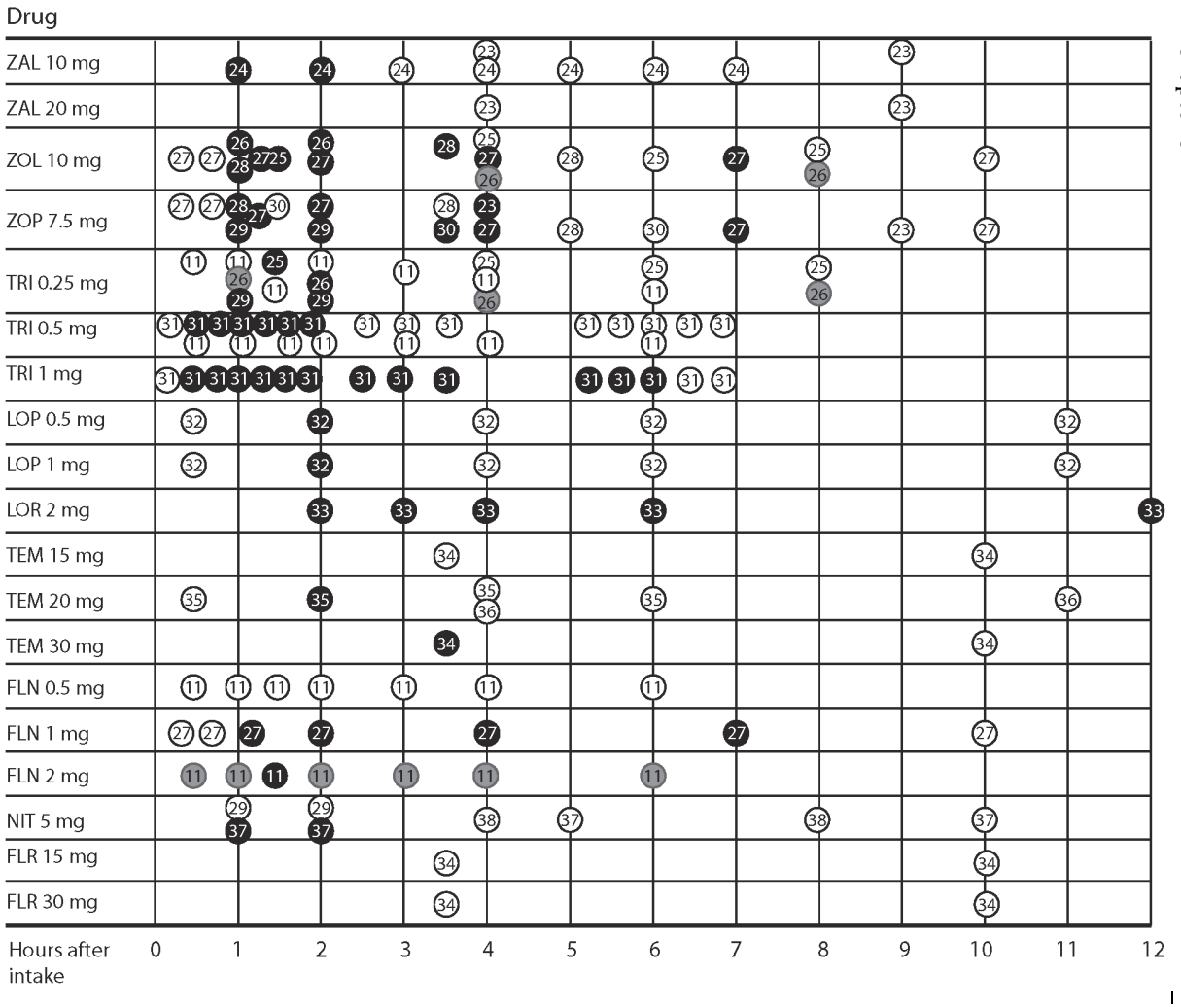

Figure 4. Single dose effects of hypnotic drugs on body sway in healthy volunteers. Each circle corresponds with a measurement in a group of subjects receiving the same dosage of the same drug. Black circles represent significant differences in postural sway compared with placebo, white circles represent no significant differences in postural sway compared with placebo, and grey circles indicate that the outcome of the measurement is unknown. The numbers in the circles indicate the corresponding references. Abbreviations: ZAL: zaleplon, ZOL: zolpidem, ZOP: zopiclone, TRI: triazolam, LOP: loprazolam, LOR: lorazepam, TEM: temazepam, FLN: flunitrazepam, NIT: nitrazepam, FLR: flurazepam.

Single dose in elderly healthy volunteers

The results from studies testing the effects of a single dose on body balance in healthy elderly volunteers are summarized in Fig. 5.

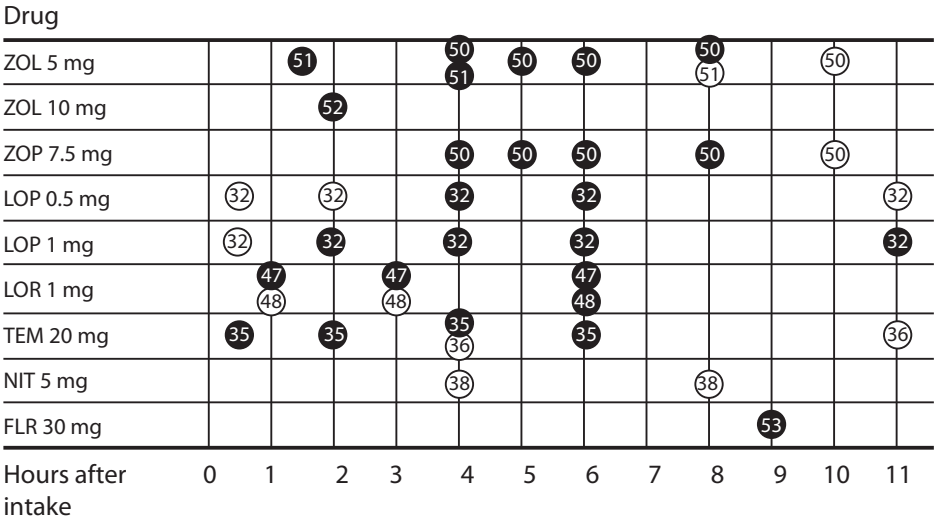

Figure 5. Single dose effects of hypnotic drugs on body sway in elderly subjects. Each circle corresponds with a measurement in a group of subjects receiving the same dosage of the same drug. Black circles represent significant differences in postural sway compared with placebo, white circles represent no significant differences in postural sway compared with placebo, and grey circles indicate that the outcome of the measurement is unknown. The numbers in the circles indicate the corresponding references. Abbreviations: ZOL: zolpidem, ZOP: zopiclone, LOP: loprazolam, LOR: lorazepam, TEM: temazepam, NIT: nitrazepam, FLR: flurazepam.

The effects of hypnotic drugs on body sway are often much more pronounced in elderly subjects than in younger adult subjects.[32,35] Moreover, when administered half the recommended dosage, which is a common practice in elderly patients, the effects on body sway are often similar to or even more pronounced than those observed in younger adults receiving the normal dose.[32,47,48] For example, dosages of 0.5 and 1 mg loprazolam increased body sway until 2 h after intake in younger adults. In contrast, elderly subjects receiving 0.5 mg loprazolam experienced balance impairments up to 6 h post dose. When receiving the normal dosage of 1 mg, their postural sway was impaired until 11 h after intake.[32]

This study also demonstrated that body sway in the older subjects had a much larger magnitude than body sway in younger volunteers in the placebo condition. Other studies support this finding and indicate that with aging control of body balance gets worse.[35,36,38] In addition, those with poor postural sway in general (often the elderly) were more sensitive to drug-induced impairment.[54]

Repeated administration and chronic use

When used on a daily basis, tolerance develops to the adverse effects of sleep medication. Fig. 6 summarizes the results of studies testing the effects on body balance of chronic treatment with hypnotics.

Insomnia itself may be a cause of postural instability. Whereas adverse effects of hypnotics may impair balance in healthy volunteers, patients may actually profit from these drugs since they relieve insomnia. For example, Mamelak and colleagues[59] showed that after 14 days of treatment with flurazepam (15 mg) or brotizolam (0.25 mg) performance on a balance test was significantly improved relative to insomnia patients who had received placebo. The effect on balance in patients is thus a combination between relief of insomnia (improved balance) and adverse effects of hypnotics (impaired balance). The outcome heavily depends on factors such as individual differences, dosage, and tolerance.

Most studies summarized in Fig. 6 were performed in healthy volunteers. Fig. 6 shows that tolerance develops after several days or weeks of treatment. Development of tolerance differs between hypnotic drugs, and also between individual patients. The impact of tolerance on balance was illustrated by Stevenick and colleagues.[60] When administering lorazepam to patients who are chronic users of this drug no effect was observed on a balance test, whereas drug naïve healthy volunteers showed significant impairment. No difference on balance performance between patients and healthy volunteers was found after administration of temazepam, illustrating that this drug has a different adverse effect profile than lorazepam.

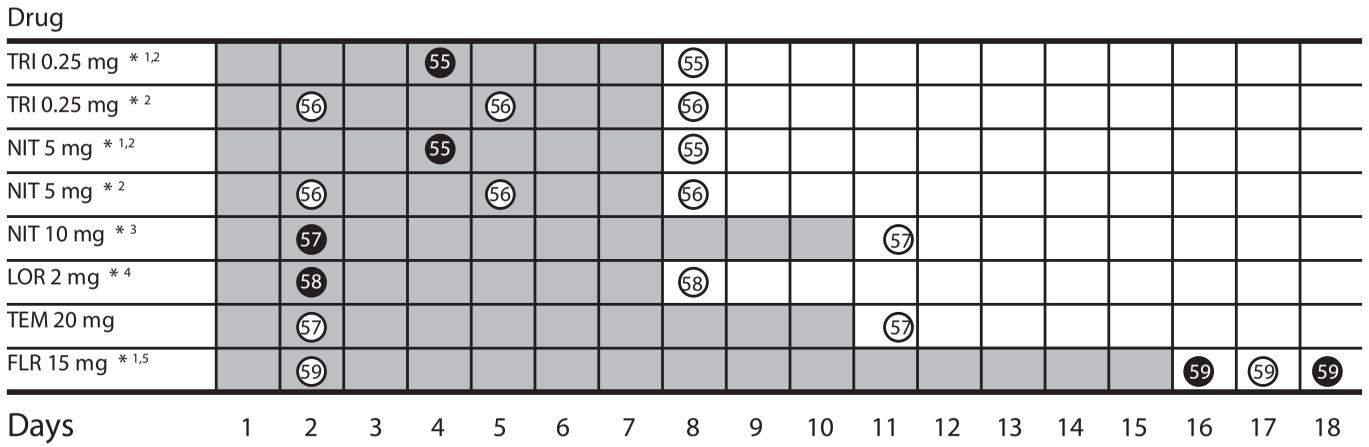

Figure 6. Effects of repeated doses of hypnotic drugs on postural sway. Each circle corresponds with a measurement in a group of subjects receiving the same dosage of the same drug. Black circles represent significant differences in postural sway compared with placebo, white circles represent no significant differences in postural sway compared with placebo, and grey circles indicate that the outcome of the measurement is unknown. Grey bars indicate the duration of treatment. The numbers in the circles indicate the corresponding references. Abbreviations: ZAL: zaleplon, ZOL: zolpidem, ZOP: zopiclone, TRI: triazolam, LOP: loprazolam, LOR: lorazepam, TEM: temazepam, FLN: flunitrazepam, NIT: nitrazepam, FLR: flurazepam. *1: Study subjects were healthy elderly. *2: Measurements took place in the morning after drug intake in the evening.*3: On day 2, a significant increase in sway was observed in the afternoon, but not in the morning. *4: On day 2, an effect was found 2 and 4 hours post dose; on day 8 the measurement was only performed 10 hours post dose. *5: On day 16 and 18, an improvement was observed in the morning.

Studies with higher dosages in former drug abusers

Studies with high dosages have been performed to examine abuse liability of hypnotic drugs. Results from these studies are summarized in Table 1.

Most subjects who participated in the studies summarized in Table 1 had a history of drug and alcohol abuse[10,12,13] or were current users.[15] These studies show a clear dose-response relationship for performance on the balance test.

Table 1. Effects on body balance of higher dosages of hypnotic drugs.

Treatment	Dose	Impairment	References
Triazolam	0.25 mg	0	10, 12,13
	0.5 mg	+ 1-4h	10
		0	15
		+	12,13
	0.75 mg	+ 0.5-4h	10
		0	15
		+ (0-5h, unspecified)	12,13
Flunitrazepam	1.25 mg	+ (unspecified)	61
	1-2 mg	0	15
	3 mg	+ (0-6h, unspecified)	15
Zolpidem	15 mg	0	12
		+1-2h	10
	30 mg	+ (0-5h, unspecified)	12
		+ 0.5-3h	10
	45 mg	+ (0-5h, unspecified)	12
		+ 0.5-4h	10
Zaleplon	25, 50, 75 mg	+ (unspecified)	13

0: no significant effect compared with placebo

+: increased postural sway compared with placebo.

Co-administration of alcohol and drugs

Several studies examined the impact on body balance when hypnotic drugs were used together with alcohol (see Fig. 7).The methodology of these studies was as follows. Alcohol was administered at the same time as the hypnotic

drug or several hours later. Body sway tests started after 1-1.5 h, the time needed to reach stable blood alcohol levels. After co-administration of alcohol and a hypnotic drug impairment often was additive. In addition, the duration of impairment was often prolonged. For example, flunitrazepam 2 mg significantly disturbed balance 9 h after intake, but not thereafter. After co-administration of alcohol, relative to placebo balance was significantly impaired up to 12 h after flunitrazepam intake.[66]

Two studies assessing the effect of daily co-administration of lorazepam and alcohol showed that tolerance developed slowly: after four days and seven days of treatment with lorazepam a single dose of alcohol still impaired test performance.[49,64]

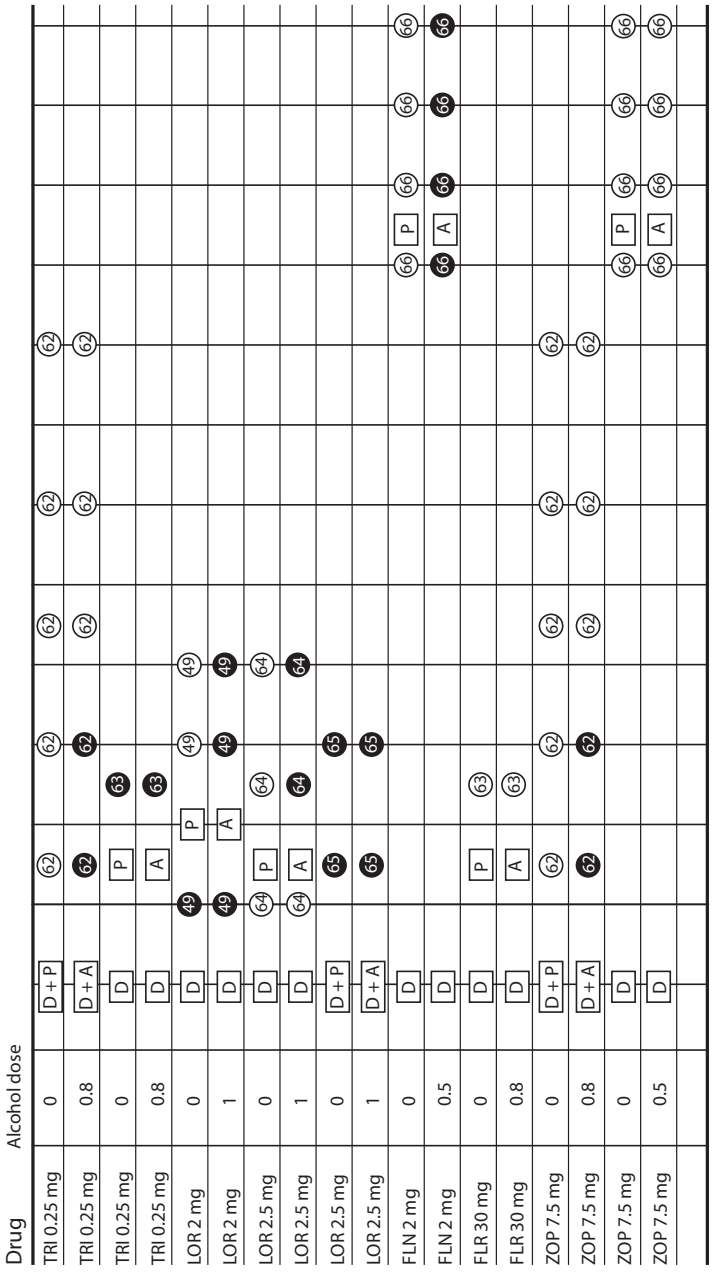

Figure 7. Co-administration of hypnotic drugs and alcohol. Each circle corresponds with a measurement in a group of subjects receiving the same dosage of the same drug. Black circles represent significant differences in postural sway compared with placebo, white circles represent no significant differences in postural sway compared with placebo, and grey circles indicate that the outcome of the measurement is unknown. The numbers in the circles indicate the corresponding references. Abbreviations: TRI: triazolam, LOR: lorazepam, FLN: flunitrazepam, FLR: flurazepam, ZOP: zopiclone, D: drug administration; P: placebo administration, A: alcohol administration, g/kg: gram per kilogram bodyweight.

Whereas alcohol consumption worsens performance on balance tests, co-administration of hypnotics with other medicinal drugs may have a different outcome. Fig. 8 gives an overview of studies that examined these effects.

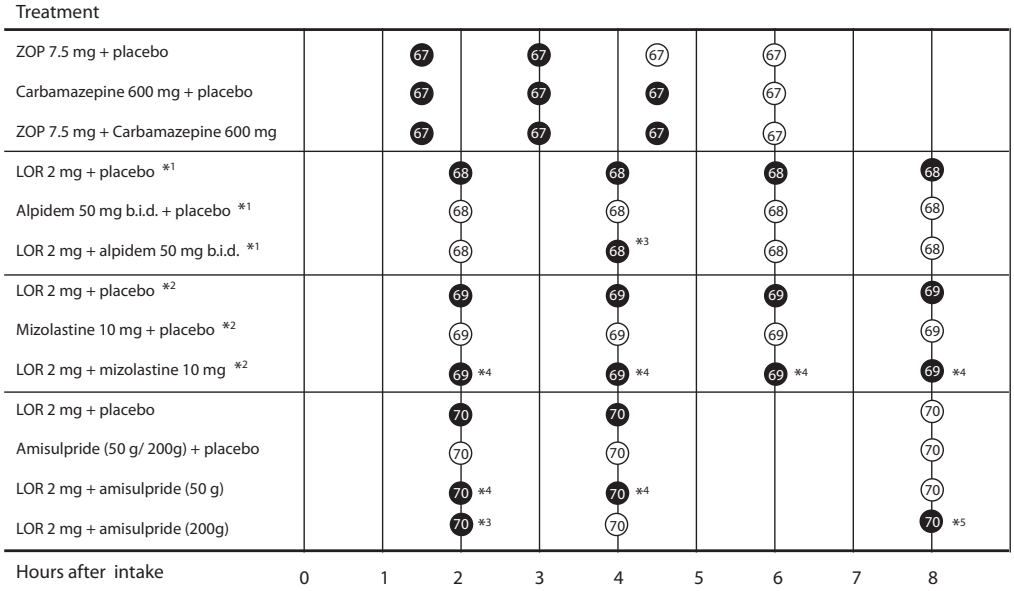

Figure 8. Co-administration of hypnotic drugs and medicinal drugs. Each circle corresponds with a measurement in a group of subjects receiving the same dosage of the same drug. Black circles represent significant differences in postural sway compared with placebo, white circles represent no significant differences in postural sway compared with placebo, and grey circles indicate that the outcome of the measurement is unknown. The numbers in the circles indicate the corresponding references. Abbreviations: ZOP: zopiclone, LOR: lorazepam, b.i.d.: two times a day.
*1: Alpidem or placebo was administered for 8 days. On day 7 and 9, a single dose of lorazepam or placebo was co-administered. Measurements took place on days 7 and 9. *2: Mizolastine or placebo was administered for 8 days. On days 6 and 8, a single dose of lorazepam or placebo was co-administered. Measurements took place on days 6 and 8. *3: The effect on postural sway was smaller than when lorazepam was co-administered with placebo. *4: The effect on postural sway was similar to the effect of lorazepam co-administered with placebo. *5: The effect on postural sway was larger than the effect of lorazepam co-administered with placebo.

Fig. 8 shows that often the effect of co-administering medicinal drugs with hypnotics was additive, but interactions may also occur. In case of an additive effect, the overall effect is the sum of the individual effects of the co-administered drugs. In the case of an interaction, the impairment may be of greater magnitude than the sum of impairments when administered separately. To make things complicated, co-administered drugs may also

reduce balance impairment produced by the hypnotic drug (e.g., alpidem). For example, lorazepam (2 mg) significantly impaired body sway up to 8 h after intake. However, when co-administered with alpidem (50 mg b.i.d.) impairment was less severe and lasted a much shorter time (4 h).[67] The partial antagonist properties of alpidem at the gamma-amino-butyric acid ($GABA_A$) receptor probably account for the significantly reduced impairment when compared to sole administration of lorazepam.

It has to be noted that although some drugs did not lead to additive effects or interactions when co-administered with hypnotic drugs, this finding cannot be generalized to other medicinal drugs. Much more research is needed to establish a more thorough overview over drug-drug interactions and other effects of co-administration on body balance.

DISCUSSION

Imbalance and postural instability may have serious consequences in terms of falls, hip fractures and even death.[9,71] The results from this review show that the use of hypnotic drugs may significantly contribute to falls, since these drugs affect balance and standing steadiness. The effect of hypnotic drugs on balance is most prominent at peak plasma concentrations, i.e. within the first few hours after intake. One can argue that this is of relatively little importance since patients go to bed after taking their sleep medication, but the reality of everyday life shows otherwise. Patients often wake up during the night, for example to visit the bathroom. On these instances, balance may be significantly impaired and increase the risk of falls. On the other hand, research shows that balance may be still significantly impaired the morning following bedtime intake of hypnotics. When selecting time points for balance assessments, peak plasma concentrations, time of rising, and times most likely for nocturesis should be taken into account. This has not always been the case in the studies summarized in this review. This may explain why some studies did not find effects on balance after the intake of a certain hypnotic drug whereas other studies did.

Impairments have not only been found for benzodiazepine hypnotics, but also for the newer hypnotics such as zopiclone and zolpidem. One cause of impairing effects of hypnotic drugs on body balance may be that they all act at the $GABA_A$ receptor complex. The acute and residual sedative effects of

benzodiazepine hypnotics and the Z-drugs on human performance have been consistently shown on various skills and abilities that are essential in real life, for example when driving a car.[72] Because maintaining postural control is governed by a number of functions, other processes may also play a role.

It should also be noted that impairment is much more profound if higher dosages are used, with a shorter time between intake and waking up, or after co-use with alcohol or other medication. Elderly consistently perform worse on balance tests when compared to young adults. Falls are reported more often in elderly, and recovery is much slower. Therefore, this group of hypnotic drug users deserves special attention in terms of prevention of falls when treated with hypnotic drugs.[73]

Studies with chronic dosing show that tolerance develops to the effect of hypnotic drugs on standing steadiness. However, this tolerance develops slowly, depends on the type of hypnotic, and may not be present in case patients use hypnotic drugs on an as-needed basis. That tolerance is only partial is illustrated by studies showing that falls and hip fractures are still over-represented in chronic users of hypnotic drugs.[9]

Studies examining the effect of sleep medication on postural balance have a number of limitations. First, balance tests are often included in a test battery, but only few studies thoroughly discuss the results obtained in the balance task. Often there is no clear rationale for the time of testing and effects corresponding to T_{max} and C_{max} are not measured. Also, relatively few studies measure next-morning residual effects; especially 7-9 h after intake little information is available (Fig. 4). Importantly, the mechanisms by which hypnotic drugs impair postural equilibrium are rarely explained. Second, it has to be noted that relatively few studies have examined balance after the combined intake of hypnotics and other drugs. Since sleeping problems occur relatively often in persons with medical conditions and psychiatric disorders, more attention should be given to the effects of co-administration of hypnotics with other drugs. Furthermore, different balance tests and parameters have been used which make study results difficult to compare. Simple tests, such as the ability to stand upright on one foot are less capable of detecting balance impairments than computerized posturographic testing. Testing with eyes open or closed has a great impact on the outcome of balance tests. Most studies found most pronounced impairments in the eyes open condition. It

was suggested that this condition is most suitable for assessing postural stability after the intake of hypnotic drugs as they impair correction of body sway through the visual system.[62] In contrast, others only found impairments in eyes closed conditions and state that the visual feedback system compensated for the decline in proprioception in eyes open conditions.[24] In addition, there is no agreement on whether dynamic or static platforms are best in predicting falls.[52, 71, 74] Comparative studies of different balance tests should give insight in this important issue. Lastly, while balance may be differently affected in males and females, especially in the aging population,[75,76] the studies that were discussed here rarely differentiated between genders.

Although many methodological issues should be solved to improve balance testing and in general researchers should more thoroughly report the complete results of balance tests, our review gives a clear picture of the potential impairing effects of hypnotic drugs on body balance. Taken together, patients should be warned that hypnotic drugs might impair their standing steadiness, even the following morning.

Practice points

1. Single dose administration of hypnotic drugs to healthy volunteers significantly disturbs body balance.
2. Impairment after bedtime intake may last until the following morning.
3. Impairment is dose-dependent.
4. The magnitude of impairment is correlated with blood plasma concentrations and is greatest at peak plasma concentrations.
5. Impairment aggravates after co-administration of alcohol or psychoactive drugs.
6. Partial tolerance develops after repeated daily use of hypnotic drugs
7. In chronic drug users, acute administration of hypnotic drugs may also result in disturbed balance although the magnitude of impairment is less profound when compared to treatment-naive subjects.

Research agenda

1. Studying the effects of chronic use of hypnotics on body balance.
2. Set-up of prevention programs to inform users of hypnotic drugs about the risk of falls.
3. Development of hypnotics that do not affect body balance.

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NARCOLEPSY AND TRAFFIC SAFETY

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ABSTRACT

Driving ability in narcolepsy patients is often affected due to excessive daytime sleepiness and disturbed vigilance. Cataplexy and sleep paralysis may also play a role, but to a lesser extent. In this chapter, epidemiological evidence and experimental studies assessing driving performance in narcolepsy patients are discussed. Subjective patient reports on crash rates show an increased risk of motor vehicle accidents in narcolepsy patients. Driving simulator studies and psychological tests show that narcolepsy may significantly impair driving performance and may lead to an increased risk of car crashes. Studies on the effect of narcolepsy treatment on driving are limited and most evidence comes from studies in other patient populations or healthy volunteers. Thus, driving studies in real traffic should be performed in narcolepsy patients, and epidemiological evidence on traffic accident risks should be obtained.

Keywords: narcolepsy, excessive daytime sleepiness, vigilance, driving, accidents

INTRODUCTION

Excessive daytime sleepiness (EDS) can have a negative effect on driving ability and traffic safety. The 2002 Gallup survey [1] revealed that 37% of all drivers reported having nodded off or fallen asleep at least once in their driving career. Similarly, the Sleep in America Poll [2] 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. The relationship between excessive sleepiness and injury risk was examined by Powell and colleagues [3] who 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 ($P < 0.0001$).

Narcolepsy is a neurological disorder that is characterized by excessive daytime sleepiness [4]. Apart from EDS, best-known symptoms of narcolepsy are cataplexy, hypnagogic hallucinations, sleep paralysis, and nocturnal sleep disturbances. Equally important, especially in the context of driving, but less well described, is disturbed vigilance [5]. A review of Fulda and Schulz [6] on 14 studies concerning cognitive functioning of patients with narcolepsy, revealed that narcolepsy is characterized by reduced alertness, poor performance on divided attention and tracking tasks, and reduced vigilance. These functions are all of importance when driving a car.

NARCOLEPSY AND ACCIDENT RISK

Broughton et al. [7] performed a survey among 180 patients with narcolepsy and 180 matched controls. Patients, as compared to healthy controls, reported more occasions of falling asleep at the wheel (67% vs. 6%), frequent experiences of near accidents (67% vs. 0%) and a higher prevalence of actual accidents (37% vs. 5%). In addition, cataplexy (29%) and even sleep paralysis (12%) while driving were reported. Cultural differences appear to play a role, as shown in a subsequent report on the survey [8] revealing differences between three different geographic populations of narcoleptics. Czech narcoleptics drove significantly less than the other populations in Japan and North America. Those who did drive reported significantly less occasions of falling asleep at the wheel, and reported fewer near accidents compared with Japanese and North American patients.

Aldrich [9] examined subjective reports of sleep related accidents in male (n=25) and female (n=31) narcoleptics, controls, and other sleep disorder patients with and without EDS. In the population of narcoleptic patients, 52% of male and 29% of female patients had ever experienced motor vehicle accidents (MVAs) due to sleepiness, for controls this was 11% and 6%, respectively. Narcoleptics had an average of one incident per subject for male and 0.42 for female subjects. In addition, 72% of males and 74% of females had near-accidents caused by sleepiness, with an average of 19.1 for males and 9.2 for females. A greater proportion of MVAs was attributed to sleepiness in narcoleptics compared to controls: 49% vs. 5% in males and 30% vs. 4% in females. Thus, the total number of accidents did not differ between patients and controls, but the proportion narcoleptic patients having sleep-related accidents was higher than in other patient groups and four times higher when compared to healthy controls. Finally, multiple sleep latency test scores did not suggest that narcoleptics who had accidents were sleepier than those who did not.

In contrast, Ozaki et al [10] did find an association between sleepiness as examined by the ESS, and number of MVAs or near-miss incidents (OR=14.63, 95% CI:1.97 to 108.67). In this study, 55% of a total of 80 Japanese narcolepsy patients experienced at least one accident or near-miss accident in the last 4 years. Other studies also reported a significantly increased traffic accident risk for patients with narcolepsy [11]. Besides these small studies, epidemiological evidence on the relation between narcolepsy treatment and MVAs is lacking.

NARCOLEPSY AND DRIVING PERFORMANCE

Driving Performance of Untreated Narcolepsy Patients

Thus far, driving performance in untreated narcoleptic patients has only been studied in driving simulators. A study by Findley and colleagues examined driving performance in ten untreated narcoleptic patients [12]. In a relatively simple RT driving task (the Steer Clear), a car driving on a two-lane highway is presented. Occasionally, obstacles appear on the road. The subjects can avoid collisions by pressing the space bar allowing the car to switch lanes. During a 30 minute-task, narcolepsy patients had a higher number of collisions compared to matched controls. In addition, larger numbers of objects hit in

the Steer Clear was associated with a higher reported number of MVAs in the patients with narcolepsy.

The Steer Clear was also used in a subsequent study [13], which compared performance of 16 narcoleptic patients with that of 31 untreated sleep apnea patients and 14 healthy controls. The number of collisions during six four-minute periods of simulated driving was significantly higher in narcolepsy and sleep apnea patients than in healthy controls. Notably, the inter-subject variability in errors in narcoleptic patients was much higher than in other groups: four times higher than in apnea patients, and one hundred times higher than in healthy controls; this indicates great differences in impairment levels between narcoleptic patients.

In a study by George and colleagues [14], a simple divided attention driving test with duration of 20 minutes, was performed to compare performance between 21 patients with sleep apnea, 16 narcolepsy patients and 21 healthy controls. Again, large individual differences were found. Overall, patients performed much worse than controls; still, half of the narcoleptic patients did not differ from healthy controls. Furthermore, only a weak relationship between multiple sleep latency test scores and tracking performance was found.

Kotterba and colleagues [15] assessed the association between driving simulator performance and neuropsychological testing in narcolepsy in thirteen patients with narcolepsy and ten healthy control subjects. A 60-minute driving simulator test was performed and included different weather and daytime conditions and occasional displays of obstacles on the road. The number of accidents, i.e. crashes with other cars, pedestrians, or obstacles on the road, was recorded. In addition, concentration lapses, such as disregarding traffic lights, speeding or driving at night with switched off headlights, were counted. Patients with narcolepsy had significantly more accidents than healthy controls, but no differences were found on the number of concentration lapses.

Treatment Effects on Driving Performance

Studies examining the effects of drug treatment on driving performance in narcolepsy patients are limited. The current first line treatment option for narcolepsy patients suffering from EDS and cataplexy is the use of gamma-

hydroxybutyrate (sodium oxybate). In addition, modafinil is used to improve symptoms of EDS. However, their respective effects on driving performance in narcolepsy patients, alone or in combination, have not been examined yet.

Up to now, only the effect of methamphetamine on driving has been studied in narcolepsy patients [16]. A daily dose of methamphetamine was administered to 8 narcoleptic patients (0, 20 or 40-60 mg) and 8 healthy controls (0, 5 or 10 mg) for 4 days for each dosage, separated by 3 days of washout. On the last day of treatment, sleep tendency was assessed in the multiple sleep latency test, which showed an increase in sleep latency from 4.3 minutes (placebo) to 9.3 minutes (highest dose) in narcoleptic patients. In healthy controls sleep latency increased from 10.4 (placebo) to 17.1 minutes (highest dose). Similar results were obtained in driving ability as assessed by the Steer Clear driving simulator. Error rate on the driving task decreased from 2.53% in the placebo condition to 0.33% in the highest dose for narcoleptic patients. In healthy controls, the error rate decreased from 0.22% (placebo) to 0.16% (highest dose). Performance after intake of the highest dose of methamphetamine in narcoleptic patients did not differ significantly from performance in healthy controls receiving placebo.

The beneficial effect of stimulant use on driving performance is confirmed in two healthy volunteer studies performed on-the-road in normal traffic. The first study [17] examined the effects of 3-4-methylendioxymethamphetamine (MDMA; 75 mg), methylphenidate (20 mg) and placebo on driving performance in recreational MDMA users. On-the-road driving tests were performed 3 to 5 hours after drug use, and the next day (27 to 29 hours after intake) to examine possible withdrawal effects. The first driving test measured the participants' ability 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 comprised following a lead car and measured speed adaptation and brake reaction time. Both MDMA and methylphenidate significantly improved driving performance as indicated by a decrease in SDLP. In contrast, MDMA negatively affected performance in the car following test, while performance after using methylphenidate did not differ significantly from placebo. No significant differences from placebo were found upon withdrawal. The second study [18] assessed the effects of

methylphenidate on driving performance in adults with attention deficit hyperactivity disorder (ADHD). After a training session and a withdrawal period of at least four 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. Similar to previous findings, methylphenidate significantly improved driving performance when compared to placebo. These results suggest that stimulant drugs may also improve driving quality in patients with narcolepsy.

While there are no studies are available on the effect of sodium oxybate on driving performance, some evidence on the effects of modafinil on simulated driving performance is available, albeit contradictory. A recent study [19] showed that in sleep apnea patients who stopped their Continuous Positive Airway Pressure (CPAP) treatment and tested the following day, modafinil (200 mg) did not improve performance in the STISIM driving simulator. In contrast, another study in the STISIM driving simulator [20] did show an effect of modafinil (300 mg) on driving performance in 16 healthy individuals during an overnight period of sleep loss. Compared with placebo, modafinil significantly decreased weaving, both on a monotonous driving ask and in a divided attention driving task. No effect on response speed in the divided attention task was observed.

Methodological Issues in Driving Simulator Studies

Apart from the fact that evidence from simulator studies is limited, there are also a number of limitations that should be taken into account when interpreting the available information. First, while some studies find that reduction in daytime sleepiness is accompanied by an improvement in driving performance [21], this does not mean that when treatment reduces sleepiness, safe driving is ensured. Second, the driving simulators that were mentioned in this chapter greatly vary. Especially the older driving simulators can be regarded as simple divided attention tasks. They do not differ from laboratory tests measuring cognitive and psychomotor skills that are generally limited in their predictive value of actual driving performance [22]. An additional limitation is the artificial environment of the driving simulator. Often other traffic is lacking, and subjects may perceive the driving simulator as a game. Testing driving performance in real traffic is therefore necessary.

GUIDELINES ON FITNESS TO DRIVE

Individual patients differ greatly in the extent to which their functioning is impaired. Therefore, fitness to drive should be assessed on an individual level. Physicians and psychiatrists usually rely on their own clinical experience and take into account the presence and severity of symptoms when making a decision on fitness to drive. Unfortunately, due to differences between physicians in interpretation of the assessment criteria, these decisions are not always uniform. In line, agreements on driving license decisions, i.e. the willingness of Medical Commissions to inform driving license authorities, ranged from 73% to 100% in an Italian study [23]. The decision correlated significantly with age, number of daytime naps, sleepiness, cataplexy, and quality of life. On a global level, guidelines on narcoleptic patients and their ability to operate a vehicle vary widely [24]. Furthermore, most European countries do not include EDS among the specific medical conditions to be considered when judging whether a person is fit to drive. Therefore, a unified European Directive seems desirable. In addition, public awareness should be raised regarding the potential hazardous effects of narcolepsy and EDS on driving in order to reduce the number of traffic accidents [25-26].

CONCLUSION

This chapter shows that untreated narcolepsy may significantly impair driving ability, which may lead to an increased risk of traffic accidents. It is also evident that more research needs to be conducted. More systematic epidemiological studies are needed to determine traffic accident risk determinants in patients with narcolepsy. In addition, although suggested by driving simulator studies, there are no real-life driving data supporting the positive effect of treatment of narcolepsy on driving performance. It is therefore of importance to examine the effect of the current treatments on driving performance in narcolepsy patients, preferably using the on-the-road driving test during normal traffic. The results of these studies are necessary to develop guidelines on decisions of fitness to drive in narcolepsy patients.

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5

SHIFT WORK AND TRAFFIC SAFETY

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ABSTRACT

A large proportion of the working population is engaged in shift work and other irregular working hour arrangements. These kinds of employment can lead to disruptions in the alignment between working hours and circadian rhythms.

Shift work is an important contributor to motor vehicle accidents. Shift workers have a higher risk of sleepy driving, falling asleep behind the wheel, near miss accidents and actual accidents, as compared to regular daytime workers. Especially night shift workers, rotating shift workers, and those working extended shifts are at risk. Countermeasures are necessary to prevent drowsy driving. Currently used methods involve stimulant drugs to enhance alertness, hypnotics to improve sleep, light treatment, melatonin, and scheduling of sleep to treat the circadian misalignment.

Keywords: Shift work, drowsy driving, modafinil, melatonin, shift work disorder, circadian rhythm

INTRODUCTION

Before the introduction of electrical light, humans largely adapted their daily activities to the natural light-dark cycle. When modern technology enabled the production of artificial light, it became possible to change this rhythm and work during the dark part of the day. After the industrial revolution, factory managers wanted to make optimal use of their machinery by designing work schedules that enabled continuous around the clock production, leading to an increase in the number of people working in the evening and night. Later, this trend progressed to other areas such as the service industry. All these developments contributed to our 24-hour society with its numerous benefits.

However, an important consequence of these kinds of working hour arrangements is that they may affect normal biological and social rhythms [1]. In line, an increasing body of literature addresses the negative effects on health, well-being, and cognitive performance [2-3]. Furthermore, a decrease in occupational performance and an increase in accident risk, both at work and on the road, may be the result.

In this chapter, the effects of irregular working hours on traffic safety will be discussed, as well as empirical evidence on road traffic accidents and driving simulator studies in shift workers.

Non-traditional Working Hours

About 15-40 percent [4-6] of the working population in industrialized countries performs their work at times at which others are asleep or enjoy leisure time. These workers are usually referred to as shift workers. Common examples are found in factories, healthcare, and police and fire departments. Yet, the concept of shift work is quite vague, which is reflected by the fact that there is no consensus over a proper definition. Although several definitions are in use, most agree on one criterion: all or part of the duties are performed outside standard working hours [7-8]. Usually, working days commencing after 6.00-8.00 AM and ending before 6.00-7.00 PM , with a maximum of 8 hours per day and approximately 40 hours per week, are considered to be standard [9,10]. In addition, standard work is performed during a continuous on-duty period, except for breaks [9].

A variety of shift working systems exists which vary in types of shifts (morning, afternoon, night), duration of shifts, number of shifts in a row, and

speed and direction (backward, forward) of rotation. In addition, a distinction can be made between 'conventional' shift work, in which people work a substantial part of the working week outside normal daytime hours, and flexible working hours, which include early starts and late finishes, overtime, compressed workweeks, and other irregular schedules. The latter has its own definition: "*Flexible Working Hours involve a continuous choice on behalf of employers, employees or both, regarding the amount (chronometry) and the temporal distribution (chronology) of working hours*" [11]. In other words, whereas 'conventional' shift work is usually organized according to strict schedules, an important feature of flexible working hours is that they are not.

One commonality between conventional shift work and flexible working hours is that people may experience conflicts between their working schedules and their natural patterns of sleep and activity. Therefore, another definition seems more appropriate: "*Shift work refers to work patterns that extend beyond the conventional 8-hour work day and that potentially disrupt workers' normal biological and/or social diurnal rhythms*" [1].

Shift Work (Sleep) Disorder

Some shift workers suffer from shift work maladaptation syndrome, which encompasses the whole of problems shift workers may run into in the long term, e.g. domestic and social problems, health problems, decreased work performance, sleep deprivation, and circadian disruption. When specifically focusing on sleep and circadian rhythms, the condition is called "shift lag" or "Shift Work Sleep Disorder" (SWSD). More recently, the term was changed into 'circadian rhythm sleep disorder, shift work type' or 'shift work disorder' (SWD). The official diagnostic criteria for SWD are insomnia during daytime sleep and excessive sleepiness associated with a work period overlapping the normal sleep period [12]. Overall, the prevalence of SWD is estimated at two to five percent of the total population [12]. Drake and colleagues made a comparison with daytime workers and established a prevalence of 14.1 percent in night workers and 8.1 percent in rotating shift workers, which is equal to an average of 10 percent in the shift worker population [13]. However, the proportion of shift workers experiencing problems may be much larger. Åkerstedt for example suggested that 75% of the total population of night shift workers experiences sleepiness on every night shift [14].

Because different diagnostic criteria are used, it is difficult to give reliable estimations regarding incidence and prevalence. In addition, the 'healthy worker effect', i.e. individuals who are resistant to negative effects keep their occupation, whereas others seek other kinds of employment, further obscures exact numbers. A further issue is that individuals may be diagnosed with SWSD according to the two previously mentioned criteria, but the question that remains is: where is the boundary between a normal response to night or shift work and a pathological response, i.e. a true diagnosable disorder [15]?

SWD is a circadian rhythm sleep disorder and as such, is caused by the misalignment between the environment and the endogenous circadian system. A number of reports focus on the mechanism leading to these sleep disturbances [16-18]. In short, sleep is regulated by homeostatic and circadian processes, two processes that also predict alertness and performance [17]. The homeostatic process refers to a need for sleep, which builds up during wakefulness and decreases during sleep. The circadian process enables an individual to remain synchronized with the surroundings. The suprachiasmatic nucleus (SCN) or body master clock is responsible for creating cycles of approximately 24 hours. Synchronizers, most importantly light, enable the endogenous rhythm to stay in tune with the environment. When night falls, the pineal gland initiates the production of melatonin, thereby inducing sleep. In the morning, light input from the retina stops the melatonin production, which in turn leads to wakefulness. The reason why some workers encounter more problems than others may be found in their social conditions, such as family life, children, social demands, increased age, but also in their biological capability to adapt. This was evident in a study by Quera-Salva and colleagues, who showed that melatonin secretion, sleep time and work performance correlated strongly. Individuals who experienced fewer difficulties in shifting to new schedules showed rapid shifts in their peak melatonin secretion [19].

So, adaptation to new schedules is possible in theory, but may take some time. However, this adaptation is often obstructed by the recurrent need to adjust, as seen in rotating schedules. Furthermore, workers often revert to normal day-night schedules during holidays and weekends. In addition, exposure to light in the morning can produce a phase shift that counteracts the process of adaptation [18,20].Thus, a situation can occur in which an

individual is oriented to the day, while working at night or in the early morning.

This mismatch can lead to a decrease in total sleep time and sleep quality. Night shift workers regularly report sleepiness and lack of alertness and vigilance while working, all of which impair performance [12]. In addition, shift workers returning home from the night shift or leaving home for an early morning shift may be at the nadir or low-point of their circadian rhythm, a time at which alertness is lowest and sleep propensity is highest. The same trough, albeit less marked, can also be observed in the afternoon.

Taken together, the problems experienced by shift workers emphasize the need of adequate management of the disorder, including an early diagnosis and recognition of its severity.

TRAFFIC SAFETY IN SHIFT WORKERS

Survey Studies

A study by the AAA Foundation for Traffic Safety showed that after alcohol consumption, drowsy driving was the most important cause of car crashes [21]. Work schedules were significantly associated with sleep related crashes. Anyone not working regular day shifts was twice as likely to become involved in a sleep related crash as opposed to a non-sleep related crash. In night shift workers, the risk was almost 6 times higher when compared with non-sleep related crashes, and over 13 times higher when compared with non-crash controls [21]. As outlined by Brown [22], apart from the scheduling of working hours, duration of the work period and the overall time available for rest play an important role. The commute to and from work is the time at which shift workers are most vulnerable for sleep related accidents, as shown by epidemiological studies.

In an Australian study in survivors of motor vehicle collisions, independent of drugs and alcohol, shift work was found to be the most important sleep-related factor contributing to collisions. Although approximately 14% of Australian employees performed shift work, 48% of injured drivers in this study were regular shift workers and 33% had worked a shift immediately before the collision [23].

Because more extreme forms of working hour arrangement can often be found in hospitals, a number of studies have focused on medical personnel. A study based on subjective reports of nurses showed that those on rotating schedules had an odds ratio (OR) of 1.14 to be involved in a car accident, and an OR of 2.63 to have a near-miss accident, when compared to those on day or evening schedules. For the night shift, the OR was 2.24 for an accident and 1.92 for a near-miss. Nearly half of all night nurses (49%; OR=3.62) and rotators (51%; OR=3.92) reported nodding off during the commute [24]. A recent study showed that nurses had less sleep prior to night and morning shift than prior to evening shifts [25]. The night shift was associated with near-misses and drowsiness. In addition, difficulties staying awake during work, feelings of exhaustion and the number of consecutive shifts predicted drowsiness and near-miss accidents. Curtailed sleep during workdays may explain the increase in accident risk, because the nurses did not report significantly longer shift durations. This confirms an earlier study that showed increased accident and near-accident risk after the night shift in emergency room residents [26]. This study also demonstrated that more night shifts per month lead to higher accident propensities. Detrimental effects of extended shifts were demonstrated in 2737 medical residents [27]. When compared with a normal shift (<24 hours), extended shifts (>24 hours) increased the risk of crashes (OR=2.3) and near-misses (OR=5.9). Moreover, each extended shift scheduled per month increased the monthly risk of a crash by 9.1 percent. Again, a significant correlation was found between odds ratios for falling asleep behind the wheel and the monthly number of extended shifts. In reports of 895 hospital nurses, 66.6% had at least one episode of drowsy driving during a four-week period [28]. Drowsy driving was reported in one out of every four shifts. Nearly 16% reported at least one crash or near-miss incident. Most incidents occurred after extended shifts (>12.5h; 59%) and after night shifts (55%). The night shift increased the risk for drowsy driving incidents (OR=3.96); 79.5% of night nurses experienced drowsy driving at least once. Furthermore, those who struggled to stay awake at work had an OR of 3.37 to have a drowsy driving episode. Hours of sleep were also found to add to drowsy driving: the risk increased by 9% per hour of sleep loss.

Marcus and Loughlin [29] compared residents who were on call every fourth night with other faculty members who did not work at night. They revealed

that 44% of the residents had fallen asleep when stopped at a traffic light compared with 12.5% of faculty staff, and 23% had fallen asleep when driving compared with 8% of faculty staff. In total, 49% of residents had fallen asleep behind the wheel, of which 90% had occurred post-call.

The most extreme findings are from focus group interviews on intensive care nurses who worked 12-h shifts. An alarming 95% reported automobile-related injuries and near-accidents that occurred during the commute to and from work [30].

Studies in other occupational areas show similar findings. Sleep durations of less than 6 hours, working night shifts, and traveling durations of over 35 minutes were associated with sleepiness and driving impairment [31]. An Australian study [32] confirmed that sleepiness after long distance driving following night work was significantly higher in shift workers (n=180) when compared to non-shift workers (n=1375). Only 1 percent of non-shift workers reported severe sleepiness as opposed to 19 percent of shift workers. In a case-control study, each hour of sleep reduction below 7 hours was found to significantly increase the odds ratio of having a sleep relating traffic accident [33]. Similar to previous results, night and rotating shifts, and working more than 60 hours per week were associated with sleep-related crashes.

The main findings are summarized in Box 1.

Box 1.

Major findings from commuting shift workers:

- high prevalence of sleepiness and nodding off when driving home after night shifts and rotating shifts
- struggle to stay awake at work, exhaustion and number of consecutive shifts can predict drowsiness and near miss accidents after shift work
- extended shifts increase the risk of crashes and near-miss incidents
- the risk of falling asleep behind the wheel increases with the number of extended shifts per month
- long driving distance after shift work is related to severe sleepiness
- sleep durations below 6-7 hours are associated with sleep related crashes

Driving Simulator Studies

A safe method of studying the effects of shift work on the commute under controlled conditions is to measure driving behavior in a driving simulator. Relatively few published studies into shift work and simulated driving performance were found in literature.

Three papers [34-36] were part of a research project in which ten shift workers with five to nine years of shift work experience were tested in the morning following a night shift and after a night of normal sleep. Driving performance, i.e. lane drifting, subjective sleepiness (Karolinska Sleepiness scale (KSS); higher scores reflect more sleepiness), and blink duration (EOG) were measured. After the night shift, subjects experienced significant higher sleepiness levels, which increased faster than after a night sleep; blink duration and lane drifting were increased and both increased during the test drive. Accordingly, more incidents, i.e. two wheels outside the lane markings, and more accidents, i.e. four wheels outside the lane markings, occurred after the night shift [34]. A subsequent paper [35] shows an association between subjective sleepiness (KSS), objective sleepiness (blink duration) and lane drifting. The results suggest that high KSS levels are associated with a sharp increase in lane drifting and blink duration. Furthermore, a large individual variation between sleepiness levels, blink durations, and number of accidents was found. Taking into account this large variation, the third paper [36] elaborated on these findings and found that KSS scores and accident risk, especially for severe events, were strongly related. On average, the estimated accident risk increased by 28.2 when the KSS score increased from 5 to 8, and increased by 185 when the sleepiness score increased from 5 to 9. Most importantly, this paper addresses the difficulties in the interpretation of group scores. Part of the subjects in the group accounted for a large proportion of accidents, which has implications for making judgments based on group averages.

Another simulator study which assessed the effect of a 40-minute nap during the night shift on driving performance in nurses (n=49) the following morning [37]. Dangerous driving, i.e. the car leaving the road or colliding with other vehicles, was observed in a large proportion of the total driving time: 8 percent, both in the nap- and in the no-nap group. However, although observations indicated that drivers in the nap-group were more alert, no

differences on driving performance were found. Individual differences probably account for this finding.

A study in medical personnel (12 male and 7 female medical residents) examined driving and sleepiness after a night on-call versus a night off-call [38]. The results were unexpected: male residents drove significantly poorer after a night on-call as expressed by lane drifting and crash frequency. However, the two conditions, i.e. on-call versus off-call, did not differ regarding their effect on driving ability. Significant differences were found on a number of sleep parameters. After a night on-call, a decrease in total sleep time and an increase in subjective sleepiness was observed. Sleepiness was significantly greater after the drive than before. It is hypothesized that male and female participants cope differently with sleep loss, which may explain the differences in driving performance.

The effect of shift schedules on driving and sleepiness was assessed in a study by De Valck and colleagues [39]. A total of 18 shift workers in a fast-forward rotating shift system were compared with 18 shift workers in a slow-backward rotating system. Each subject performed a 25-minute drive after each shift (morning, afternoon and night). However, not the shift system, but the shift type proved to influence driving performance: lane drifting was increased after the night shift compared to the afternoon shift, while no differences were found between the shift systems. Still, sleepiness was affected by the shift system, with higher levels of sleepiness in the slow-backward rotating group compared with the fast-forward rotating group. Highest sleepiness levels were reported after the night and the morning shift. Similarly, in the night and morning shift, higher levels of caffeine consumption were reported.

Arnedt and colleagues [40] compared performance impairment post-call after four weeks of heavy call with alcohol-induced impairments. They examining simulated driving ability, sustained attention, vigilance, and self-reports on sleepiness and performance in 34 pediatric residents. Post-call performance was assessed in four conditions: a heavy call rotation schedule (90 hours per week), heavy call with placebo-alcohol, light call (44 hours per week), and light call with alcohol up to a blood alcohol concentration (BAC) of 0.04-0.05%. Compared with light call *without* alcohol, the heavy call condition led to an increase in lane variability of 27%, an increase of 29% in speed

variability, and an increase in driving off-road. When comparing heavy call to light call *with* alcohol, lane variability and driving off-road did not differ, while speed variability was increased by approximately 70%. Subjective reports showed that 58.8% of heavy call residents rated their driving as poor or worse compared with 5.9% in the light call group with no alcohol. In the heavy call and placebo group, 44.1% rated their driving as worse, compared to 11.7% in the light call with alcohol group. Self-ratings in both heavy call groups were associated with lane and speed variability. This was not the case in either light call group. In addition, performance on tasks of attention and vigilance was worse in heavy call than in light call and comparable in heavy call versus light call combined with alcohol. Box 2 summarizes findings from driving simulator research.

The major findings derived from simulator studies are summarized in box 2. It has to be noted that, although simulator studies aim to reflect real life situations, assessing driving performance in a simulator has limitations. Driving simulators may enhance sleepiness [34]; subjects experience no real risk, may be less stimulated, less willing to exert effort and fall asleep sooner. The accident risk derived from these studies may therefore be larger than in real life situations. In addition, as different aspects and different shift worker populations in different shift systems were assessed, the comparability is limited. Future research should aim to examine uniform groups of shift workers, preferably in on-the road driving studies in normal traffic.

Box 2.

Major findings from driving simulator studies in shift workers:

- night shifts and early morning shifts lead to increases in lane drifting, accident risk and subjective sleepiness scores
- afternoon shifts have few negative consequences
- napping may improve alertness
- subjective sleepiness levels are predictive of accident propensity
- few drivers account for relatively large numbers of accidents
- personality traits are likely to be involved in the adaption to shift work
- males seem to be more at risk than females

Occupational Drivers

In the transportation industry, the effects of disrupted sleep-wake schedules may have serious consequences. Truck drivers often work irregular hours including night work, and often spend long hours behind the wheel. Taken into account that a fully loaded truck may weigh over 45,000 kg, truck crashes regularly lead to serious injuries or death. These and other occupational drivers such as bus and taxi drivers face additional challenges when confronted with irregular working hours. Especially the combination of circadian disruptions and long driving hours may lead to drowsiness and increased accident risk.

A study by the United States National Transportation Safety Board (NTSB) revealed that 31 percent of all fatal commercial truck crashes were attributable to fatigue. This was the most likely cause of crashes, preceding the use of alcohol and drugs [41]. However, large differences in the percentages of accidents attributed to fatigue are seen, probably caused by underestimation of the role of sleepiness in police reports [42].

Another study by the NTSB showed that drivers with irregular working hours were more often (67 percent) involved in fatigue-related accidents than drivers working regular hours (38 percent). The duration of the sleep period, the total amount of sleep in the preceding 24 hours and split sleep patterns were most predictive for fatigue-related crashes [43]. This study confirms that sleep deprivation plays an important role: truck drivers who were involved in a fatigue-related accident had on average 2.5 hours less sleep than drivers involved in other types of accidents.

Several studies support this finding. Sleep durations of 5-6 hours per night are often reported by drivers [44-46]. As many as 30 to 47 percent of commercial drivers reported falling asleep behind the wheel [47,48]. The numbers differ depending on the driver population: a distinction between long and short haul driving is often made. Especially in long haul truck driving, i.e. long distance driving, which requires sustained attention, truck drivers are believed to be primarily are at risk for accidents. Yet, short distance driving may also be influenced by sleep restriction. In a study in daytime short haul drivers, fatigue was reported by 38 percent of subjects at least once a week and 45 percent reported nodding off while driving in the preceding year. Factors associated with a higher frequency of experienced fatigue were long

work hours, high subjective workload, and the proportion of cargo movements from customers to depots [49]. A study comparing long and short-haul drivers showed that 40 percent of long haul and 21 percent of short-haul drivers had problems maintaining alertness in 20 percent or more of their drives. Approximately 25 percent of long haul drivers reported having nodded off at least twice while driving, whereas about 8 percent of short haul drivers reported this. Two or more near-miss accidents within the last 3 months were reported by 10 percent of long haul drivers and approximately 4 percent of short haul drivers [50]. In bus drivers, similar results were found. For example, 60 percent of Brazilian interstate bus drivers who worked in shifts reported sleep-related complaints, and 16 percent reported dozing off while driving [51]. This suggests that commercial driving per se leads to increased sleepiness in large numbers of drivers.

Several studies in truck drivers established a correlation between excessive sleepiness and driving accidents [44,45,52]. Long daily work hours and extended time on the road increase the accident risk. This was demonstrated in a study in Sydney taxi drivers. While the majority (67 percent) worked long shifts, breaks were short and a negative correlation between total average break time and accident risk was observed [53]. Other studies examining the total driving time demonstrated that accident risk significantly increases after four to six hours of driving [54,55] and that accident risk significantly increases to a three-fold risk in the eleventh hour of driving [55].

Overall, sleep related crashes occur more frequently at night or in the early morning and in the early afternoon [56-58]. A study using EEG parameters supported this by demonstrating that sleep-like states while driving were predominantly present during the late night and early morning [46].

Personality traits and coping strategy are quite probably of high importance in driver fatigue. Moreno et al. [59] compared the sleep duration and frequency of truck drivers on fixed schedules with truck drivers on irregular working hours. The latter displayed a polyphasic sleep pattern with more sleep episodes that had a shorter duration, whereas the drivers on fixed schedules displayed a monophasic sleep pattern. It is suggested that the ability to fragment sleep may be an individual trait or a coping strategy, which manifests itself under certain circumstances, such as work pressure. On the other hand, another possibility might be that truck drivers' unhealthy lifestyle

leads to sleep disturbances displayed by fragmented sleep. Still, similar to studies in commuting shift workers, commercial driver-studies have shown that few drivers account for a large percentage of accidents [60].
Stress and high work demands also influence driving performance [47,48]. To protect drivers from extreme working hours, most countries limit driving times by setting up driving and resting time regulations controlled by using tachograph discs to record driving times. However, commercial pressure sometimes leads transportation companies to force their drivers to break the driving time regulations. Cheating with tachograph discs is a quite common procedure, but solutions that are more creative are also regularly exerted. An example is the provision of false permission letters before sending drivers abroad. This way, a driver can 'prove' to have had a day off, while in fact the driver has been working.

To keep up with high work demands, drivers often resort to stimulating substances to remain alert, although other reasons of abuse should not be excluded. Two Brazilian studies demonstrated that stimulant drug use was highly prevalent in truck drivers: 11.1 percent used stimulant drugs such as amphetamines and 77.1 percent of amphetamine users took them 6 times per week or more [44]. In the second study, 66 percent of drivers used amphetamines [61]. Two Australian surveys, as part of one study, support these findings: respectively one in five and one in three truck drivers reported stimulant use to fight fatigue. Frequent stimulant use was associated with breaking traffic rules, having extended working hours, and reporting higher sleepiness levels and falling asleep while driving [62].

The truck drivers in the Brazilian studies also reported high levels of alcohol use: 50.9 percent [44] and 91 percent [61]. About half of the drivers consumed alcohol at gas stations alongside the highways. In previous research, the combined effects of extended wakefulness and alcohol proved to have tremendous negative effects on simulator driving ability and on alertness, even when low, legal doses were consumed [63] and when the sleep restriction was moderate [64].

The final factor of importance is the prevalence of sleep disturbances in commercial drivers. A combined effect of shift work related fatigue and sleep disorders may have serious results. Sleep disordered breathing or sleep apnea are overrepresented in commercial drivers [52,65] and the effects on traffic

safety may be substantial. One study demonstrated a two-fold higher accident rate per mile in commercial drivers with sleep-disordered breathing as compared to healthy drivers [52].

The major findings on sleep deprived commercial drivers and traffic safety are summarized in Box 3.

Box 3.

Main factors associated with accident risk in commercial drivers:

- higher levels of daytime sleepiness
- poor sleep
- work schedules with long work hours and few breaks
- long total driving time
- circadian, i.e. time-of-day influences: higher risk at night/early morning and in afternoon
- high subjective job demands
- personality trait
- substance abuse
- sleep disorders

Flexible working schedules

Most studies involving shift workers were not performed in flexible workers. Extreme cases, such as interns at medical hospitals working extended shifts of more than 24 hours, can seriously endanger traffic safety, but the effects of less pronounced flexible schedules are largely unknown. Due to the great variability of existing working hour arrangements, they have not been thoroughly investigated. Fact is that flexible work is becoming more common than in the past. One trend that may be of importance is early morning work, developed to avoid night work regulations and avoid traffic congestion in the morning. As mentioned previously, early morning shifts are related to sleep deprivation and thus may lead to an increase in road traffic accidents [66].

More research into various flexible working hour arrangements is necessary to examine possible accident risk in these groups of workers.

COUNTERMEASURES

The information provided in this chapter shows that shift workers are at increased risk of traffic accidents. It is evident that countermeasures to avoid drowsy driving in shift workers are desired. On a larger scale, shift work systems can be improved to enable workers to adapt to changes in working times. A recent meta-analysis of interventions in organizations redesigning shift work schedules pointed at three types of interventions that were beneficial to health and well-being: (1) adopting fast rotation schedules, (2) switching to forward rotating, i.e. clockwise rotating schedules, and (3) self-scheduling of shifts [67]. It is also possible to treat symptoms caused by shift work on an individual level by improving sleep, realigning the circadian rhythm and increasing alertness with stimulant drugs.

Promoting Sleep

The first and most obvious strategy is to get additional sleep. An effective way to combat sleepiness is napping [18]. Different sleeping and napping strategies can be implemented to cope with nightly shift work in terms of length and timing [68]. The advantages of napping are outlined by Dhand et al. [69] highlighting the recuperative effects of daytime napping on alertness, performance and learning. In shift workers, napping prevents fatigue and increases performance [70-72]. A simulator study in shift workers showed that napping had a small but positive effect on driving [37]. More studies of this type are needed to determine the usefulness of napping in improving shift workers' driving ability.

Sleep during the daytime can be improved by improving sleep hygiene. When circadian processes prevent sleep, hypnotics may be used. A number of studies demonstrated a positive effect of triazolam [73], zopiclone [74, 75], zolpidem [76], and temazepam [77] on sleep in (simulated) shift work. The effects of hypnotics on driving ability in real traffic in a group of shift workers were examined in a study by Riedel and colleagues (1988) [78]. Midazolam (15 mg), triazolam (0.5 mg), temazepam (20 mg), and placebo were administered in the morning, followed by an on-the-road driving test in the afternoon. Daytime sleep was significantly improved by midazolam and less, but still significantly, improved by triazolam. Temazepam had no effect on any sleep parameter, and did not have an effect on driving performance.

Midazolam slightly increased car weaving after 5 days of intake, whereas triazolam had serious effects on weaving, steering behavior, time out of lane and time to lane crossing with larger effects after 5 days of intake than on the first day of intake. These results suggest that triazolam, should not be recommended to shift workers, temazepam is safe, but not very effective, and midazolam seems to be both safe and effective, at least for short-term use.

Nevertheless, it has to be noted that intake of hypnotics should not be regarded as a permanent solution for shift work related sleeping problems due to the risk of tolerance, dependence, and abuse.

Synchronizing the Circadian Rhythm

A second method is to realign the circadian rhythms. Because circadian misalignments are viewed as the main cause of drowsiness in shift workers, this also seems to be the preferred treatment. However, reaching this goal is not straightforward and depends on the motivation of shift workers and demands of their environment. To reach this objective, several methods have been developed. Melatonin is an important marker of the circadian phase [79] and an essential compound in sleep regulation. Exogenous melatonin may act as a chronobiotic, i.e. melatonin can advance or delay the circadian phase, depending on the time of intake. The desired time of administration depends on the timing of the minimum core body temperature (T_{min}), which reflects the low-point in the circadian cycle. Exogenous melatonin intake after T_{min} can result in a phase delay, i.e. later wake-up time and sleep onset; intake in the late evening (before T_{min}) can result in a phase advance. This way, the misalignment of working hours and the normal sleep-wake pattern can be corrected [79]. However, when looking at studies into the efficacy of exogenous melatonin in shift workers, some confirm that melatonin (5 mg, and 1.8 mg extended release) improves sleep [80-82], one study demonstrated moderate effects of melatonin (10 mg) [83], and others demonstrate no beneficial effect of melatonin (doses ranging from 1 to 6 mg) compared with placebo [84-86]. It is not clear if melatonin affects driving performance. One study, in which a test battery of driving-related tasks was used, did not show an effect of melatonin on the several tests, except for selective attention, which still had values within the normal range [87]. Other

substances, such as the melatonin agonist ramelteon, and its use in shift work are still being studied.

Another method to induce phase shifting is the use of bright light. Similar to melatonin, the effect depends on the time of administration. Light exposure prior to T_{min} delays the sleep phase and late night exposure leads to a phase advance. The effect is larger if the light is administered just before or after T_{min}. The effect is influenced by the light intensity and duration of the exposure. It is possible to apply bright light during the night shift, or to develop schedules to achieve gradual phase shifts. However, in many shift workers, exposure to natural bright light after the night shift suppresses melatonin production, counteracting the effect [48]. Several studies suggest that melatonin suppression mainly takes place in the blue portion of the visible light spectrum. Because a decrease in visibility when wearing dark goggles can compromise driving, blue blocker glasses seem to be a preferable option [88]. A study in which this type of glasses was tested showed that although melatonin levels were high, attention, concentration and response accuracy were not affected [89]. As pointed out in a review by Gooley, bright light is effective in the treatment of SWD [90]. However, the greatest effect can be gained when combining bright light at the appropriate time, combined with dim light or darkness in the morning, and the adoption of regular sleep-wake schedules. A pilot study showed positive effects of napping combined with bright light on shift workers' sleepiness behind the wheel, as demonstrated by EEG and sleepiness scale recordings [91]. Furthermore, a simulator study into the effects of nocturnal exposure to blue light showed effects on alertness, EEG and activity, and reaction times on a psychomotor vigilance task, but not on driving simulator performance, subjective sleepiness and melatonin levels, as compared with ambient or red light [92].

Psychostimulant Drugs

Fatigue can be counteracted by the intake of psychostimulants. These drugs show an improvement of alertness and cognitive performance [93]. For example, methylphenidate improved on-the-road driving in healthy volunteers [94] and patients with ADHD [95]. Modafinil (Provigil ®, Modiodal ®) is a wake promoting agent registered in the US and a number of European countries for the treatment of narcolepsy, sleep apnea and SWD [96]. Night

shift studies demonstrated positive effects of modafinil on alertness, performance and vigilance [97, 98] and on patients' well-being [98]. Few studies have addressed the influence of modafinil on driving, with varying results. When administered 200 mg of modafinil, shift workers suffering from SWD (N=153) reported fewer car accidents or near-miss accidents on the way home after work, as compared with placebo (29% vs 54%) [99]. In a more recent study in 25 emergency department residents, modafinil (200 mg) administered in the morning led to less difficulty attending lectures, more difficulty falling asleep and had no effect on the subjective difficulty driving home [100]. One single-blind driving simulator study was performed in 16 healthy volunteers during an overnight period of sleep loss [101]. Modafinil (300 mg) was administered at 2.30 or 3.30 AM and driving performance was examined at 4.30 or 5.30 AM in a monotonous driving task that lasted 36 minutes. After the intake of modafinil, the ability to maintain a stable lane position was improved, accompanied by reduced KSS ratings. Modafinil improved driving as reflected by a decrease in car weaving compared with placebo. When examining only the first ten minutes of the drive, the authors pose some concern regarding the ability to rate one's own driving performance as the ability to assess lane position was exaggerated after the use of modafinil, and underestimated after placebo. Double-blind studies in which other aspects of driving behavior are included are therefore recommended. Recently, armodafinil, the R-enantiomer of modafinil, became available in the US, which is approved for the same indications as modafinil. Its effect lasts longer than that of modafinil. Armodafinil was shown to improve wakefulness, memory, and attention during night work in patients with SWD [102].

Although stimulants appear to enhance driving performance, the risk of abuse and dependence of some of these substances makes their use in combating drowsy driving in shift workers questionable. In addition, they only improves symptoms of sleepiness, but do not treat the cause of SWSD. Interestingly, a comparison between the use of modafinil and caffeine after extended wakefulness showed no superiority for Modafinil [103]. Positive effects of caffeine on driving have been demonstrated in a number of simulator studies in conditions of sleep curtailment [104, 105]. Caffeine, in

higher dosages or in energy drinks, may therefore serve as a safer and cheaper substitute.

CONCLUSIONS

Many shift workers rely on participation in traffic in order to go to work. However, sleep disruptions and resulting effects on health, alertness, and psychomotor performance can greatly affect traffic safety.

Self-reports from shift workers confirm that they are indeed sleepier and more at risk for near or actual traffic accidents. However, these studies rely on subjective reports instead of objective measurements. In addition, it is difficult to estimate what proportion of motor vehicle accidents is actually sleep-related. Driving simulators, on the other hand, enable testing in controlled circumstances, but also have limitations concerning their validity. Subjects often have a decreased perception of risk as opposed to driving on the road. Still, the majority of studies point in the direction of an increase in drowsiness, impaired attention and an increase in traffic accident risk in shift workers during the commute.

An interesting result derived from a study utilizing a driving simulator was the finding of large individual differences in the number of crashes. It is likely that a proportion of workers is more sensitive to changes in sleeping patterns than others. Although some studies have provided insight in this matter by pointing at differences in shifting melatonin secretion [15], more attention should be given to these individual differences. Shift workers vary widely in their social conditions, working hours, type of occupation, genetic background, psychological characteristics, and commuting time, all of which may affect alertness or the ability to adapt. These differences make research in shift work difficult and require proper screening of the specific uniform sample of shift workers that one wants to study. Furthermore, no study has specifically studied those shift workers actually experiencing problems, i.e. SWD patients, and their driving performance. Furthermore, studies vary in the diagnostic criteria applied for SWD, which further decreases comparability.

Various countermeasures are available to combat the negative consequences of shift work. Although they appear to reduce the symptoms of shift work, few studies have examined the influence of these countermeasures on driving performance. As seen in driving simulator studies, sleepiness and

driving performance are not always affected simultaneously. This means that the possibility exists that subjects experience less sleepiness while driving performance is not improved. Therefore, it seems reasonable to examine the available countermeasures in actual shift workers or SWD patients in real driving conditions.

In conclusion, society benefits from shift work, but at the same time, shift work can be harmful due to the consequences for traffic safety. More insight in the mechanisms leading to shift work disorder and driving impairment is needed to develop optimal treatment methods. In addition, public awareness should be raised to increase understanding of the problems shift workers may encounter and to enhance the willingness to take measures that limit detrimental effects.

Box 4.

Future studies should:

- establish the effects of different types of shift work on actual driving: on-the road studies during normal traffic should be performed
- elucidate the influence of personal characteristics on the ability to adapt to shift work
- examine the effects of different treatment options on driving performance
- examine the risks of flexible working schedules

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6

SLEEP DISORDERS AND FITNESS TO DRIVE: A SURVEY AMONG SLEEP SPECIALISTS

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Submitted

ABSTRACT

Objective Whether patients with sleep disorders are fit to drive, and who should determine this, is a matter of debate. This survey examined the opinion of sleep specialists.

Methods Survey of sleep specialists assessed views on fitness to drive for patients suffering from apnea, insomnia, and narcolepsy.

Results The response rate among 1000 sleep specialist was 11%. Most of the 112 respondents (66%, 95%CI: 57-74%) indicated that insomnia patients would be fit to drive within either days or weeks after initiating treatment, but 44% (95%CI: 35-53%) felt that, depending on the amount of excessive daytime sleepiness (EDS), they should not drive if untreated. Around half of respondents (49%, 95%CI: 40-58%) indicated that untreated patients with apnea should not drive, but the majority (66%, 95%CI: 57-74%) felt they could drive after Continuous Positive Airway Pressure (CPAP) treatment was established, though EDS was a significant factor. For untreated narcoleptic patients 77% of respondents (95%CI: 68-84%) indicated they should not drive, and similarly, that treated patients could drive, although EDS levels were again seen as important.

Conclusions Specialists recognize the importance of this issue. However, patient education remains the most practical approach to improving compliance and reducing accidents associated with excessive daytime sleepiness.

Keywords: driving, fitness to drive, insomnia, narcolepsy, sleep apnea, excessive daytime sleepiness

INTRODUCTION

Driver sleepiness and reduced alertness are the most common causes of traffic accidents, accounting for 10-30% of all traffic accidents (Alford 2009; Horne and Reyner 1995; Maycock 1996). Data from the 2009 Sleep in America poll (NSF 2009) show that 28% of respondents reported that they had been driving when drowsy at least once per month during the past year, and for 11% this happened at least once a week. About a quarter of respondents (28%) reported that they had nodded off or fallen asleep while driving during the past year, and 1% reported having had an accident or near accident due to drowsiness. The number of near misses is also associated with the frequency of actual accidents (Powell et al 2007).

The most common causes of drowsy driving are lack of sleep or poor sleep quality, prolonged driving, a monotonous driving environment (e.g., a highway with low traffic density), and circadian factors, most notably driving during the night, after a night shift, or in the early afternoon(Safetynet 2009). Also, individual differences, medical condition and pharmacological treatment may cause driver sleepiness (Safetynet 2009).

Driver sleepiness and lapses of attention play an important role in highway accidents (Kerr 1991; May et al. 2009; Wertheim 1991). A recent comparison of on-the-road driving data (Verster et al. 2011) showed that driving impairment after 2 hours of nocturnal driving in healthy volunteers equaled impairment seen with a blood alcohol concentration of 0.05%, i.e. the legal limit for driving in many countries. As drivers reported higher levels of sleepiness and drove a longer distance without having a break, driving impairment was more pronounced.

Sleep disorders may contribute to drowsy driving, since patients with sleep disorders such as insomnia, sleep apnea, and narcolepsy often experience daytime sleepiness. Although the prevalence is often underestimated, sleep disorders are very common with chronic insomnia the most prevalent at around 10% of the population (Alford and Wilson 2008). Surveys show that the prevalence of sleep apnea in the driving population lies around 6%; for narcolepsy the prevalence is less than 1% (Powell et al, 2007; Philip et al. 2010).. Although patients in some European countries who suffer from sleep apnea or narcolepsy are not allowed to drive a car, most European driving

laws do not include specific statements on sleep disorders or excessive daytime sleepiness (EDS) (Rodenstein 2008).

There is an ongoing debate about whether patients with sleep disorders are fit to drive. Also, it is unclear how fitness to drive should be established, and by whom. The current survey among sleep specialists was undertaken to investigate their opinion regarding the fitness to drive of patients with sleep disorders and how this should be assessed.

MATERIALS AND METHODS

A survey was held among sleep specialists who attended the WorldSleep 2007 conference in Cairns, Australia. The approximately 1000 attendants listed in the conference proceedings were contacted by email to complete the survey. They were contacted once, and no follow up was done. Questions asked included whether and when they regarded it safe to drive a car in case of treated and untreated insomnia, narcolepsy, and sleep apnea. In addition, they were asked *who* should determine if a patient is fit for driving, and *how* this should be determined. Space was provided to comment on each question or explain their views. No ethical approval was needed to conduct this survey, and respondents were not compensated for their participation. The survey took about 10 minutes to complete.

RESULTS

N=112 sleep experts completed the survey, which is equal to a response rate of approximately 11%. Respondents were 24 women and 88 men. Half of them (56) classified themselves as sleep specialists and/or researchers, about 20% were physicians, and about 10% were psychologists. Almost all of the respondents who see patients (69.4%) acknowledged informing patients about the possible effects of sleep apnea, narcolepsy or insomnia, and their respective treatments, on driving ability. Only 1.8% stated they did not inform their patients, and 28.8% reported not seeing patients. Their views are summarized below.

Insomnia and Driving

About half of respondents (56%, 95% Confidence Interval (CI): 46-64%) indicated that people with untreated insomnia should be allowed to drive a car. Only 17% (95%CI: 20-37%) stated they should not drive, and 27%

(95%CI: 11-25%) answered that their fitness to drive depends on the amount of EDS. Regarding pharmacologically treated patients, sleep specialists had a diverse opinion (see Figure 1).

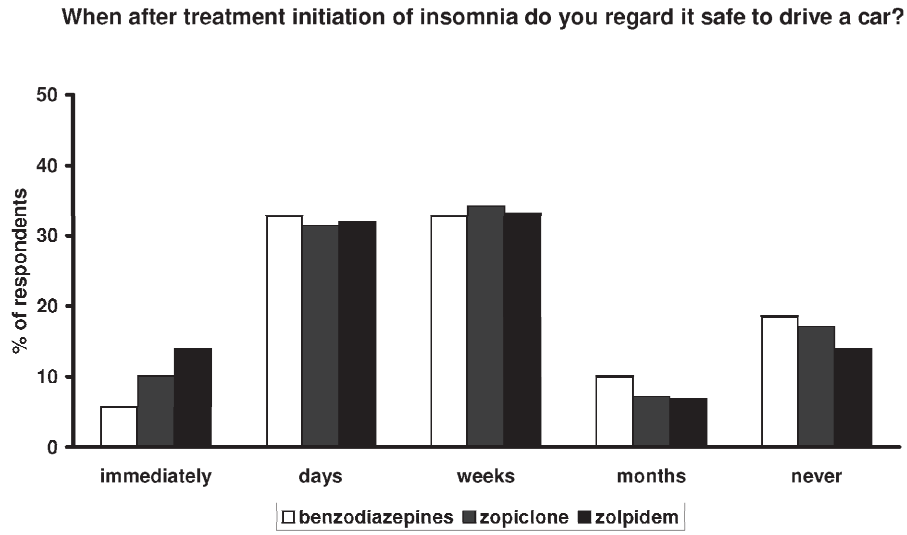

Figure 1. Answers to the question when after treatment initiation with benzodiazepine hypnotics, zopiclone and zolpidem sleep specialists regard it safe to drive a car.

Most sleep specialists indicated that it would take days or weeks after treatment initiation with hypnotic drugs before driving was considered safe (66%, 95%CI: 57-74%). 18.6% (95%CI: 13-27%) reported that it is never safe to drive when treated with benzodiazepine hypnotics, whereas about one third of respondents (33%, 95%CI: 25-42%) stated that patients can drive safely a couple of days after treatment initiation. About 14% (95%CI: 9-22%) of respondents report that patients can drive immediately after treatment initiation with zolpidem, whereas another 14% (95%CI: 9-22%) answered that they should never be allowed to drive. A similar variety of answers was found for zopiclone. From Figure 1, it can also be concluded that sleep specialists do not differentiate significantly between the effects on driving ability of treatment with benzodiazepine hypnotics and the newer benzodiazepine receptor agonists (BzRA's) zopiclone, and zolpidem.

Sleep Apnea and Driving

Only 19% (95%CI: 13-27%) considered that untreated patients with sleep apnea should be allowed to drive a car, yet 32% of the respondents stated this depends on the amount of EDS. About half (49%, 95%CI: 40-58%) indicated they should not drive when untreated. Two third of the respondents (66%, 95%CI: 57-74%) agreed that successfully treated patients with sleep apnea should be allowed to drive a car. In this questionnaire, successful treatment was defined as Continuous Positive Airway Pressure (CPAP) treatment for more than 4 hours per night and compliance for at least one month. One in five respondents (22%, 95%CI:16-31%) answered this depends on the amount of EDS, whereas 11%, 95%CI: 6-18%) felt apnea patients should not drive even when treated with CPAP.

Narcolepsy and Driving

Whereas most respondents indicated that untreated patients with narcolepsy should not drive a car (77%, 95%CI: 68-84%), they also felt that after successful treatment driving should be allowed (71%, 95%CI: 62-79%). A minority (11%, 95%CI: 6-18%) disagreed with the statement that untreated narcolepsy patients should not drive, and a further 7% (95%CI: 4-13%) disagreed that successfully treated patients should be authorized to drive. Relative minorities of specialists indicated that whether untreated patients should drive (12%, 95%CI: 7-19%), and whether successfully treated patients should be authorized to drive (21%, 95%CI: 15-30%) would depend on the level of EDS.

Who Should Judge Fitness to Drive a Car?

Most respondents stated that physicians (30%, 95%CI: 23-39%), researchers (26%, 95%CI: 19-35%), or a combination of both (28%, 95%CI: 21-38%) should determine fitness for driving. To a lesser extent, driver license authorities (12%, 95%CI: 7-19) and patients (5%, 95%CI: 2-11%) were mentioned as those who should judge fitness to drive. Most respondents accepted the view that "*driving is a privilege and not a human right*". Others, however, indicated that "*It is ultimately an individual's responsibility and should not be delegated to anybody else, including the physician*". The most important reason given for this was that in the end the autonomy of the

patient in making their own decisions is more important than the views of other people or legislation. Patients, however, may not be objective in judging their own fitness for driving. Patients may have various reasons why they should drive (e.g., to go to work, visit friends), and therefore perceive driving a car as a right. A patient's view on fitness for driving is therefore likely to be very biased. Most respondents agreed that the patient's opinion was the least credible when determining fitness for driving. However, information *about* the patient that can be verified, such as their history for type and number of traffic accidents, may be usefully taken into account when determining fitness to drive.

The Role of Driver License Authorities

About 80% (95%CI: 72-87%) of sleep specialists indicated that all drivers should be questioned regarding sleep apnea, narcolepsy or insomnia when applying for a driver license. About 15% (95%CI: 10-23%) felt this was only necessary for professional drivers. As sleep disorders may develop after the driver's license has been obtained, about half (53%, 95%CI: 44-61) considered all drivers should be questioned on a regular basis, whilst 37% (95%CI: 28-46) felt this should only apply to professional drivers. The most preferred frequencies for questioning professional drivers was every year (33%, 95%CI: 25-42%) and every 5 years (35%, 95%CI: 27-45%). More respondents (39%, 95%CI: 31-49%) believed this should be done independent of age, whereas 20% (95%CI: 13-28%) indicated that drivers above the age of 40 should be questioned. 13% (95%CI: 8-21%) argued that this should be done/performed at the renewal of the drivers license.

Many specialists acknowledge that simply asking the patient if he is diagnosed for having a sleep disorder is not sufficient. In fact, most people are not diagnosed and thus may be unaware of having a sleep disorder. Also, just being diagnosed does not provide sufficient information about fitness for driving. Most important in this regard is whether patients are successfully treated, and if they experience EDS or not. In addition, according to sleep specialists the decision of whether a patient is fit to drive should not be made by licensing authorities themselves.

How Should Drivers Be Tested?

Sleep specialists were asked what they regard as the highest form of evidence that driving is safe (see Figure 2). Most often, respondents answered that the on-the-road driving test provides the best evidence to determine if a patient is fit for driving (38%, 95%CI: 30-48%). For example, the 100-km driving test is performed on a public highway in normal traffic. The Standard Deviation of Lateral Position (SDLP), i.e. the weaving of the car, is the primary parameter of vehicle control.

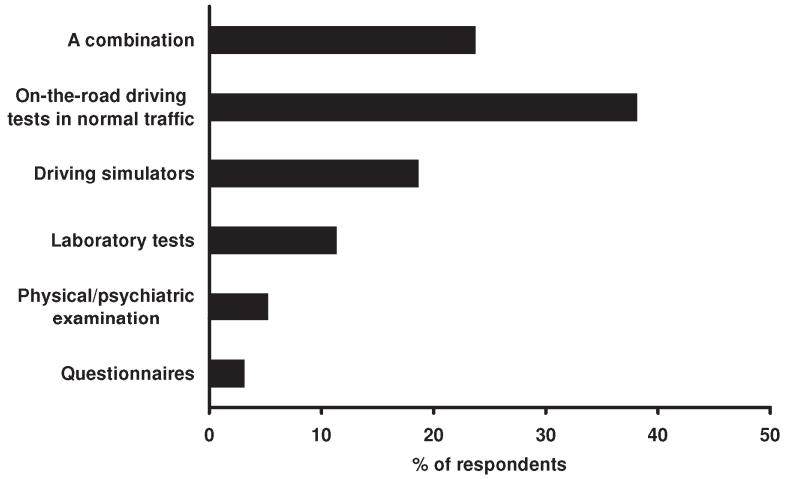

Figure 2. Overview of sleep experts' opinion on what they regard as the best method to determine if driving is safe.

Driving simulator tests were selected by 19% of the respondents (95%CI: 13-27%), 11% (95%CI: 6-18%) preferred cognitive and psychomotor tests, and 24% (95%CI: 17-33%) stated that a combination of tests is the best way to determine fitness for driving. Interestingly, amongst the sleep specialists, physical and psychiatric examination (5%, 95%CI: 2-11%) and questionnaires completed by patients (3%, 95%CI: 1-8%) were the least popular methods, emphasizing the importance of a direct measure of driving competence.

Test Drivers for Sleep Problems on a Regular Basis?

About half of the respondents indicated that professional drivers should be tested for sleep problems on a regular basis. Most sleep specialists stated that testing should be done every 5 years (46%, 95%CI:36-55%). The preferred

age for testing professional drivers was above 40 years (32%, 95%CI: 23-41%), followed by any age (27%, 95%CI: 19-35%). Only 10% (95%CI: 4-16%) reported that testing should apply to *all* drivers, whereas 40% (95%CI: 31-49%) felt testing was not necessary. Those opposed to testing considered that it was very time consuming and too expensive to test all drivers.

DISCUSSION

The results of the 2007 World Sleep Survey showed that amongst the sleep specialists who responded (around 11%), there was agreement on certain subjects related to sleep and driving, but great variation on others. These results reflect an overall lack of consensus regarding fitness to drive in patients with sleep disorders. The detailed comments given by respondents emphasized that information on EDS for patients with sleep disorders is vital in order to judge their fitness to drive. Importantly, the amount of EDS may differ significantly between patients or can be absent. It also has to be noted that sleepiness behind the wheel represents a specific type of daytime sleepiness, which may occur in individuals who do not experience high levels of sleepiness during other types of activities (Masa et al. 2000). Hence, legislation that simply determines a patient's fitness to drive based on having a diagnosis of a sleep disorder per se will not be effective. Such laws would infringe upon a great number of drivers that are not at a higher risk of impaired driving and becoming involved in traffic accidents.

Scientific evidence on driving ability of untreated patients with insomnia, narcolepsy and sleep apnea is scarce. Surprisingly, no direct on-the-road driving studies have been performed to compare untreated with treated patients. The fact that some sleep specialists report that successfully treated patients are fit for driving and untreated patients are not seems wishful thinking, as it may not be sufficiently supported by scientific evidence. For example, CPAP treatment was found to reduce crash risk (Tregear et al. 2010), which suggests that the treatment leads to an improvement in driving performance. Notwithstanding that this may indeed be the case, crash rate constitutes an indirect measure that is potentially subjected to bias and depends on exposure. An individual diagnosed with a sleep disorder may be more careful, or limit driving to essential trips. Furthermore, when driving simulators are used to assess driving performance in sleep disorder patients,

the tests being used are often very simple. When looking at narcoleptic patients, the only treatment that was assessed was methamphetamine, and then tested in a relatively simple reaction time driving task (Steer Clear; Mitler et al. 1993), whereas information on the effects of commonly used narcolepsy treatments on actual driving is absent (e.g. sodium oxybate, modafinil). Finally, although it is believed that driving is impaired in insomnia patients, there is no scientific proof that this actually is the case.

There is, however, abundant scientific literature reporting the effects of hypnotic drugs on driving ability (Verster et al. 2004; Verster et al. 2006). On-the-road driving tests show that benzodiazepine hypnotics may significantly impair driving performance next day after one or two nights of treatment. Epidemiological evidence shows that the use of benzodiazepine hypnotics is associated with an increased risk of having a traffic accident (Smink et al. 2010). In particular, the use of benzodiazepines with a long half-life, the first weeks after treatment initiation and higher dosages appear to be associated with the highest accident risk. Also, a 4-fold increase in traffic accident risk has been reported for zopiclone (Barbone et al. 1998). Tolerance develops slowly, and increased accident risks have been reported after months of treatment initiation (Verster et al. 2004). Zolpidem, when used as recommended, seems relatively safe (Verster et al. 2007). Nevertheless, sleep specialists disagree about whether and when it is safe to drive or not. Moreover, they do not differentiate between the magnitude and duration of impairment. This is in contrast to the scientific evidence available, and the drug list of the International Council on Alcohol, Drugs and Traffic Safety, that categorizes zolpidem as different from benzodiazepines and zopiclone (Verster et al. 2009).

Asking patients whether they feel they are fit for driving is likely to yield biased answers. For example, it has been shown that 80% of drivers judge their driving skills as above average (McCormick et al. 1986). Although most individuals are aware of increased sleepiness levels some time before they would actually fall asleep, this is not the case for all drivers, and some drivers are unaware of falling asleep behind the wheel (Horne and Reyner 1999). Also, they may not be aware that their driving is impaired, nor may they all recognize or acknowledge signs of sleepiness and reduced alertness (Kaplan et al. 2007). In addition, patients often have reasons why they feel driving is

important in their lives and therefore may not report the complete truth when asked about their driving and daytime sleepiness. They may also be reluctant to acknowledge sleepiness as a factor after an accident for legal reasons (Connor 2009).

Objective tests of excessive daytime sleepiness such as the Multiple Sleep Latency Test (MSLT), Maintenance of Wakefulness Test (MWT), and the Oxford Sleep Resistance (OSLER) test can indicate whether people suffer from EDS. This gives rise to the question whether these tests can be used as an indication of driving performance in patients with sleep disorders. Philip et al. (2008) demonstrated a correlation between MWT scores and actual driving ability in untreated apneics. In addition, Drake et al. (2010) showed that MSLT scores predict motor vehicle crashes in the general population. However, in an earlier study (Aldrich, 1989) MSLT scores did not indicate that narcoleptics or apneics who had more accidents were also sleepier. Also, relying solely on these tests to judge an individual's driving ability is insufficient, as the conditions under which these tests take place differ greatly from driving conditions. Furthermore, the available information does not prove that an improvement in EDS after treatment of any given sleep disorder means that driving is also improved because it is possible that mechanisms other than sleepiness are involved.

Psychomotor and cognitive tests can show the impact of sleepiness and reduced alertness on performance. Unfortunately, psychomotor and cognitive tests poorly predict actual driving (Verster et al. 2009). Driving simulators can also give insight into people's ability to drive a car. Some studies suggest that driving simulators may be useful in determining daytime sleepiness levels in sleep apnea patients and, as a result, fitness for driving (Pizza et al. 2009). However, standardization of driving tests and their outcome measures is necessary before general statements can be made about their usefulness in predicting actual driving performance (Verster and Roth 2011). Most sleep specialists acknowledge that the on-the-road driving test provides the most reliable evidence whether driving is safe or not. Scientific literature confirms that SDLP correlates significantly with reported sleepiness (Ramaekers 2003), and is sensitive to differentiate between dose-dependent impairment of alcohol and psychoactive drugs, including hypnotics (Verster et al. 2004; Verster et al. 2006; Verster et al. 2009). Because of the monotonous character

and its long duration (approximately 1 hour), the on-the-road driving test is very suitable for measuring the impact of driver sleepiness on vigilance performance. Sleep specialists state that testing all drivers for driver sleepiness would be best, but acknowledge that it would be cumbersome and costly to do so. Testing professional drivers only is considered as a suitable compromise. Most sleep specialists note this should be done every 5 years.

A limitation of this study may be the relative low response rate (11%). It is known however that the larger the sample size that is invited to complete a survey, the lower the response rate will be. An analysis of 199 surveys including over half a million invited people yielded an average response rate of 13.35% (Hamilton 2009), which is comparable to ours; although surveys employing a smaller sample size generally have response rates of 26% or more (Hamilton 2009). An explanation for non-respondence may be that sleep specialists are too busy. Also, no reminder e-mail was sent to complete the survey. Because the attendants at a world conference are varied, it would be interesting also to examine opinions on a local level and compare the opinion of sleep specialists with those of patients who actually suffer from sleep disorders, as well as with legislators and licensing authorities. Finally, because the next World Sleep Conference will be held in 2011, this can be an interesting opportunity to see if the opinion of sleep specialists has changed over the past 4 years.

CONCLUSIONS

Sleep disorders and excessive daytime sleepiness can affect driving performance significantly and increase the risk of becoming involved in traffic accidents. Determining whether patients are fit to drive is therefore of high importance but effective methods of assessment are resource intensive. Educating patients about the potential risks of sleepy driving and assurance of treatment compliance are of vital importance, and may result in more success than introducing unenforceable traffic laws. This survey shows that sleep specialists acknowledge the importance of this issue, but the range of preferences reported by them indicated only limited concordance with the available scientific evidence, and direct evidence may itself be lacking, including fitness to drive after treatment. It must therefore be concluded that regular continuing education remains necessary.

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7

CRITICAL APPRAISAL OF RAMELTEON IN TREATMENT OF INSOMNIA

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ABSTRACT

Ramelteon is the first member of a novel class of hypnotics and acts as a selective melatonin receptor agonist. In 2005, ramelteon was approved by the US Food and Drug Administration for the treatment of insomnia characterized by sleep onset problems. Its unique mechanism of action made it a promising candidate compared with the widely used hypnotics that act on the benzodiazepine receptor complex. Several studies have examined its efficacy and safety as a hypnotic agent. The primary efficacy of ramelteon was found to lie in a decrease in latency to persistent sleep, as measured by polysomnographic tests. Other sleep-related measures, such as total sleep time and number of nightly awakenings, show less pronounced improvement when treated with ramelteon. In addition, no rebound insomnia or abuse potential was observed in clinical studies. Although additional studies are necessary, current data on the acute and next-morning effects of ramelteon did not indicate cognitive or psychomotor impairment. Overall, ramelteon is safe and well tolerated, although some questions remain regarding its long-term efficacy and safety. These issues and possibilities for use in other patient groups should be addressed in future research.

Keywords: ramelteon, melatonin, insomnia, hypnotics

INTRODUCTION

Until recently, pharmacologic treatment of insomnia largely relied on the prescription of hypnotic drugs belonging to the class of benzodiazepine receptor agonists. These include benzodiazepines, such as lormetazepam, temazepam, and triazolam, and z-drugs, including zaleplon, zolpidem, and zopiclone. Unfortunately, benzodiazepines have a number of adverse effects, including daytime sedation, memory and psychomotor impairment, dependence, and abuse potential.[1] The more recently introduced z-drugs are equally effective, but have an improved safety profile. Because z-drugs also act at benzodiazepine receptors, similar adverse effects can be observed as seen with benzodiazepine hypnotics.[2,3]

Ramelteon is one of the new hypnotic drugs that does not act on the gammaaminobutyric acid (GABA) receptor, and is therefore believed to be an improvement relative to the traditional hypnotic drugs. Ramelteon is a selective melatonin receptor agonist, a hormone that is of importance in regulating the sleep-wake cycle. Although ramelteon was approved by the US Food and Drug Administration (FDA)[4] for use in insomnia characterized by sleep onset difficulties in 2005, the European Medicines Agency refused marketing authorization in 2008. The refusal was primarily based on a lack of consistent subjective efficacy.[5] Since that time, a number of clinical studies have been published. This review updates previously published reviews,[6–8] and aims to give an overview of the current knowledge on ramelteon.

Pharmacology

The endogenous agent melatonin, a hormone synthesized in the pineal gland, aids sleep by shortening the latency to sleep onset and by maintaining sleep. It is a key component in regulating circadian cycle. Besides its sleep-promoting effects, melatonin can also function as a chronobiotic, ie, it can regulate the internal clock. Melatonin exerts its sleep-promoting and chronobiotic actions by acting on the melatonin receptor-1 (MT1) and MT2 in the suprachiasmatic nucleus in the hypothalamus. The suprachiasmatic nucleus functions as an inner biologic clock regulating the sleep-wake cycle. The hypothalamus reacts to levels of light. In darkness, the hypothalamus will signal the pineal gland to produce melatonin. High levels of melatonin are associated with darkness, whilst low levels indicate light and wakefulness. When MT1 is occupied by a

ligand, neuronal firing is restrained and, hence, sleep is induced. Phase shifting requires MT2 involvement.[9,10] The third melatonin binding site is the enzyme quinone reductase 2, which most likely mediates the antioxidant properties of melatonin.[11]

Furthermore, there is evidence that melatonin facilitates sleep by promoting spindle formation. Sleep spindles are characteristic of stage 2 sleep in the sleep electroencephalogram (EEG). They are generated in the reticular nuclei of the thalamus, and are of importance in the induction and maintenance of sleep.[12] Changes in plasma melatonin levels were found to coincide with changes in EEG activity in the spindle range.[13] In addition, an increase in power density in the sleep spindle frequency range was observed when exogenous melatonin was administered during the daytime.[14]

Ramelteon is a selective MT1 and MT2 agonist. Compared with melatonin, ramelteon has a six-fold higher binding potency for the human MT1 and a three-fold higher affinity for the human MT2. Ramelteon shows no affinity for quinone reductase 2. Ramelteon also has no affinity for GABA-ergic, cholinergic, or monoaminergic receptors.[15] Its selectivity for MT1 and MT2 and lack of GABA affinity are found in both animals[16–19] and humans.[20] Because ramelteon is a selective melatonin receptor agonist, it exerts its pharmacologic actions in a similar manner to melatonin.[9] The effect of ramelteon on sleep spindles has not been studied.

Pharmacokinetics

After oral administration, ramelteon is rapidly absorbed and reaches peak serum concentrations after one hour. Its bioavailability is less than 2%, due to extensive first-pass metabolism. The active M-II metabolite is formed after hydroxylation mediated through the cytochrome P-450 (CYP450) isoenzyme 1A2. M-II has about one-tenth and one-fifth the binding affinity of ramelteon for the MT1 and MT2 receptors, respectively, and is 17- to 25-fold less potent in in vitro functional assays. However, systemic exposure to M-II is 20- to100-fold greater than the parent compound itself, with peak concentrations after approximately one hour. Its elimination half-life is two to four hours, compared with the one- to two-hour elimination half-life of ramelteon. With the exception of a weak affinity for the serotonin (5-HT) 2B receptor, M-II has no noteworthy affinity for other receptors or enzymes.[20–22] Given its

availability and affinity, M-II is likely to contribute to the effect of ramelteon, but the magnitude of this effect is unknown. The influence of age and gender on kinetics and dynamics was investigated in healthy volunteers.[20] Age significantly influenced the pharmacokinetics of ramelteon. In older subjects (60–79 years), the maximum serum concentration, elimination half-life, and area under the curve (AUC), ie, biologic availability, of ramelteon were increased compared with younger subjects (18–35 years). In addition, the M-II metabolite had a longer elimination half-life and higher AUC, as well as a reduction in clearance of 43%. Unlike age, gender does not influence the kinetics of ramelteon.[20]

EFFICACY

Various studies described in the following sections have examined different dosages of ramelteon. It should be kept in mind that the recommended dose of ramelteon for the treatment of insomnia is 8 mg, taken at bedtime.

Single administration in healthy subjects

Two randomized, double-blind, placebo-controlled studies examined the efficacy of a single dose of ramelteon. Transient insomnia was induced in healthy adult volunteers by introducing a novel sleep environment, ie, a sleep laboratory. In the first study,[23] healthy adult volunteers (35–60 years) received a single dose of ramelteon 16 mg (n =126), 64 mg (n =126), or placebo (n =123) 30 minutes before bedtime. Polysomnographic recordings showed that compared with placebo, the 16 mg dose reduced latency to persistent sleep by 10.5 minutes and increased total sleep time by 14.1 minutes. Ramelteon 64 mg reduced latency to persistent sleep by 9.1 minutes and increased total sleep time by 11.1 minutes. In the second study,[24] adult subjects (18–64 years) received a single dose of ramelteon 8 mg (n=98), ramelteon 16 mg (n=94), or placebo (n=97) 1.5–2.0 hours before bedtime. A significant decrease in latency to persistent sleep (7.5 minutes) was found after administration of 8 mg ramelteon, but no statistically significant effect was found for the 16 mg dose. Total sleep time increased by 17.1 minutes with the 8 mg dose and by 13.4 minutes with the 16 mg dose. Neither study showed an effect on sleep architecture, ie, pattern of sleep stages and number of nightly awakenings, or on subjective sleep measures.

Table 1. Objective and subjective data on sleep-related measures in double-blind, placebo-controlled studies in chronic insomnia patients treated with ramelteon

Abbreviations: LPS, latency to persistent sleep; TST, total sleep time; WASO, wake time after sleep onset; Eff, sleep efficiency (TST/total time in bed × 100); sSL, subjective sleep latency; sTST, subjective total sleep time; sWASO, subjective wake time after sleep onset; NAW, number of awakenings; SQ, sleep quality; w, week; NS, no significant change compared with placebo; m, month; +, significant increase; -, significant decrease.

Subjects	Dose (mg)	Treatment duration	Time of test	LPS (min)	TST (min)	WASO (min)	SE (%)	sSL (min)	sTST (min)	sWASO (min)	NAW	SQ	Ref.
Adults, n=335, 159 ramelteon, 176 placebo; mean age 46,2 (18-79 years)	8	6 months											25
			w1	-	+15.4			-	NS	NS	NS	NS	
			m1	-	NS			-	NS	NS	NS	NS	
			m3	-	NS			NS	NS	NS	NS	NS	
			m5	-	NS			-	NS	NS	NS	NS	
			m6	-	NS			NS	NS	+11.4	NS	NS	
Adults, n=405, divided over 3 treatments; mean age approx 39 years		35 nights											26
	8		w1	-15.7	+19	NS	+4	-17.3	+24.2	-13.8		NS	
			w3	-12.9	NS	NS	NS	-18.5	+20.2	NS		NS	
			w5	-11	NS	NS	NS	-16.7	+18.3	NS		NS	
	16		w1	-19	+22.4	NS	+5.1	-13.9	+22.4	-18.3		NS	
			w3	-17.6	NS	NS	NS	-11.4	+9.6	NS		NS	
			w5	-13	NS	NS	NS	NS	NS	NS		NS	
Adults, n=103; age 18-64 years		2 nights											27
	4			-13.7	+10.7	NS		NS	NS			NS	
	8			-13.4	+12.6	NS		NS	NS			NS	
	16			-13.7	+10.9	NS		-13.1	NS			NS	
	32			-14.8	+17.9	NS		NS	NS			NS	
Older adults, ≥65 years; n=829 divided over 3 groups		35 nights											30
	4		w1					-8.3	+10.7		NS	NS	
			w3					NS	+11.7		NS	NS	
			w5					-7.2	NS		NS	NS	
	8										NS	NS	
			w1					-8.3	+7.2		NS	NS	
			w3					-9	+7.8		NS	NS	
			w5					-12.9	NS		NS	NS	
Older adults, n = 100 (m/f=37/63; 65-83 years)		2 nights											31
	4			-9.7	+9		+1.8	-10	NS	NS	+0.8	NS	
	8			-7.6	+11.6		+2.4	NS	NS	NS	NS	NS	

Chronic insomnia in adults

An overview of double-blind clinical studies in chronic insomnia patients is provided in Table 1. All studies were randomized, double-blind, and placebo-controlled, with ramelteon administered at bedtime. Latency to persistent sleep, the primary endpoint in three studies performed in adults,[25–27] was significantly reduced by ramelteon 4–32 mg. This decrease was sustained when patients were treated for up to six months (see Figure 1).

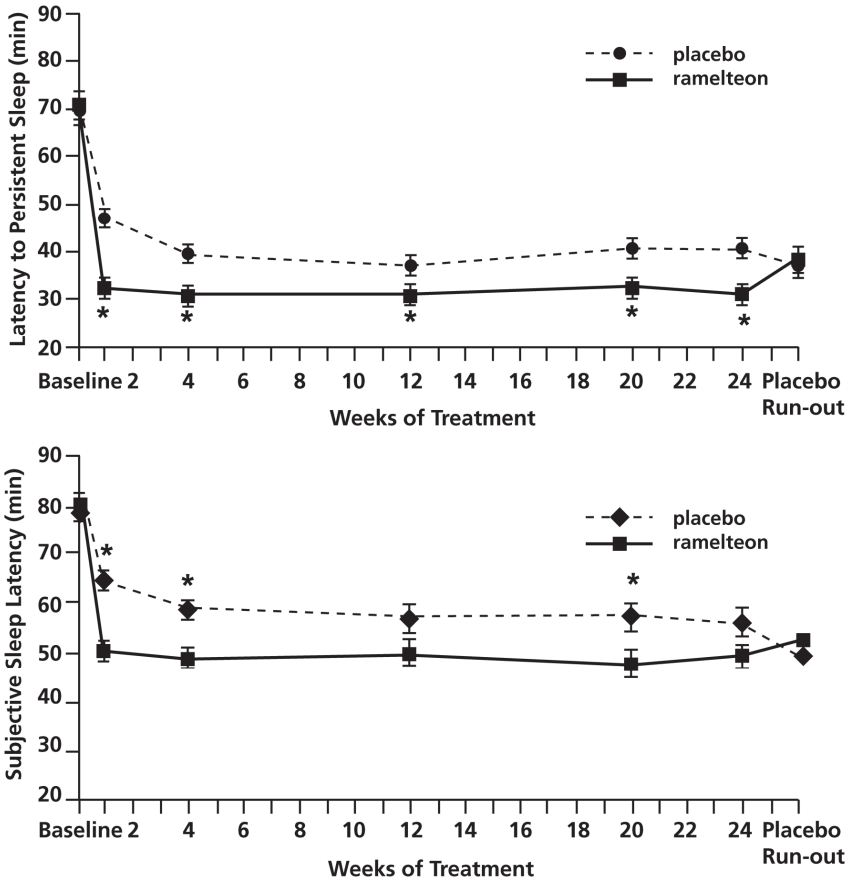

Figure 1. Polysomnography-measured latency to persistent sleep (top) and subjective sleep latency (bottom) over six months of double-blind ramelteon 8 mg or placebo treatment at night. Data are least-squares means with standard error bars.

Notes: *Significantly different from placebo (P , 0.05). Copyright © 2010, American Academy of Sleep Medicine. Adapted with permission from Mayer G, Wang-Weigand S, Roth-Schechter B, Lehmann R, Staner C, Partinen M. Efficacy and safety of 6-month nightly ramelteon administration in adults with chronic primary insomnia. Sleep. 2009;32(3):351–360.25

In patients treated for up to five weeks, the decrease in latency to persistent sleep varied from 11 to 19 minutes. Total sleep time increased for all dosages of ramelteon, but after one week of treatment, significant effects compared with placebo were no longer present. Overall, sleep architecture was slightly affected by ramelteon. Compared with placebo, decreases in percentage of time spent in slow wave sleep, ie, sleep stages 3 and 4, were found up to six months of treatment.[25–27] This was accompanied by an increase in stage 2 sleep in one study.[25] An increase in percentage of time spent in rapid eye movement sleep was found after three weeks of treatment with ramelteon 16 mg.[27] The relative decrease in sleep in stages 3 and 4 may be accounted for by an increase in total sleep time, and was therefore considered to be clinically irrelevant.[27]

Studies of ramelteon have revealed inconsistent effects on subjective sleep assessments. One study showed consistent decreases in subjective sleep latency and increases in total sleep time,[26] but this was not the case in the other studies.[25,27] Patients did not rate their sleeping quality as improved in any of the studies.

In an open-label study, 965 adult and 248 elderly insomniacs were administered ramelteon 8 mg and 16 mg, respectively, for 48 weeks.[28] During the study, self-reports in both groups revealed significant reductions in subjective sleep latency and increases in total sleep time. The self-reports were consistent with clinicians' reporting of reduced insomnia and therapeutic efficacy of ramelteon at months 6 and 12.

Finally, a pooled analysis of four studies in subjects with chronic insomnia[29] showed that when using ramelteon 8 mg for two nights, latency to persistent sleep decreased by 13 minutes when compared with placebo.

Chronic insomnia in the elderly

Two studies were performed in elderly insomnia patients.[30,31] An overview of the results is provided in Table 1. The first study examined subjective reports of sleep using sleep diaries. The study started with a single-blind placebo run-in week, followed by five weeks of double-blind ramelteon 4 mg or 8 mg administration, and ended with a single-blind placebo run-out period.[30] Compared with placebo, sleep latency was decreased up to five weeks after treatment onset, except for the 4 mg dose after three weeks. Subjective total

sleep time was increased for up to three weeks of treatment. Results showed reductions in sleep latency ranging from 4.4 minutes (4 mg after three weeks; *P*=0.142) to 12.9 minutes (8 mg after five weeks; *P*< 0.001).

Subgroup analysis revealed that patients with higher baseline sleep latency (>67.1 minutes) had greater benefit from ramelteon. In these patients, reductions in subjective sleep latency compared with placebo ranged from 13.9 minutes (week 1, 4 mg) to 23.3 minutes (week 5, 8 mg). Additional analysis confirmed these findings.[32] No rebound insomnia or withdrawal effects were found during the placebo run-out week.

In a second randomized, double-blind study in elderly insomniacs,[31] ramelteon 4 mg and 8 mg produced a significant decrease in latency to persistent sleep, a lower percentage of time spent in sleep stages 3 and 4, and a higher percentage of time spent in stage 1 sleep. Ramelteon 8 mg also increased time spent in stage 2 sleep.

Generalized anxiety disorder

An open-label study was conducted in adults (n =27, mean age 41 years) with generalized anxiety disorder and comorbid insomnia.[33] Generalized anxiety disorder patients were partially responsive to a selective serotonin reuptake inhibitor or serotonin norepinephrine reuptake inhibitor. For a period of 10 weeks, patients were also treated with ramelteon 8 mg. Sleep latency and total sleep time significantly improved when comparing data with baseline and post study visits (-42.85 minutes and +2.5 hours, respectively). No effect on subjective wake time after sleep onset was observed. In addition, reductions were observed in insomnia symptoms, daytime sleepiness, and anxiety symptoms. These results should be confirmed by double-blind, placebo controlled studies.

Use of ramelteon as a chronobiotic

Limited data are available on the efficacy of ramelteon as a chronobiotic, ie, its capability to act on the circadian clock. In rats, ramelteon enhanced adaptation to a new sleep-wake schedule.[17] In humans, the chronobiotic effects of ramelteon were assessed in 75 healthy volunteers aged 18–45 years.[34] Five hours before their habitual bedtime, lights were switched off, thereby shifting the sleep-wake cycle by four hours. Subjects were randomized to treatment

with ramelteon 1, 2, 4, or 8 mg or placebo, administered 30 minutes prior to lights out for four consecutive days. The dim-light melatonin secretion offset time, ie, the time at which melatonin production stops, was the primary measure for phase-advancing properties. In other words, the efficacy of ramelteon to induce phase shifts was measured by the extent to which endogenous melatonin levels adapted to the new sleep-wake schedule. After one day, the 4 mg group achieved a significant shift compared with placebo, and a significant shift was evident after two days for the 1 mg and 2 mg groups. No significant effect was found for the highest dose.

This is in agreement with a subsequent study in which jet lag was examined.[35] Ramelteon dosages of 1, 4, or 8 mg were administered to individuals who had flown eastward across five time zones, leading to a five-hour phase advance. Ramelteon was administered five minutes before the local bedtime. Ramelteon 1 mg significantly decreased mean latency to persistent sleep after two to four nights of intake, but no effect was seen for the higher dosages. A possible explanation may be that remaining levels led to a phase shift in the opposite (undesired) direction. There was no effect on any of the other objective or subjective sleep measures. In contrast with the previous study, there were no differences in dim light melatonin offset. Therefore, it is possible that the observed effects may not be due to shifts of the circadian phase. Only the 4 mg group showed improvements in subjective daytime functioning, alertness, and ability to concentrate.

SAFETY AND TOLERABILITY

Withdrawal effects and rebound insomnia

Several double-blind studies[25,26,30] with a single-blind placebo run-out week were conducted to detect possible withdrawal effects or rebound insomnia. Rebound insomnia was defined as a mean latency to persistent sleep during placebo run-out that was equal to or worse than sleep latency at baseline. A range of symptoms commonly experienced during benzodiazepine withdrawal were explored using the Tyrer Benzodiazepine Withdrawal Symptom Questionnaire.[36] No withdrawal symptoms or rebound insomnia were detected after treatment with ramelteon 8 mg for six months in adult insomniacs.[25] Furthermore, no effects were found in a population of elderly patients when discontinuing after five weeks of treatment with ramelteon 4

mg or 8 mg. Improvements relative to baseline were found on nights 1, 2, and 6 of the placebo run-out week, as compared with placebo.[30] Similarly, an absence of rebound insomnia was demonstrated by Zammit et al after administering ramelteon for five weeks in adults.[26] On the first night after discontinuation of ramelteon, a significant greater reduction in latency to persistent sleep was found in the ramelteon 8 mg group. There was no evidence of withdrawal effects.

Adverse events

According to the summary of product characteristics, based on 2861 patients with chronic insomnia, the most commonly observed adverse effects of ramelteon 8 mg (versus placebo) were somnolence (3% versus 2%), fatigue (3% versus 2%), dizziness (4% versus 3%), nausea (3% versus 2%), and exacerbated insomnia (3% versus 2%).[22]

Endocrine function

Effects on endocrine function in adults with chronic insomnia (aged 18–45 years) were examined during treatment with ramelteon 16 mg or placebo for six months.[37] Patients had no significant endocrine pathology. No significant differences were found in thyroid function or adrenal function, or for most reproductive hormones. Women treated with ramelteon had higher prolactin levels, but this was not considered clinically relevant because no effects on the reproductive cycle were observed.

Endocrine function was also assessed in an open-label study in adult (n =965; ramelteon 16 mg) and elderly (n =248; ramelteon 8 mg) insomnia patients.[28] Ramelteon was administered for 48 weeks. Some changes in thyroid function were detected. With the exception of thyroxine, thyroid function returned to normal by the last visit, which was three days after withdrawal. Free testosterone was elevated in younger men in the initial months of the study, and was decreased throughout the study in older men. Morning cortisol levels were decreased at nearly all visits. In female participants, duration of menses was increased by one day on average.

Safety in patients with breathing disorders

Treating patients with sleep-related breathing disorders and comorbid insomnia can be challenging. Although clinical evidence is not straightforward, some benzodiazepines may have a potential for respiratory depression in certain patients.[38–40] Therefore, it is of importance to assess the safety and efficacy of hypnotics in these patient populations. Ramelteon was examined in patients with sleep apnea and chronic obstructive pulmonary disease (COPD).

In double-blind, placebo-controlled studies of patients with mild to moderate COPD[41] and moderate to severe COPD,[42] no effects of ramelteon 16 mg and 8 mg were found on arterial oxygen saturation (SaO2) during sleep, or on the apnea-hypnopnea index (AHI, ie, the number of apneas and hypopneas per hour). Total sleep time and sleep efficiency increased in both studies. Similarly, in patients with mild to moderate obstructive sleep apnea,[43] ramelteon 16 mg had no effect on AHI or SaO2 compared with placebo, except for a significant increase in SaO2 compared with placebo during rapid eye movement sleep. No effects on objective or subjective sleep measures were found. Overall, ramelteon did not worsen sleep-disordered breathing, and is unlikely to exacerbate sleep apnea in patients with mild to moderate sleep apnea. However, the effects of prolonged intake have not been studied.

Patients with hepatic or renal impairment

In patients with mild hepatic impairment, exposure to ramelteon 16 mg per day over a period of seven days was increased by almost four-fold. In patients with moderate hepatic impairment, exposure was increased by more than 10-fold. No studies have been performed in patients with severe hepatic impairment. Therefore, ramelteon should be used with caution in patients with mild to moderate hepatic impairment, and is not recommended for patients with severe impairment.[22] For patients with mild, moderate, or severe renal impairment or patients with chronic hemodialysis, no effects of ramelteon 16 mg on systemic exposure to ramelteon or M-II were observed. As a result, no adjustment of dosage is required in these patients.[22]

Abuse potential

Concerns exist regarding the possible abuse of hypnotics. Clinical trials and animal studies have demonstrated no indications for abuse of ramelteon.[4] In

subjects with a history of drug use, Johnson et al[44] examined the abuse potential for ramelteon, comparing the drug with placebo and triazolam. Drug strength and effect were examined using the Drug Effect Questionnaire and the Addiction Research Centre Inventory, respectively. In addition, monetary value was assessed with the Drug versus Money Choice procedure. Triazolam treatment led to significant differences compared with placebo in drug strength, abuse potential, and sedative drug effects. No indication of abuse potential was found for ramelteon. Griffiths and Johnson[45] undertook a comparison of 19 of the most commonly used drugs in the treatment of insomnia. They compared relative abuse potential by assessing the interaction of the likelihood of abuse (ie, relative reinforcing effects) and toxicity (ie, probability that adverse effects harm the individual or society). Hypnotics that lacked affinity for the GABA receptor, ie, diphenhydramine, trazodone, and ramelteon, showed less likelihood of abuse. Ramelteon was the only drug in this group that scored very low on both measures.

Drug interactions

Drug-drug interactions are mainly expected with drugs that influence or are influenced by CYP1A2. Because CYP2C and CYP3A4 are involved in ramelteon metabolism, drugs that inhibit these isoenzymes should be used with caution. Fluvoxamine was found to raise serum ramelteon levels by 70-fold, and should not be combined with ramelteon due to a risk of adverse effects. Rifampin, a strong CYP enzyme inducer, decreases ramelteon efficacy by lowering exposure to ramelteon and M-II. Ketoconazole increases the availability of ramelteon and M-II. The same was found for fluconazole. These drugs may increase the risk of adverse events when combined with ramelteon.[4,22]

BEHAVIORAL EFFECTS

Acute effects

Three studies have examined the effects of ramelteon administered in the morning to assess possible dose-response effects. Pharmacodynamic effects were assessed in two studies. Age and gender effects of a single dose of ramelteon 16 mg versus placebo were studied in 48 participants aged 18–79 years in a double-blind crossover study,[20] in which no effects on cognitive

performance, assessed by the digit symbol substitution test (DSST,) or word recall were found. Self-rated sedation was significantly higher compared with placebo in young, elderly, male, and female subjects. Observer-rated sedation was increased in male and elderly subjects. Of importance is the lack of an association between serum AUC values for ramelteon, M-II or both, and AUC values for self-rated sedation, observer-rated sedation, or the DSST. This suggests that the pharmacodynamic effects of ramelteon do not depend on systemic exposure to ramelteon and/or its metabolite. Similar results were obtained by Karim et al,[21] who examined healthy adults aged 35–65 years assigned to receive ramelteon 4, 8, 16, 32, or 64 mg (n = 8 per group) or placebo (n = 20) in the morning. Again, no effect was found on the DSST, with small effects on alertness found in the 64 mg group, but this was unrelated to peak plasma concentration.

Johnson et al examined ramelteon 16, 80, and 160 mg, placebo, and temazepam 0.25–0.75 mg in 14 healthy adults aged 19–50 years with histories of recreational drug abuse.[44] Ramelteon was administered in the morning, and measurements were performed 0.5 hours before intake and at hourly intervals for 1–12 hours after intake and 24 hours after intake, except for word learning (presented two hours and measured six hours after administration). Temazepam significantly impaired postural balance compared with placebo and ramelteon.

Furthermore, in contrast with temazepam, ramelteon did not impair performance on the DSST, circular lights test, or word recall and recognition. Furthermore, another study that assessed immediate and delayed memory recall in a word learning test in the middle of the night (two hours after dosing) found no effects of ramelteon, unlike zolpidem which impaired immediate memory recall.[46]

Postural stability

Hypnotics have the potential to impair postural balance, which may, in turn, lead to falls and hip fractures. This is of special importance in the elderly. In addition, balance impairments are likely to occur around the time of peak plasma concentration.[47] This does not seem to be the case for ramelteon. When the effect of ramelteon on balance, ie, the ability to stand upright on one foot with eyes closed, was assessed 1–12 hours after morning intake and after

24 hours, no effects were observed for doses up to 160 mg. In the same study, triazolam did show significant impairment.[44] A study that utilized a more advanced technique to measure balance impairment confirmed this finding. In a single-dose crossover design, Zammit et al[46] examined the influence of ramelteon 8 mg, zolpidem 10 mg, and placebo on a number of parameters of postural control in elderly adults with chronic insomnia (n =33, age ≥ 65 years). Two hours after bedtime, treated subjects were woken to test balance and mobility. Compared with placebo, zolpidem showed impairment in both the balance and mobility test, while no effect was found for ramelteon.

Next-morning residual effects

Hypnotics that act on the benzodiazepine receptor are known to produce residual next-morning sedation that may affect cognitive and psychomotor performance. Impairment of memory and psychomotor functioning and drowsiness can impair daily activities, such as driving a car.[48] Studies assessing next-morning residual effects have measured DSST performance, memory, and subjective effects on mood using visual analog scales (VAS).

No study has found an effect of ramelteon on DSST performance.[23,25–27,31] Furthermore, no effects were found on memory functioning assessed by immediate or delayed word recall,[25,27,31] except for two studies. In the first, ramelteon was administered for five weeks.[26] After weeks 1, 3, and 5, subjects had to remember a list of words and were tested on immediate recall in the evening. Delayed recall was tested the next morning. Relative to placebo, immediate word recall was decreased after three weeks of treatment (7.5 versus 8.2 words), and delayed word recall was impaired after one week of treatment (3.6 versus 4.2 words). No effects were found at other time points. The second study examined the phase-shifting properties of ramelteon, and showed impairments in immediate word recall after four nights of intake of ramelteon 1, 4, and 8 mg.[35]

Reports of subjective mood, feelings, and alertness varied between studies. Alertness and ability to concentrate were not affected by ramelteon,[25,27] or even improved,[26] except for dosages of 64 mg which led to small impairments after a single intake.[23] One study found effects on individual items in VAS scores for drowsiness, being slowed down, and sleepiness after one week of intake of ramelteon 8 mg, and slowed thinking and fatigue after six months of

treatment.[25] An increase in the VAS for mood was also found after a single dose of ramelteon 16 mg on the items of drowsiness, sleepiness, tiredness, and sluggishness.[24]

This was confirmed by another study in which effects on fatigue, irritability, and sluggishness were reported at several time points (week 1–3).[26] In contrast, no effects were found after two nights of ramelteon 4–32 mg,[27] whereas a study in the elderly showed improvements in irritability and calmness.[31]

DISCUSSION

Ramelteon has a number of benefits over the benzodiazepine hypnotics and z-drugs. Ramelteon is well tolerated, has a low probability of abuse, and no next-day residual effects have been demonstrated. However, there are also a number of limitations. First, efficacy data obtained by polysomnography primarily show an effect on sleep onset latency. A moderate decrease in latency to persistent sleep was demonstrated, both in models of transient insomnia in healthy volunteers and in chronic insomnia patients. When compared with placebo, this reduction varied from 7 to 19 minutes and averaged around 13 minutes. This effect was found to last up to six months after initiation of treatment, and is comparable with that of other hypnotics. Findings from a meta-analysis[49] showed an average of 10 minutes (95% CI: −16.6, −3.4) reduction in sleep onset latency for benzodiazepine hypnotics, and 12.8 minutes for nonbenzodiazepines (95% CI: −16.9, −8.8). Other polysomnographic measures showed limited effects, with increases in total sleep time found in all studies, but the effect was relatively small, ie, 9–22 minutes, and lasted for up to only one week after treatment onset. Second, patient reports on sleep measures showed some inconsistency, in that subjective sleep latency and total sleep time were improved in some but not all studies, whereas sleep quality was not affected in any of the studies. Because insomnia is defined as a subjective report of sleep disturbance,[50] a hypnotic should ideally improve subjective sleep measures. Subjective sleep latency was only decreased in some studies and was sustained when treatment was given for five weeks, whereas subjective reports on total sleep time varied. Other subjective effects were lacking or inconsistent. A few studies have demonstrated significant decreases in subjective sleep latency,

ranging from 11.4 to 18.5 minutes in adults, and from 7.2 to 12.9 minutes in elderly subjects. According to the aforementioned meta-analysis, averages for benzodiazepine hypnotics are 19.6 minutes (95% CI: -23.9, -15.3) and 17.0 minutes (95% CI:-22.3, -2.2) for nonbenzodiazepine hypnotics.[49] Although an active control has been used in a number of clinical studies, no direct comparisons have been made between the efficacy of ramelteon and benzodiazepine receptor agonists.

Likewise, the effects of ramelteon have not been compared with those of melatonin or its agonists. The efficacy of melatonin is inconclusive, and a recent meta-analysis failed to show a significant effect on sleep onset latency.[51] However, another meta-analysis[52] showed that melatonin, in varying dosages, led to an average decrease in objective sleep onset latency of four minutes, as well as to increases in sleep efficiency and total sleep duration. Still, the clinical relevance of this decrease is unclear.

Safety data show that, overall, ramelteon is well tolerated and has little or no effect on next-day performance. Memory and psychomotor tests show no noteworthy impairment, whereas there have been only a few reports on mood. However, most studies only applied two methods to test memory and psychomotor functioning, ie, the world learning test and the DSST. One study also used the circular lights test and showed no effect. More complex behavioral skills may show impairments and should therefore be studied. Balance was not influenced by ramelteon, which suggests it is a safe alternative, especially for elderly patients. Although balance impairment on the morning after intake is unlikely, this has not been assessed thus far. Studies show that ramelteon is safe in patients with sleep-related breathing difficulties and in those with renal failure, but this agent should be used with caution in patients with mild to moderate hepatic impairment. No major endocrine effects have been observed, but the findings of one open-label study suggest that further studies related to hormonal functioning in females and on age-related effects are necessary. In addition, there is some evidence that the use of melatonergic agonists may be problematic in patients with autoimmune diseases, Parkinsonism, and irritable bowel syndrome Type II.[53] An important benefit of ramelteon over other types of hypnotics is that it is the only hypnotic drug that has been found to have virtually no abuse potential. In addition, no rebound insomnia has been observed.

In line with its indication for use, ramelteon may be preferred in patients with sleep onset difficulties. However, this is unlikely for sleep maintenance problems. In addition, some evidence for application in patients with anxiety warrants further investigation in this and other types of mental disorders with comorbid insomnia. Furthermore, preliminary evidence suggests that ramelteon may be effective in the treatment of circadian rhythm disorders. Future studies in patient populations, such as individuals with shift work sleep disorder or delayed sleep phase disorder, should provide more insight into its use for these indications and provide information on long-term safety and efficacy. Overall, in patients with insomnia and in patients with circadian rhythm disturbances, long-term treatment may occur and should therefore be carefully evaluated. Moreover, to clarify the chronobiotic actions of ramelteon, a phase-response curve for ramelteon should be determined, as has been established for melatonin.[54]

In conclusion, currently available knowledge on ramelteon shows that it is both safe and well tolerated. Its usefulness seems primarily limited to patients with sleep onset difficulties. The applicability of ramelteon in other disorders has yet to be established.

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8

NEXT-DAY EFFECTS OF RAMELTEON (8 MG), ZOPICLONE (7.5 MG), AND PLACEBO ON HIGHWAY DRIVING PERFORMANCE, MEMORY FUNCTIONING, PSYCHOMOTOR PERFORMANCE AND MOOD IN HEALTHY ADULT SUBJECTS

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ABSTRACT

Study Objectives: To evaluate the next-morning residual effects of ramelteon (8 mg), zopiclone (7.5 mg), and placebo on driving performance, memory functioning, psychomotor performance, and mood in healthy adult subjects following bedtime dosing and a middle of the night awakening.

Design: single-center, randomized, double-blind, double-dummy, placebo-controlled, crossover study

Setting: Utrecht University, The Netherlands

Participants: 30 healthy volunteers (15 males and 15 females)

Interventions: a single dose of ramelteon (8 mg), zopiclone (7.5 mg), and placebo, administered at bedtime

Measurements: A balance test was performed at night. Other tests were performed the following morning, 8.5 h after administration. Subjects performed a 100-km highway driving test in normal traffic. Primary outcome measure was the standard deviation of the lateral position (SDLP), i.e., the weaving of the car. After driving, cognitive, memory, and psychomotor tests were performed and mood was assessed.

Results: SDLP was significantly increased after the intake of ramelteon (+2.2 cm) and zopiclone (+2.9 cm). Ramelteon and zopiclone produced significant impairment on reaction time ($P < 0.024$) in the Sternberg Memory Scanning Test, slow ($P < 0.007$) and fast ($P < 0.010$) tracking, reaction speed ($P < 0.015$) and tracking ($P < 0.001$) in the Divided Attention Test, and delayed recall ($P < 0.032$) in the Word Learning Test. In contrast to ramelteon, zopiclone additionally impaired performance on the Digit Symbol Substitution Test ($P < 0.001$) and the balance test ($P < 0.001$).

Conclusions: Ramelteon (8 mg) and zopiclone (7.5 mg) significantly impaired driving performance, cognitive, memory, and psychomotor performance the morning following bedtime administration. In contrast to zopiclone, ramelteon produced no balance impairments.

Keywords: driving, ramelteon, zopiclone, memory, balance, psychomotor

INTRODUCTION

The most commonly prescribed drugs in the treatment of insomnia are benzodiazepines and the "Z-drugs" (i.e., zaleplon, zopiclone, and zolpidem). These hypnotics bind to the γ-*aminobutyric* acid-A ($GABA_A$) *receptor* complex, which mediates a large number of physiological functions including sedation, anxiolytic effects, and muscle relaxation.[1] In this fashion, these drugs are able to initiate and maintain sleep. Unfortunately, they may also produce next-morning residual effects, including drowsiness and cognitive and psychomotor impairment. These unwanted residual effects are of specific concern to patients who want to drive a car the morning after having taken a sleep medication. On-the-road driving studies have shown that benzodiazepine hypnotics significantly impair driving performance.[2,3] Consistent with these findings, epidemiological studies have demonstrated an increased risk of traffic accidents and related injuries in patients using benzodiazepine hypnotics.[4-6] Significant driving impairment has also been found for zopiclone,[7-9] comparable to that observed with benzodiazepine hypnotics. In fact, Barbone et al.[6] reported a four-fold increase in traffic accident risk for patients treated with zopiclone.

The other "Z-Drugs," zolpidem and zaleplon, do not impair driving ability when used as recommended.[9-11] However, with higher dosages and shortened time between drug use and driving, zolpidem may seriously compromise traffic safety.[12,13] In addition to an increased risk of traffic accidents, hypnotic drugs may also have a negative effect on postural balance,[14] increasing the risk of falls and hip fractures, especially in the elderly.[15] This highlights a need for the development of new hypnotics without these unwanted residual effects.

Ramelteon is the first drug in a novel class of hypnotics currently licensed for the treatment of chronic insomnia in the US, Japan, Philippines, Indonesia, and Taiwan. Ramelteon is a selective melatonin receptor agonist and exerts its effect through selectively binding to melatonin receptors 1 and 2 (MT1/2), thereby inducing sleep.[16] Since the sleep-promoting effect of ramelteon does not incorporate the sedative effects associated with the GABA-benzodiazepine receptor agonists, clinically important sedative and performance-impairing effects of ramelteon are minimal.[17-19] Ramelteon has minimal affinity for benzodiazepine, dopamine and opiate receptors, ion channels, and a number of receptor transporters.[17] However, its active metabolite M-II has weak

affinity for the serotonin 5-HT_{2B} receptor.[20] Until now, no clinically relevant next-morning residual effects on cognitive or memory functioning have been reported.[18,19,21-27] Consequently, it is expected that ramelteon will not show the next-morning impairing effects that are common with benzodiazepine hypnotics. The aim of the present study was to examine the residual effects of ramelteon (8 mg) versus placebo on driving performance, memory, and cognitive and psychomotor functioning. Because of its known impairing effects on driving,[2,3] zopiclone (7.5 mg) was included as positive control.

METHODS

Subjects

Thirty healthy volunteers (15 male, 15 female) were recruited by means of public advertisements on and around the campus of Utrecht University. Inclusion criteria for subjects were: age 21-55 years, body mass index 18-34 kg/m^2, normal vision, and possession of a valid driver's license ≥3 years with a reported average annual mileage ≥5,000 km during the 3 years prior to inclusion in the study. To exclude subjects with any evidence of clinically relevant diseases, each subject was medically examined before inclusion. This screening comprised clinical laboratory tests (hematology, serum chemistry, and urinalysis), 12-lead electrocardiogram, urine pregnancy test (for women), urine drug screen, and an alcohol breath test. Subjects were excluded if they had abnormal findings in the laboratory tests; history or presence of any clinically significant physical or mental disease; history of alcohol or drug dependence; past or current drug use; excessive caffeine consumption (>5 cups/day), smoking (>10 cigarettes per day), or alcohol intake (>21 drinks per week). On the last visit, 1 week after the last experimental session, subjects underwent a post-study medical examination. The use of concomitant medication was prohibited except for oral contraceptives and peripherally acting analgesics. Alcohol was prohibited from 24 h before each dose of study drug until the end of the test day. Smoking and caffeine were not permitted on test days. The study was conducted according to good clinical practice as laid down in the Declaration of Helsinki and its latest amendments. The medical ethics committee approved the protocol, and participants provided written informed consent prior to enrollment.

Study Design and Procedure

This was a double-blind, double-dummy, randomized, placebo-controlled, 3-way crossover study in healthy adult volunteers examining the single-dose effects of ramelteon (8 mg), zopiclone (7.5 mg), and placebo.

Subjects participated in 1 training session and 3 experimental sessions, with wash-out periods ≥1 week between sessions. They were habituated to the sleep facility during a sleep rehearsal night. Subsequently, subjects' eligibility to participate in the study was assessed during the training session. Participants were included if the standard deviation of the lateral position (SDLP) at the end of the training driving test did not exceed 24 cm. In addition, subjects were familiarized with the procedures and were trained on the tests (car driving, balance and psychometric test battery) to avoid learning effects in the experimental sessions.

Figure 1. Flow chart of each test day

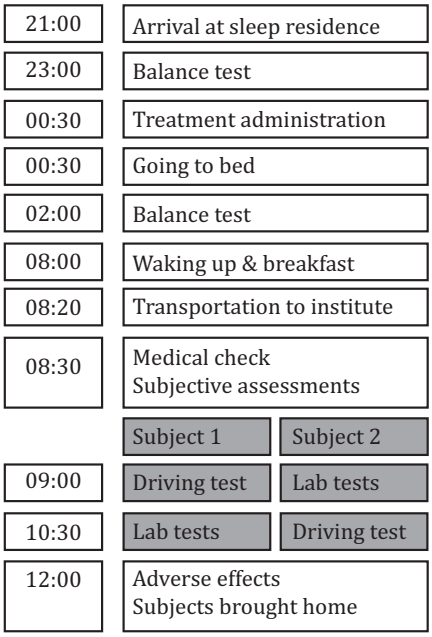

Figure 1 displays the flow chart of a regular test day. During each experimental session, 2 subjects reported to the sleep residence at 21:00. At 23:00, a balance test was performed. Immediately before bedtime and lights out, at 00:30, each subject received a single oral dose of ramelteon 8 mg, zopiclone 7.5 mg, or placebo administered with water. To ensure study

blinding, treatment was administered in double-dummy fashion. Subjects received one tablet of zopiclone or matching placebo and one capsule of ramelteon or matching placebo. At 02:00, 1.5 h after drug intake and at peak plasma concentration, the subjects were woken up for the balance test. After the test, subjects went back to sleep and were woken up at 08:00. A light, standard breakfast was provided, and at 08:20 subjects were taken to the institute where they received a medical check. At 09:00, 8.5 h after treatment administration, one subject started the driving test, while the second subject started the laboratory tests. At 10:30, 10 h after treatment administration, the first subject started the laboratory test and the second subject started the driving test. At 12:00, subjects underwent a short medical check for adverse events and were brought home.

The On-the-Road Driving Test

A standardized method of measuring driving ability, the on-the-road driving test[28] was performed on a 100 km-primary highway circuit, i.e., the primary highway (A12) between the cities of Utrecht and Arnhem. To guard safety during the test, a licensed driving instructor who had access to dual controls accompanied the subject.

Subjects were instructed to drive with a steady lateral position between the delineated boundaries of the right (slower) traffic lane while maintaining a constant speed of 95 km/h. A camera mounted on the roof of the car continuously recorded the position of the car within the traffic lane, by measuring the relative distance of the car from the left lane delineation. The speed and lateral position of the car were continuously recorded, digitally sampled at 2 Hz, and edited off-line to remove data that were disturbed by extraneous events (e.g., overtaking maneuvers, traffic jam). The standard deviation of lateral position (SDLP), i.e., the amount of weaving of the car, was the primary outcome measure. Standard deviation of speed (SDS, km/h) was the secondary outcome measure. Mean lateral position (MLP, +/- cm) to the right (+) or left (-) of the lane center, and mean speed (MS, km/h) were control variables.

Subjective Assessments

After the driving test, subjects indicated the perceived quality of their driving performance on a visual analog scale, which ranged from "I drove exceptionally poorly" to "I drove exceptionally well" around a midpoint of "I drove normally." The level of effort they had to invest in performing the task was indicated on a 15-cm equal-interval scale.

The ARCI-49 questionnaire[29] was also completed after the driving test. It comprised 5 scales that indicated mood changes accompanying different drug classes: pentobarbital-chlorpromazine-alcohol group scale (measuring sedation), Benzedrine group scale (measuring intellectual efficacy and energy), morphine-Benzedrine group scale (measuring euphoria), amphetamine scale (measuring amphetamine-like effects), and the lysergic acid diethylamide scale (measuring dysphoria and somatic symptoms).

Sleep Quality

Each morning after waking up, quality of sleep was assessed using the 14-item Groningen Sleep Quality Scale (GSQS).[30] GSQS scores range from 0 to 14. The GSQS has previously been used in patients with seasonal affective disorder[31] and shift-workers.[32] In general, if sleep is unrestricted and undisturbed, subjects score 0 to 2 points. A higher score (6 to 7) indicates disturbed sleep.

Balance Test

At presumed peak plasma concentration,[18,33] i.e., 1.5 h after bedtime, subjects were woken to perform the balance test. Body sway was measured using the AccuSway Plus platform (Advance Medical Technology, Massachusetts, USA). Subjects were instructed to stand on the balance platform with their arms at their side. Subjects' balance was recorded standing on the platform for 60 sec with their eyes open and then 60 sec with their eyes closed. Recordings took place in a quiet room, and speaking was not allowed during the recordings. The primary performance measure was the change in center of pressure (CoP). Subjects performed the test approximately 5 min after waking up and returned to bed within 15 minutes.

Psychometric Test Battery

The psychometric test battery comprised 4 different tasks: Word Learning Test, Sternberg Test, Tracking Test, and Divided Attention Test, which were

selected from a larger set of tasks predefined in ERTS 3.17 (Experimental Run Time System). Different versions of the tests were used at each training session and test day. The test battery was carried out with subjects seated at a table in a sound-attenuated test room with constant luminosity during the entire study.

Word Learning Test (Immediate and Delayed Recall)

The Word Learning Test (WLT) is the Dutch language version of the standardized, clinically validated test for verbal memory. A list of 15 monosyllabic meaningful nouns was presented on a screen at a fixed rate of 2 sec per word. As soon as the presentation stopped, the subjects were given 1 min to write down as many words as they were able to remember. The highest separate test score of 5 subsequent trials was the Immediate Recall Score (WLT-IR). Following a 30-min delay in which the other psychometric tests were performed, subjects were asked to write down as many of the previously shown words as possible within 1 minute. The number of correct responses was the Delayed Recall Score (WLT-DR). Finally, a series of words were presented on the computer screen, including the original set and 15 distracter words in random order. Subjects indicated by button press whether the given word was part of the original set. The number of correct recognitions and the average speed (ms) of correct recognitions were recorded as the Recognition Score (WLT-RS) and the Recognition Time (WLT-RT).

Sternberg Memory Scanning Test (Working Memory)

Subjects were asked to memorize a list of successively presented digits (i.e., 0-9). Probe digits were subsequently presented on the computer screen. By pressing a button, subjects had to indicate whether a digit was part of the memory set. The mean reaction time (RT, ms) and percentage of errors were the outcome measures.

Tracking Test (Motor Control)

Participants were instructed to keep an unstable moving bar in the middle of a horizontal plane by using a computer mouse. The task consisted of 2 parts: a slow moving bar and a fast moving bar. The root mean square (RMS) deviation of the mouse movements was the primary response measure.

Divided Attention Test

The objective of this task was to memorize a fixed set of digits and subsequently perform 2 tasks simultaneously. After the presentation of the memory set, the subject had to keep an unstable slow moving bar in the middle of a horizontal plane. Simultaneously, probe digits were presented on the computer screen, on which the subject had to decide whether a digit was part of the initially presented memory set. Outcome measures were reaction time (ms), percentage of errors, and RMS deviation of the mouse movements.

Digit-Symbol Substitution Test (DSST)

Subjects were presented with a code in which the numbers 0 to 9 were matched with a simple symbol, and with a list of digits randomly arranged in rows. Subsequently, participants were asked to attempt as many correct symbol-for-digit substitutions as possible within 1.5 minutes. Outcome measures were the total number of correctly completed pairs and the percentage of errors.

Statistical Analysis

Statistical analysis was performed using SAS, Version 8.2. The treatment groups were compared using a 3-way crossover analysis of variance (ANOVA) model with treatment, sequence, and period as fixed factors, and subject within sequence as a random effect. A pairwise comparison between the active treatments and placebo was conducted. Differences from placebo were considered significant if $P < 0.05$.

RESULTS

A total of 31 subjects were screened. One subject voluntarily withdrew from the study. Thirty subjects completed the study. Their mean age was 25.9 (6.53 SD) years old. The mean (SD) sleep quality score was 3.96 (3.77) for placebo, 5.22 (3.67) for ramelteon, and 2.63 (1.55) for zopiclone. Neither hypnotic significantly differed from placebo ($P > 0.05$). No significant order effects or gender effects were observed. Results of the driving test are summarized in Table 1 and Figure 2.

Table 1. Driving test results

	ramelteon	zopiclone	placebo
SDLP (cm)	20.9 (0.7)*	21.6 (0.8)*	18.7 (0.7)
SDS (km/h)	2.7 (0.2)	2.6 (0.1)	2.5 (0.1)
MLP (cm)	26.3 (3.0)	26.7 (3.0)	27.2 (3.1)
MS (km/h)	93.5 (0.3)	93.8 (0.3)	93.8 (0.2)

Data are reported as mean (SEM). Abbreviations: SDLP = Standard Deviation of Lateral Position, SDS = Standard Deviation of Speed, MLP = Mean Lateral Position, MS = Mean Speed, cm=centimeter, SEM = standard error of the mean.
* $P < 0.05$ vs placebo

All subjects completed their driving tests. Relative to placebo, ramelteon (+2.2 cm) and zopiclone (+2.9 cm) significantly increased SDLP ($P < 0.001$). Standard deviation of speed, mean speed, and mean lateral position did not differ significantly between treatments. When compared to placebo, subjective driving quality was rated as significantly worse after ramelteon ($P < 0.001$), but not after zopiclone. Also, mental effort to perform the test was significantly higher after ramelteon ($P < 0.01$), whereas no differences were reported between zopiclone and placebo. A summary of performance on the psychometric and balance tests are presented in Table 2.

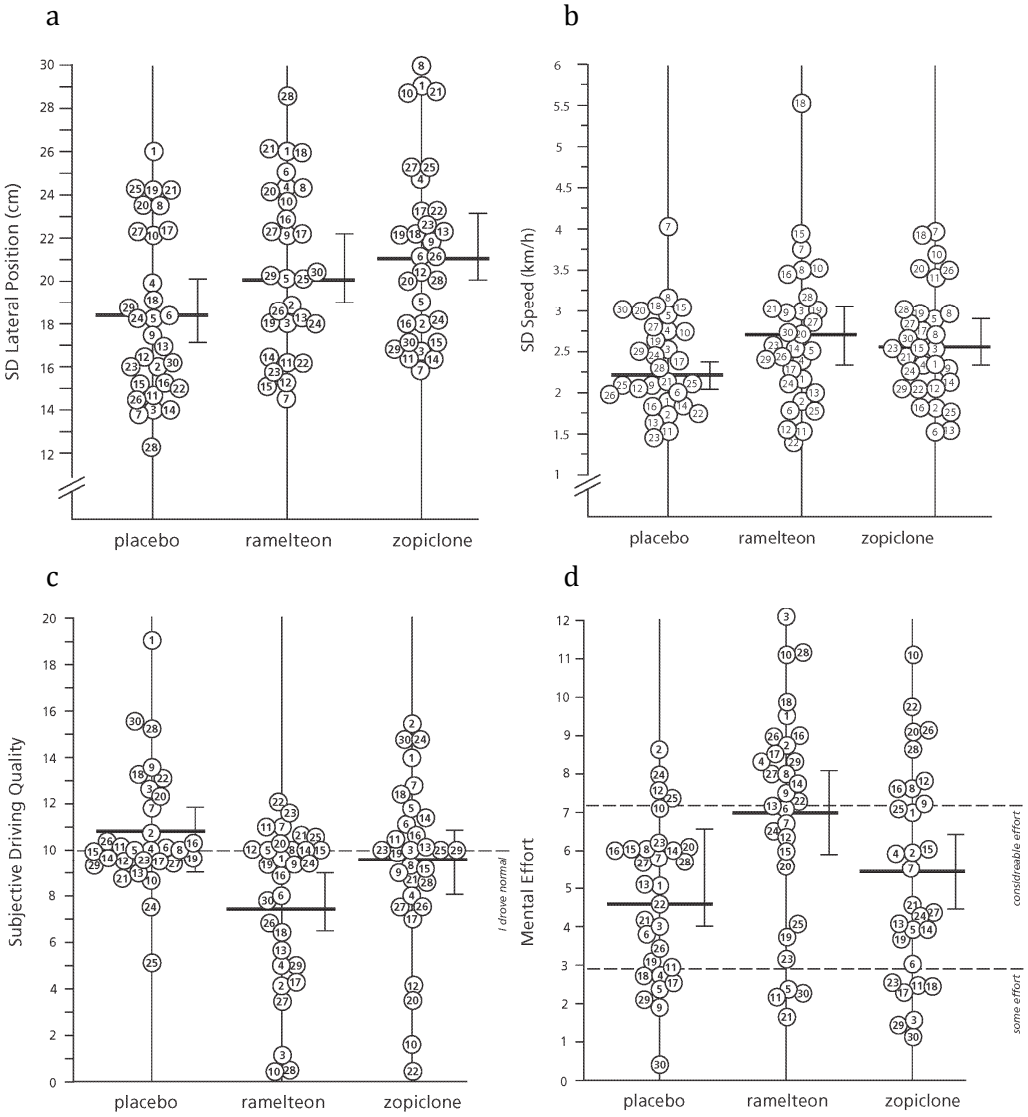

Figure 2. Driving test results
Individual data for (a) Standard Deviation of Lateral Position (SDLP), (b) standard deviation of speed, (c) subjective driving quality, and (d) mental effort to perform the test. Same numbers represent same subjects. Group mean and 95% confidence interval are indicated for each treatment.

Table 2. Performance on the memory and psychomotor tests.

	Ramelteon	Zopiclone	Placebo
WLT-IR	13.5 (0.4)	13.1 (0.4)	13.5 (0.3)
WLT-DR	11.1 (0.6)*	10.1 (0.6)*	12.2 (0.5)
WLT-RS	13.7 (0.3)	13.6 (0.2)	13.9 (0.2)
WLT-RT (ms)	722.1 (33.2)	767.4 (32.7)	713.6 (31.3)
SMST-RT (ms)	565.6 (22.2)*	584.1 (19.3)*	536.1 (20.1)
SMST- errors (%)	5.2 (0.8)	5.2 (0.9)	4.2 (0.6)
Tracking-Slow	11.1 (1.5)*	11.0 (1.4)*	8.6 (1.3)
Tracking-Fast	26.1 (0.9)*	25.5 (1.0)*	23.8 (1.1)
DAT-tracking	14.0 (1.5)*	13.9 (1.5)*	10.8 (1.5)
DAT- errors (%)	4.3 (0.5)	4.1 (0.5)	6.7 (3.1)
DSST	67.0 (2.1)	64.3 (2.1)*	68.5 (2.0)
COP-change from pre-dose (eyes open)	1.5 (0.3)	5.5 (1.1)*	1.5 (0.6)
COP-change from pre-dose (eyes closed)	1.2 (0.3)	5.7 (1.5)*	1.4 (0.6)

Data are reported as mean (SEM). Abbreviations: WLT = Word Learning Test, IR = Immediate Recall, DR = Delayed Recall, RS = Recognition Score, RT = Reaction Time, SMST = Sternberg Memory Scanning Test, DAT = Divided Attention Test, DSST=digit symbol substitution test, COP= Center of Pressure, ms= milliseconds. * $P < 0.05$ vs placebo

In the word learning test, immediate word recall was not affected by any treatment. Also, no significant differences between treatments were found for word recognition. Delayed word recall was significantly impaired after ramelteon ($P < 0.032$) and zopiclone ($P < 0.01$). In the Sternberg Memory Scanning Test, mean reaction time was significantly higher after both ramelteon ($P = 0.024$) and zopiclone ($P < 0.001$) than after placebo. No differences from placebo were found in the percentage of errors in the Sternberg Memory Scanning Test. Ramelteon and zopiclone significantly impaired performance in the tracking test, in both the slow ($P \leq 0.007$) and fast condition ($P \leq 0.010$). In the Divided Attention Task, tracking was significantly impaired after both ramelteon and zopiclone ($P < 0.001$), and mean reaction speed was significantly slower after zopiclone ($P = 0.007$) and ramelteon ($P = 0.015$). There were no statistically significant differences between treatments in the percentage of errors. In the DSST, when compared to placebo, the number of correct pairs were significantly less after zopiclone

($P < 0.001$) but not after ramelteon ($P = 0.084$). On the balance test, ramelteon did not affect performance, whereas zopiclone increased postural sway in both eyes open and eyes closed conditions ($P < 0.001$).

Results from the ARCI-49 Questionnaire showed that when treated with ramelteon, subjects reported significantly less euphoria ($P < 0.007$), more dysphoric/ somatic symptoms ($P < 0.049$), more sedation ($P < 0.001$), less intellectual efficiency ($P < 0.0001$), and less activation ($P < 0.006$), compared to placebo. After zopiclone treatment, subjects did not report any significant differences from placebo.

Adverse Events

No serious adverse events were reported. Somnolence, disturbance in attention, and fatigue were most frequently reported. Somnolence was reported by 20 subjects (66.7%) taking ramelteon, 22 subjects (73.3%) taking zopiclone, and 10 subjects (33.3%) taking placebo. Disturbance in attention was reported by 12 subjects (40.0%) taking ramelteon, 7 subjects (23.3%) taking zopiclone, and 6 subjects (20.0%) taking placebo. Fatigue was reported by 11 (36.7%) subjects taking ramelteon, 6 (20.0%) taking zopiclone, and 8 (36.7%) taking placebo.

DISCUSSION

Contrary to expectations, this study showed that on the morning following bedtime administration, ramelteon significantly impaired performance on driving, psychometric and memory tests and affected mood. In line with previous studies, zopiclone significantly impaired performance on most tests.

As established in studies on the effect of alcohol on driving performance, an increase in SDLP of 2.4 cm (i.e., the relative difference in weaving between placebo and the active substance) is considered to be the cut-off point for a clinically relevant difference. This SDLP increment was found previously for a blood alcohol concentration (BAC) of 0.05%, the legal limit for driving a car in many countries.[34] A BAC of 0.05% is the point at which the ability to perform skills necessary for driving becomes affected and at which the risk of being involved in a traffic accident increases substantially.[35-37] The mean increase in SDLP after the intake of ramelteon (+2.2 cm) was just below this limit.

However, relative to placebo, one-third (10/30) of subjects receiving ramelteon had an SDLP increment of more than 2.4 cm. Zopiclone caused a mean SDLP increment of 2.9 cm, and more than half (17/30) of the subjects drove worse than the BAC 0.05% limit. The mean effect of zopiclone is comparable to that observed with a BAC between 0.05 and 0.08%.[34]

The clinical implication of these findings is that patients initiating treatment with ramelteon (and zopiclone) should be cautioned when they want to drive a car, because there is a potential risk that driving may be impaired the morning following bedtime administration. In this context, the VAS scales assessing subjective driving quality and mental effort to perform the driving test yielded important information. That is, whereas subjects acknowledged reduced subjective driving quality and increased mental effort to perform the driving test after using ramelteon, they did not after using zopiclone. Of concern, after using zopiclone subjects rated their driving quality as normal, whereas in fact driving was more impaired than after using ramelteon. Our findings for zopiclone were similar to those observed in previous on-the-road driving studies.[38,39] In line with impairment on the driving test, both ramelteon and zopiclone produced significant impairment on psychomotor, memory, and cognitive tests. Similar to previous studies,[21,23] and in contrast to benzodiazepine hypnotics,[14] body balance, assessed in the middle of the night at peak plasma concentration, was not affected by ramelteon. In contrast, zopiclone significantly increased postural sway.

Significant next-day residual effects on psychomotor performance, memory, performance, and mood were found for both ramelteon and zopiclone. The effects of both hypnotics are comparable with those found in a study examining the effects of BAC 0.05%, using the same driving test and psychometric test battery.[12]

The unexpected results of this study are difficult to explain when compared to most previous studies as well as the kinetics of the drug. Effects of ramelteon on memory functioning have not been demonstrated in most other studies.[18,21-25,27] However, a study including a simulated night shift demonstrated significant impairment on Probed Recall Memory recognition.[40] Two studies using word learning tests similar to the one used here, also reported significant impairment, one in chronic insomniacs[41] and one in subjects experiencing jet lag.[42] The study in insomniacs demonstrated small

decreases in delayed memory performance after one week of treatment with ramelteon (8 mg) and on immediate recall after three weeks of treatment. The jet lag study showed effects on immediate memory recall in all dosages (1, 4, and 8 mg) after four days of bedtime intake. In the present study, both immediate and delayed recall were tested in the morning after bedtime intake. In other studies, words were presented in the evening before ramelteon administration and delayed memory was tested in the morning. The fact that subjects were asleep between learning and retrieval may have facilitated retention,[43] and may thus explain differences with the current study. One study in patients with chronic insomnia did conduct a memory test in the morning after intake, but measurements were performed not earlier than one week after treatment onset.[24] It remains uncertain why pharmacodynamic studies performed during the day did not show negative effects.[18,21,23]

Regarding psychomotor functioning, no other study found an effect on DSST[18,19,21,22,24-27,41] or on a circular lights test.[21] In contrast to these studies, the present study used an elaborate test battery including more complex psychomotor tests, e.g., Sternberg memory scanning, tracking, and divided attention. There is a possibility that impairments in daytime functioning after bedtime intake of ramelteon cannot be revealed by simple tests of relative short duration. This would also explain why the night shift study, that also used an elaborate test battery, also reported significant impairment after administration of ramelteon.[40] In the present study, duration of the driving test was about 1 hour, and most psychometric tests took about 8 to 10 minutes to complete. It can therefore be assumed that in the present study mental effort to perform the test battery and driving test was higher than tests performed in other clinical trials.

It is unlikely that performance of the middle-of-the night balance task (requiring a short disruption of sleep) may have influenced next-morning test performance in this cross-over design. Since the balance test was performed approximately five minutes after being woken up, sleep inertia most likely had already disappeared and did not influence results. The fact that zopiclone and ramelteon have a different mechanism of action may explain why zopiclone does impair balance and ramelteon does not.

Due to its half-life of 0.83 to 1.90 hours,[19] it seems unlikely that ramelteon still had an effect in the morning. There is, however, a possibility that the

active metabolite M-II, which has a half-life of 2.27 to 3.39 hours,[19] caused the effects. Future studies should examine the possible causes of the residual effects of ramelteon.

Limitations

The absence of polysomnography as objective measure of sleep parameters, or any other objective measure of sleep, may be seen as a limitation of the current study. An important rationale for not conducting polysomnography was that the previous studies that specifically examined sleep found either an improvement with ramelteon relative to placebo, or no difference. In fact, in no study did ramelteon impair sleep.[22,26] Thus, there was no a priori reason to expect sleep disturbance associated with ramelteon use, or much less than the degree of sleep disturbance to impair next-day performance.

In retrospect, given the surprising nature of our results, data on sleep and circadian phase would have been helpful in explaining these results. However, it must be recognized that explanations would not negate the current finding of impaired driving with ramelteon use.

In the current study, healthy volunteers were included instead of patients with insomnia. This was done on purpose. The vast majority of driving studies have been done in healthy volunteers[44]; similarly, on-the-road studies examining the residual effects of hypnotic drugs have been performed in healthy volunteers.[2,3] These studies provide the most direct measure of drug effects, which also emphasizes the importance of our results. Studies in healthy volunteers are critical to understand the specific effects of drugs in the absence of disturbed sleep. In our study, disturbed sleep was an exclusion criterion, and all participants underwent a sleep rehearsal night. If studies in insomniacs would negate these residual effects, and if tolerance develops after daily use of ramelteon, are interesting topics for future research.

In summary, our data show that both ramelteon (8 mg) and zopiclone significantly impair next-morning driving performance, memory, cognitive, and psychomotor functioning. In contrast to zopiclone, ramelteon had significant effects on next-day mood but produced no impairment on the DSST or middle-of-the night balance test. Future studies should aim at finding explanations for the residual effects of ramelteon by assaying both sleep and circadian phase.

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9

EFFECTS OF ALCOHOL ON HIGHWAY DRIVING IN THE STISIM DRIVING SIMULATOR

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ABSTRACT

Objective: The STISIM driving simulator is widely used. To enhance its usefulness in pharmacological research, a calibration study was performed to test a standardized highway driving test scenario after administration of three different dosages of alcohol and placebo.

Methods: 27 healthy young adults (14 men and 13 women; mean age (SD) = 22.8 (1.4)) participated in this randomized, single-blind crossover trial. Subjects received alcohol to gain a blood alcohol concentration (BAC) of 0.05%, 0.08%, and 0.11%, or placebo-alcohol. In each condition, subjects completed a 100-km highway driving simulator test. The Standard Deviation of Lateral Position (SDLP), the weaving of the car, was the primary parameter of the test.

Results: Alcohol produced dose-dependent driving impairment. SDLP and standard deviation of speed were significantly increased relative to placebo ($p<0.05$). Subjective driving assessments were in line with the objective driving measurements.

Conclusion: The STISIM highway driving simulator test is able to differentiate dose-dependent impairment after administration of alcohol. The highway driving test scenario is suitable for future psychopharmacological research.

Keywords: alcohol, driving, STISIM, SDLP, simulator

INTRODUCTION

Currently, a wide range of driving simulators exist which vary in their level of complexity and representativeness for actual driving. Where older driving simulators primarily measured divided attention skills and lacked other traffic, modern driving simulators are much more sophisticated and offer more realistic driving scenarios to evaluate driving impairment (Cox and Taylor, 1999; Lee et al., 2003a; Reimer et al., 2006).

One of the most widely used simulators is the STISIM driving simulator. This fully interactive system enables the driver to control both steering and speed while visual and auditory feedback is provided. In addition, driving test scenarios can be adapted to meet specific test requirements (Liguori, 2009) by varying road characteristics, weather conditions, and traffic density. The STISIM driving simulator allows objective measurement of a great number of parameters such as speed, lane position, and the number of collisions (Lee et al., 2003b; Shechtman et al., 2009).

At present, the on-the-road driving tests in actual traffic are regarded as the gold standard to examine driving ability (O'Hanlon et al., 1982; Verster and Roth, 2011). In this test, subjects are instructed to drive with a steady position and constant speed over a 100-km highway track. A driving instructor guards safety, because the test is conducted on a public highway in normal traffic. The Standard Deviation of Lateral Position (SDLP), i.e. the weaving of the car, is the primary parameter of the highway driving test. SDLP is a sensitive measure that differentiates between dose-dependent driving impairment after administration of various psychoactive substances, including alcohol (Louwerens et al, 1987), hypnotics (Verster et al., 2006), antihistamines (Verster and Volkerts, 2004), antidepressants (Ramaekers, 2003), anxiolytics (Verster et al., 2005), and drugs of abuse (Penning et al., 2010).

Using a driving simulator may be an alternative for on-road tests if one wishes to use more controlled circumstances, or manipulate specific test conditions such as traffic density and weather conditions. Therefore, Utrecht University developed a standardized highway driving test scenario in the STISIM driving simulator, with the aim being representative for the highway track driven in actual traffic.

The objective of this study was to calibrate the STISIM driving simulator by examining driving performance after administration of three different dosages of alcohol (0.05, 0.08 and 0.11%) and placebo. Because the effects of alcohol on driving are well-studied and easy to interpret, alcohol levels provide a straightforward and clinically relevant reference to give an indication of the severity of other drugs on driving ability. It was hypothesized that alcohol will produce dose-dependent impairment on the test, expressed in increased SDLP with higher Blood Alcohol Concentration (BAC).

METHODS

This study was a single-blind, placebo-controlled randomized crossover trial. The study was approved by the Medical Ethical Committee of the University Medical Center Utrecht and the study was conducted according to the ICH Guidelines for 'Good Clinical Practice' (ICH, 1996), and the Declaration of Helsinki and its latest amendments. Written informed consent was obtained from each subject before the start of the study.

Subjects

A total of 27 healthy volunteers were included in the study. Subjects were recruited by means of local advertisements. Subjects were included if they were between 21 and 50 years old, had a valid driver's license for at least 3 years, and if they were self reported to be social drinkers (7 to 21 alcoholic drinks per week). Exclusion criteria were current or past drug use, being pregnant, present use of psychoactive medication, positive alcohol breath test, physical or mental illness, simulator sickness, excessive smoking (more than 10 cigarettes per day), and consumption of more than 5 caffeine-containing beverages per day. Before every session, urine drug screening was performed to detect the presence of amphetamines (including MDMA), barbiturates, cannabinoids, benzodiazepines, cocaine, and opiates; for female participants a β-HCG pregnancy test was carried out. Subjects with positive test results were excluded. Alcohol use was examined using a breath analyzer (Dräger Alcotest 7410 Breath Alcoholmeter). Participants were told to refrain from alcoholic drinks 24 hours before the start of each test day, and were not allowed to smoke or consume caffeinated beverages on the test days.

Procedure

The study started with a training session to screen the subjects and to familiarize them with the procedures. If they met the inclusion and exclusion criteria, participants had a practice session in the STISIM driving simulator. During this session, simulator sickness was determined using the Simulator Sickness Questionnaire (Kennedy et al., 1993). Participants without simulator sickness were randomly assigned to a treatment order comprising four treatments: placebo, 0.05 % BAC, 0.08% BAC, or 0.11% BAC. On the test days, subjects' compliance was checked by urine drug testing and alcohol breath testing.

The amount of ethanol necessary to reach the desired BAC level was calculated based on body weight and gender (Watson et al., 1981). A dosage of ethanol (ethanol (99.9%) mixed with orange juice up to a volume of 250 ml) or placebo-ethanol (250 ml orange juice) was administered. To enhance treatment blinding, all beverages were flavored with cognac aroma and a nose-clip was worn while consuming the drink. Subsequently, on each test day, blinded BAC measurements were performed every 5 minutes after treatment administration until the desired peak BAC was reached and alcohol levels started to descend. When the desired BAC was reached the driving test was performed. On the placebo tests day, a series of breath analyzer tests were performed in a similar manner, to enhance blinding of the subjects. Subjects could not see the reading of the breath analyzer.

STISIM Highway driving test

Driving tests were performed using STISIM Drive™ (Systems Technology Inc, Hawthorne, CA). The simulator consists of a car unit with adjustable car seats and a dashboard and includes a steering wheel, turn sign indicators, gear lever, and brake, clutch, and gas pedals (see Figure 1). A realistic roadway scenery is projected on a wide screen (2.10m by 1.58m), placed 1.90m in front of the center of the steering wheel. Speed and gear number are displayed on the dashboard and the screen. Auditory feedback is provided by speakers and included sound of the engine, braking, speeding in curves, wheels, and driving off-road. Whenever a collision occurs, a broken wind-shield is projected, and the sound of braking glass can be heard. Subsequently, the car

is placed back in the middle of the right traffic lane, and subjects can continue their driving test.

Figure 1. STISIM driving simulator

A 100 km highway driving test scenario was developed by EyeOctopus B.V, tailored to Dutch traffic situations (e.g. Dutch traffic signs, vehicles, buildings and sceneries were included). The test scenario aims to resemble the on-the-road highway driving test Utrecht University performs in normal traffic. The scenario consists of a two lane highway in each direction with a lane width of 3.5m (See Figure 2).

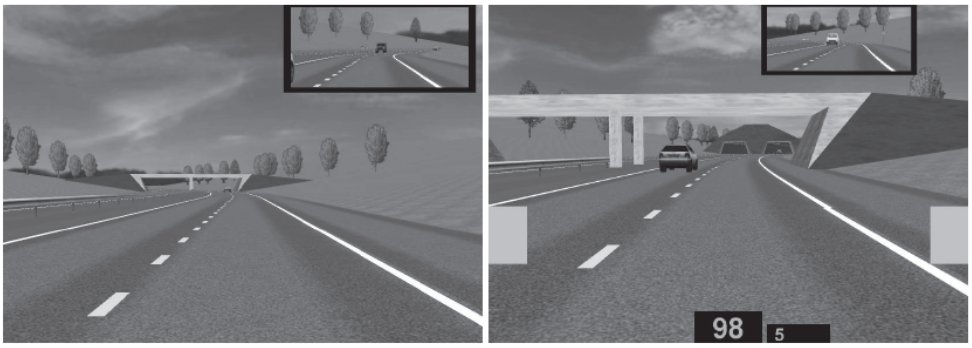

Figure 2. STISIM highway driving test scenario

Subjects are instructed to drive with a steady lateral position in the right (slower) traffic lane while maintaining a steady speed of 95 km/h. Overtaking maneuvers are allowed only if a subject approaches a slower moving car. These events are removed during the data editing process, to allow calculation of statistics based on the 'clean' data. Weaving of the car, expressed by the

standard deviation of the lateral position (SDLP, cm) is the primary outcome measure of the test. A second outcome measure is the standard deviation of speed (SDS, km/h). Mean lateral position (MLP, cm) and Mean speed (MS, km/h) are control variables. Test duration is approximately 1 hour.

Subjective assessments

After each driving test, participants indicated their perceived driving quality on a visual analog scale, ranging from 0 which means: 'I drove exceptionally poorly' to 20 which means 'I drove exceptionally well' and which included a midpoint of 'I drove normally'. In addition, they rated the mental effort to perform the driving test on an interval scale (15 cm) ranging from 'almost no effort' to 'very great effort' (Meijman et al., 1986; Zijlstra and Van Doorn, 1985). Furthermore, driving style was assessed using bipolar scales labeled foolish-wise, unpredictable-predictable, dangerous-safe, tense-relaxed, inconsiderate-considerate, and irresponsible-responsible (McCormick et al., 1987).

Statistical analysis

Statistical analyses were carried out employing the SPSS statistical program (version 16). For each parameter, the mean, standard deviation (SD), and 95% confidence interval (95% CI) were computed. The data were tested for significance by using analysis of variance (ANOVA) for repeated measures (two-tailed, $p \leq 0.05$). Missing values (about 1%) were replaced by the group average of the parameter.

RESULTS

Subjects

Five subjects were excluded because of simulator sickness, one subject was insensitive to alcohol, and three individuals withdrew voluntarily. These subjects were replaced. A total of 27 completing subjects were included in the statistical analysis. They participated in all four conditions of the crossover trial. Data from one test day of one subject (BAC 0.08%) were missing. These data were replaced by the group average. Subjects' demographics are shown in table 1.

Table 1. Demographics. Mean (SD). BMI=Body Mass Index

Gender	N	Age (years)	BMI (kg/m2)	Mean driving distance (km/year)	Alcohol consumption (# standard drinks/week)	Possession of drivers license (years)
Men	14	23.4 (1.3)	22.4 (1.4)	7500 (6961)	14.3 (4.2)	5.0 (1.2)
Women	13	22.2 (1.1)	23.1 (2.1)	5050 (10603)	13.9 (3.7)	3.9 (0.9)
Total	27	22.8 (1.4)	22.7 (1.8)	6320 (8813)	14.1 (3.9)	4.4 (1.2)

BAC levels and blinding

Table 2 shows the mean (SD) BAC that was obtained before and after the driving test. Each test day, participants were asked to guess their BAC. Overall, 53.7% of the alcohol dosages were correctly guessed, indicating accurate blinding.

Table 2. Mean (SD) of desired and obtained Blood Alcohol Concentration and percentage of correctly guessed suspected treatment.

	Desired BAC			
	0.00 %	**0.05 %**	**0.08 %**	**0.11 %**
obtained BAC before driving	0.00	0.050 (0.003)	0.081 (0.003)	0.108 (0.007)
obtained BAC after driving	0.00	0.033 (0.007)	0.063 (0.009)	0.092 (0.010)
% correctly guessed	61.5	55.6	48.0	44.4

Driving performance

Dose-dependent impairment was found on the driving test (See Figure 3 and Table 3). Mean ± SE SDLP values (cm) in each condition were 28.0 ± 1.2 (placebo), 29.7 ± 1.4 (BAC 0.05%), 33.8 ± 1.4 (BAC 0.08%), and 36.3 ± 1.9 (BAC 0.11%). For all BACs, SDLP differed significantly from placebo ($p < 0.05$). SDLP changes from placebo correlated significantly with BAC ($r=0.459$; $p<0.0001$).

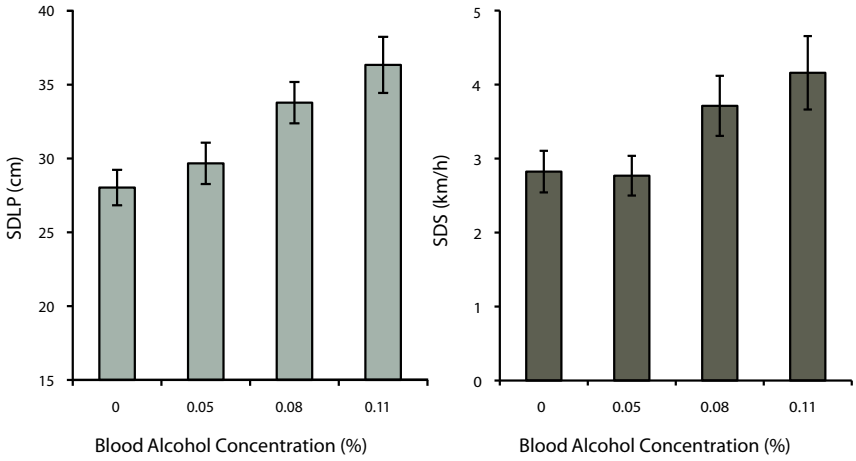

Figure 3. Mean (SE) Standard Deviation of Lateral Position (SDLP; cm) and Standard Deviation of Speed (SDS; km/h) for each Blood Alcohol Concentration.

Standard deviation of speed significantly differed from placebo for BAC 0.08% ($F_{(1,26)}=6.7$, $p < 0.015$) and BAC 0.11% ($F_{(1,26)}=13.0$, $p < 0.001$), confirming reduced vehicle control (see Figure 3). No statistically significant differences in mean speed and mean lateral position were found, indicating that subjects performed the tests according to the instructions.

Of the eight subjects who had collisions, two accounted for the majority of them (60%). A total of 25 collisions occurred in the highway study: 4 after placebo, 6 after BAC 0.08% and 15 after BAC 0.11%. No significant differences were found between the treatments and placebo, although a clear trend for an increasing number of collisions with increased alcohol concentrations is apparent.

Subjective assessments

At each BAC, subjects rated their driving quality as significantly worse when compared to placebo ($p < 0.05$). In addition, with increasing BAC subjects generally rated their driving style as significantly more dangerous, foolish, tensed, unpredictable, inconsiderate, and irresponsible ($p < 0.05$). However, no significant differences between the treatments were reported in mental effort to perform the driving test.

Table 3. Overview of driving test parameters and subjective assessments.

BAC (%)	0	0.05	0.08	0.11
Driving test results				
SD Lateral Position (cm)	28.0 (6.5)	29.7 (7.1)*	33.8 (7.2)*	36.3 (9.8)*
SD Speed (km/h)	2.8 (1.5)	2.8 (1.4)	3.7 (2.1)*	4.2 (2.6)*
Mean Lateral position (cm)	-6.1 (13.9)	-5.9 (13.6)	-5.6 (11.9)	-7.1 (13.6)
Mean Speed (km/h)	95.9 (1.7)	95.6 (1.3)	96.1 (2.8)	96.3 (3.4)
Subjective Assessments				
Driving Quality (cm)	10.7 (3.0)	9.0 (3.6)*	8.6 (2.4)*	7.4 (2.4)*
Mental Effort (cm)	5.6 (2.4)	6.3 (2.0)	6.2 (2.3)	6.4 (2.4)
Driving style (cm):				
Wise - foolish	2.1 (1.3)	3.1 (1.7)*	3.2 (1.5)*	4.0 (1.9)*
Predictable -unpredictable	2.4 (1.5)	3.0 (1.5)*	3.5 (1.4)*	4.0 (1.6)*
Safe - dangerous	2.4 (1.7)	3.4 (1.7)*	3.6 (1.9)*	4.3 (1.9)*
Relaxed- tense	2.5 (1.6)	3.3 (1.7)*	3.3 (2.1)	3.9 (2.1)*
Considerate- inconsiderate	2.3 (1.3)	3.0 (1.4)	3.6 (1.7)*	4.0 (1.8)*
Responsible - irresponsible	2.4 (1.4)	3.4 (1.8)*	3.9 (1.6)*	4.4 (2.0)*

* $P<0.05$ compared to placebo (BAC 0.00 %)

Mean (SD) are shown for each parameter. Driving quality scores range from 0 ('exceptionally poorly') to 20 ('exceptionally well'), with a midpoint of 10 ('normally'). Mental effort scores range from 0 ('almost no effort') to 15 ('very great effort'). Driving style score range from 0 to 10 as indicated in the table (eg, 0 indicates 'extremely wise'; 10 indicates 'extremely foolish'). Abbreviation: BAC= Blood Alcohol Concentration, SD=Standard Deviation, cm=centimeter, km/h=kilometer per hour

DISCUSSION

The highway driving test scenario has proven to be suitable for future psychopharmacological studies that aim to examine driving performance under controlled circumstances. This study demonstrated that the STISIM highway driving test is sensitive to dose-dependent effects of alcohol. Significant differences from placebo in weaving of the car (SDLP) were found for BAC 0.05% and higher dosages. Similar performance impairment was observed for SD Speed.

The results are in accordance with previous experiments using other STISIM driving simulator scenarios that also demonstrated significantly increased SDLP values after administration of BAC 0.05% (Lenné et al., 1999) and 0.08% (Harrison and Fillmore, 2005; Marczinski et al., 2008; Marczinski

and Fillmore, 2009). One of these studies also reported an effect of alcohol on SD speed at a BAC of approximately 0.08% (Marczinski et al., 2008).

Support for external validity of the STISIM driving simulator was provided by experiments that compared parameters such as driver mistakes (e.g. obeying traffic rules, running red lights, and tailgating), road-tracking error, and speed maintenance measured in the STISIM driving simulator with those measured during actual driving (Lee, 2002; Lee et al., 2003b; Shechtman et al., 2009). Ideally, the results of the current study should be compared with those of the standardized on-the-road highway driving test in real traffic. However, because Dutch legislation prohibits driving on a public highway with a BAC above 0.05% it is not possible to make such a direct comparison for the effect of higher BAC levels on driving performance. The findings in our study are however in line with those observed in a closed-road highway driving test performed by Louwerens and colleagues (1987). Although in our study the differences from placebo for each alcohol dosage fall within the 95% confidence interval established in the Louwerens et al. study, the absolute SDLP values obtained in the STISIM driving simulator were higher than those observed by Louwerens and colleagues. Higher SDLP values in the simulator compared with on-the-road have also been found in other studies (Blaauw, 1982; Blana and Golias 2002; Reed and Green, 1995), but baseline SDLP values vary greatly between studies and individual drivers. The latter is important, since not absolute SDLP values but differences from placebo are of primary interest when analyzing and interpreting the data.

The development of the STISIM highway driving simulator test is of significance because it enables conducting experiments that are not allowed in actual traffic. In addition to testing higher BAC dosages than allowed by law drug-alcohol interaction studies can be performed. The objective of this study was to develop a standardized test scenario. However, the STISIM driving simulator provides a great number of measures, such as steering wheel and throttle input, acceleration, time to lane crossing, speeding, vehicle curvature, and traffic offenses. In addition, illegal and/or dangerous driving behaviors (e.g. using a cell phone while driving) can now be examined safely and under controlled circumstances. In future studies, it would be interesting to examine the effect of alcohol on city driving, using measures such as time to collision, speeding, and tailgating. In contrast to older and less sophisticated driving

simulators, the STISIM driving simulator is suitable to program new scenarios that can be used for this future research.

The present study showed that the highway driving test scenario is suitable for future psychopharmacological research.

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10

EFFECTS OF COFFEE ON DRIVING PERFORMANCE DURING PROLONGED DRIVING

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Submitted

ABSTRACT

Coffee is often consumed to counteract driver sleepiness. The aim of this study was to examine the effects of a single cup of coffee (80 mg caffeine) on simulated driving performance.

Non-sleep deprived healthy volunteers (n=24) participated in a double-blind, placebo-controlled, crossover study. After 2 hours of monotonous highway driving, subjects received caffeinated or decaffeinated coffee during a 15-minute break, before continuing driving for another 2 hours. The primary outcome measure was the standard deviation of lateral position (SDLP), reflecting the weaving of the car. Secondary outcome measures were speed variability, subjective sleepiness, and subjective driving performance.

The results showed that caffeinated coffee significantly reduced SDLP as compared to decaffeinated coffee, both in the first (p=0.024) and second hour (p=0.019) after the break. Similarly, the standard deviation of speed (p=0.024; p=0.001), mental effort (p=0.003; p=0.023), and subjective sleepiness (p=0.001 ; p=0.002) were reduced in both the first and second hour after consuming caffeinated coffee. Subjective driving quality was significantly improved in the first hour after consuming caffeinated coffee (p=0.004).

In conclusion, these findings demonstrate a positive effect of one cup of caffeinated coffee on driving performance and subjective sleepiness during monotonous simulated highway driving.

Keywords: Caffeine, Automobile Driving, Fatigue, Sleepiness

INTRODUCTION

Drowsy driving is an important cause of traffic accidents (Connor et al., 2002; Horne and Reyner, 1995; Maycock, 1996), and therefore the development of effective countermeasures is essential. Consuming a cup of coffee is one of the most commonly used ways to combat driver sleepiness. An estimated 80% of the population consumes caffeine-containing beverages, often on a daily basis (Fredholm et al., 1999; Heckman et al., 2010). Caffeine (1,3,7-trimethylxanthine) is rapidly and completely absorbed in the body within approximately 45 minutes (Blanchard and Sawers, 1983). It reaches its peak plasma concentration within 15 to 120 minutes after intake (Arnoud, 1987), averaging around 30 minutes (O'Connell and Zurzuola, 1984; Blanchard and Sawers, 1983). Its elimination half life is 1.5 to 9.5 hours (Arnoud, 1987; Bonati et al., 1982). Although additional mechanisms of action are involved, it is now believed that caffeine's stimulant effects are exerted by antagonizing adenosine, primarily by blocking the adenosine A1 and A2A receptors. Adenosine is considered to be a mediator of sleep (Dunwiddie and Masino 2001; Fredholm et al., 1999).

A great number of studies have demonstrated effects of caffeine on mood and performance (Childs and De Wit, 2006; Christopher et al., 2005; Haskell et al., 2005; Lieberman et al., 1987; Olson et al., 2010). However, the effects are complex and depend on the specific tasks examined, dosages, subjects, and test conditions (Lorist and Tops, 2003). Overall, caffeine was found to be specifically effective in restoring performance to baseline levels when individuals are in a state of low arousal, such as seen during the dip in the circadian rhythm, after sleep restriction, and in fatigued subjects (Nehlig, 2010; Smith, 2002). Indeed, many people consume coffee with the purpose to refresh or stay awake, for example when driving a car (Anund et al., 2008; Vanlaar et al., 2008).

Several driving studies showed that caffeine improves performance and decreases subjective sleepiness both in driving simulators (Biggs et al., 2007; Brice and Smith, 2001; De Valck et al., 2001; Horne and Reyner, 1996; Regina et al., 1974; Reyner and Horne, 1997; Reyner and Horne, 2000) and on the road (Philip et al., 2006; Sagaspe et al., 2007). Most of these studies tested sleep-restricted subjects. In addition, relatively high dosages of caffeine (100-300 mg), were examined. These studies showed that relatively high dosages of

caffeine had a positive effect on driving performance and reduced driver sleepiness. In real life however, it is more likely that a driver consumes only one cup of coffee (80 mg of caffeine) during a break, before continuing driving. Up to now, the effects on driving performance of lower dosages of caffeine, e.g. a regular cup of coffee, have not been examined.

Therefore, the objective of this study was to examine the effects of one cup of coffee (80 mg caffeine) on non-sleep deprived individuals during the daytime on driving, sleepiness, and subjective driving assessments.

EXPERIMENTAL PROCEDURES

This study was a double-blind, randomized, placebo-controlled, cross-over study. The study was conducted according to the ICH Guidelines for 'Good Clinical Practice', and the Declaration of Helsinki and its latest amendments. Written informed consent was obtained from the participants before taking part in the study. The study was approved by the Institutional Review Board; no medical ethical approval was required to conduct the study.

Subjects

Twenty-four adult healthy volunteers (12 male and 12 female), with a mean age of 23.2 (SD 1.6) years were recruited by means of public advertisements at and around Utrecht University campus. Subjects were included if they were healthy volunteers, moderate caffeine drinkers (2-4 cups a day), non-smokers, had a body mass index between 21 and 30, possessed a valid driver's license for at least three years, and drove more than 5.000 km per year.

Sleep disturbances were assessed with the SLEEP-50 questionnaire (Spoormaker et al. 2005) and excessive daytime sleepiness was examined using the Epworth Sleepiness Scale (ESS; Johns, 1991).

Before the start of each test day, urine samples were collected to test for drugs of abuse including amphetamines (including MDMA), barbiturates, cannabinoids, benzodiazepines, cocaine, and opiates (Instant-View, Alfa Scientific Designs Inc) and pregnancy in female subjects (β-HCG test). To test for the presence of alcohol the Dräger Alcotest 7410 Breath Analyzer was used. From 24 hours before the start of the test day until completion of the test day, alcohol consumption was not permitted. Caffeinated beverages and

smoking were not allowed from awakening on test days until the end of the tests.

Study design

Participants were screened and familiarized with the test procedures during a training day. When meeting all inclusion and passing all exclusion criteria, subjects performed a practice session in the STISIM driving simulator and completed the Simulator Sickness Questionnaire (Kennedy et al., 1993) to identify possible simulator sickness. Included subjects were randomly assigned to a treatment order comprising decaffeinated coffee and caffeinated coffee (80 mg) administered during a break.

Upon arrival, possible use of drugs or alcohol, pregnancy, illness and medication were checked. In addition, quality and duration of sleep was assessed using the 14-item Groningen Sleep Quality Scale (Mulder-Hajonides van der Meulen et al. 1980). When all criteria were met, a 120-minute drive in the STISIM driving simulator was conducted. Thereafter, a 15-minute break was scheduled in which subjects received the double-blind treatment. After the break, another 120-minutes driving session was performed. Every hour, subjective assessments of driving quality, driving style, mental effort to perform the test, and sleepiness were conducted. Test sessions were scheduled at the same time for each subject, either in the morning (8.00-13.00) or in the afternoon (13.00-17.00).

Treatments

This study aimed to mimic the effect of a cup of coffee drivers consume when having a break along the highway. Treatments were 2.68 gram of Nescafé Gold® instant coffee containing 80 mg caffeine, or 2.68 gram of Nescafé Gold® decaffeinated coffee dissolved in 180 ml boiled water. To confirm that each cup of coffee contained 80 mg of caffeine, the amount of caffeine in the instant coffee was determined with High-performance liquid chromatography (HPLC; Shimadzu LC-10AT VP equipped with UV-VIS detector). The column was a Reversed Phase -Select B column Lichrocart HPLC C18, 5µm, length 0,125 m, Ø= 4,6 mm. All of the procedures were carried out isocratic. The separation was done at room temperature. Caffeine and the spiked matrices were separated with a mobile phase of 20% MeOH and 10mM $HClO_4$, at a

flow-rate of 0.5mL/min. The injection volume was 5µL and the detection was carried out at 273 nm. The mean (SD) amount of caffeine per gram Nescafé Goud instant coffee samples (n=10), was 29.79 (0.656) mg/gram. The mean amount of caffeine in decaffeinated coffee was 0.79 mg/gram. The accuracy of determinations was 98.1% (SD 0.56). Because both the precision and the accuracy met up to the requirement demands, all of the results of this HPLC determination can be concluded with certainly.

Treatments were administered double-blind, and a nose clip was worn to enhance treatment blinding. Drinks were consumed within five minutes, starting from five minutes after onset of the break.

STISIM Highway driving test

Driving tests were performed in a fixed-base driving simulator employing STISIM Drive™ (version M300, Systems Technology Inc, Hawthorne, CA). This is an interactive system in which the roadway scenery is projected on a screen (2.10 m by 1.58 m), 1.90 m in front of the center of the steering wheel of the car unit (Mets et al., 2010). The 100 km highway driving test scenarios were developed (EyeOctopus BV) in accordance to Dutch traffic situations, including a two-lane highway in each direction and a monotonous environment with trees, occasional hills and bridges, and other traffic. The duration of each 100-kilometer scenario is approximately 60 minutes. Two scenarios (200 km) were conducted before a 15-minute break and 2 other scenarios thereafter.

Subjects were instructed to drive with a steady lateral position within the right, slower, traffic lane with a constant speed of 95 km/h. Overtaking slower-moving vehicles was allowed. During blinded editing, these maneuvers were removed from the data, before statistical analysis of the 'clean' data. The primary outcome variable was the standard deviation of the lateral position (SDLP, cm), expressing the weaving of the car. The standard deviation of speed (SDS, km/h) was the secondary outcome measure. Mean speed (MS, km/h) and mean lateral position (MLP, cm) were control variables.

Subjective assessments

After each hour of driving, questionnaires were administered on subjective sleepiness and driving performance. Subjective sleepiness was measured by means of the Karolinska Sleepiness Scale (KSS), ranging from 1 (very alert) to

9 (very sleepy, fighting sleep) (Åkerstedt and Gillberg, 1990). Driving-task related questionnaires comprised mental effort to perform the driving test (Meijman et al., 1986; Zijlstra et al., 1985), subjective driving quality, and driving style (McCormick et al., 1987). Completing the questionnaires took approximately 2 minutes, after which the driving task was immediately resumed.

Statistical analysis

For each variable, mean (SD) was computed for each subsequent hour. Data of the first two hours were compared, to confirm that no significant differences between the treatment days were present before the break and treatment administration. To determine whether caffeinated coffee has an effect on driving performance, data from the 3rd and 4th hour were compared using a General Linear Model for repeated measures (two-tailed, $p \leq 0.05$).

RESULTS

A total of 24 subjects (12 male and 12 female) completed the study. Their mean (SD) age was 23.2 (1.6) years old, on average they consumed 2.5 (0.7) caffeinated drinks per day, had a mean (SD) body mass index of 23.9 (2.7), possessed a valid driver's license for 58.8 (17.9) months, and on average drove 12979 (SD 10785) km per year. All subjects reported normal sleep quality and duration on the nights before the test days with no differences observed between the two test conditions. Results from the study are summarized in Table 1.

Table 1. Effects of caffeinated coffee in comparison to decaf on simulated driving performance and subjective sleepiness.

	Hour	Decaffeinated coffee	Caffeinated coffee
Driving test results			
Standard Deviation of Lateral Position	1	21.43 (4.37)	22.11 (3.67)
	2	23.65 (5.90)	24.13 (4.76)
	3	22.92 (4.61)	21.08 (3.74)*
	4	23.69 (4.72)	22.41 (4.37)*
Standard Deviation of Speed	1	0.85 (0.44)	0.88 (0.35)
	2	0.98 (0.51)	1.1 (0.61)
	3	1.03 (0.72)	0.78 (0.34)*
	4	1.15 (0.77)	0.87 (0.56)*
Mean Lateral Position	1	-18.04 (12.71)	-18.03 (10.47)
	2	-19.24 (12.60)	-18.98 (9.98)
	3	-18.63 (12.31)	-20.16 (11.05)
	4	-18.17 (11.54)	-18.93 (10.80)
Mean Speed	1	95.40 (0.19)	95.42 (0.21)
	2	95.46 (0.16)	95.40 (0.26)
	3	95.44 (0.31)	95.54 (0.18)
	4	95.53 (0.15)	95.54 (0.25)
Subjective Driving Assessments			
Driving Quality	1	9.75 (3.66)	9.08 (4.10)
	2	9.01 (2.81)	8.48 (3.46)
	3	9.70 (3.89)	11.84 (2.82)*
	4	9.23 (3.02)	10.60 (3.41)
Mental Effort	1	5.33 (2.30)	5.70 (2.47)
	2	5.84 (2.76)	6.39 (2.50)
	3	5.89 (2.82)	4.50 (2.36)*
	4	5.72 (2.38)	4.90 (2.93)*
Subjective Sleepiness Scores			
Karolinska Sleepiness Scale	baseline	3.25 (0.94)	3.33 (0.87)
	1	6.08 (1.67)	5.83 (2.16)
	2	6.17 (1.95)	6.29 (1.97)
	3	6.13 (2.11)	4.21 (1.47)*
	4	5.79 (1.59)	4.54 (1.86)*

Mean (SD) are shown for each parameter. * $P<0.05$ compared to decaf

Driving test

Figure 1 shows the effect of caffeinated coffee consumption on driving performance. No significant differences in SDLP were observed before the break. However, both in the first ($F_{(1,23)}$=5.8;p=0.024) and in the second hour ($F_{(1,23)}$=6.4; p=0.019) after the break, caffeinated coffee significantly reduced SDLP.

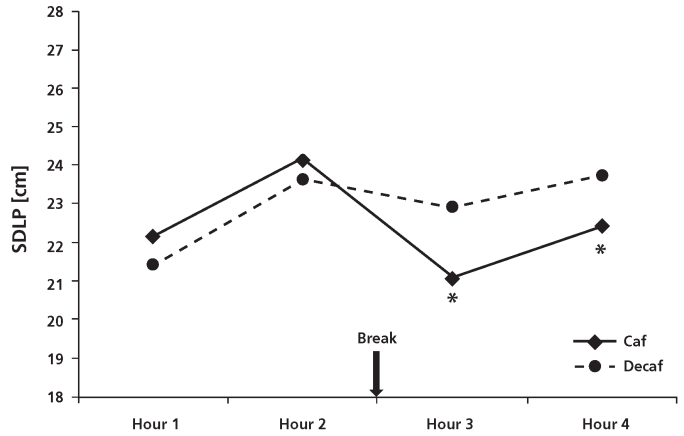

Figure 1. Standard Deviation of Lateral Position (SDLP)
* significant difference compared to placebo (p < 0.05)

In line, caffeinated coffee significantly reduced SD speed in the third ($F_{(1,23)}$=5.8; p=0.024) and fourth hour ($F_{(1,23)}$=13.0; p=0.001) of driving (see Figure 2). No effects were found on mean speed or mean lateral position, confirming that subjects performed the test according to the instructions.

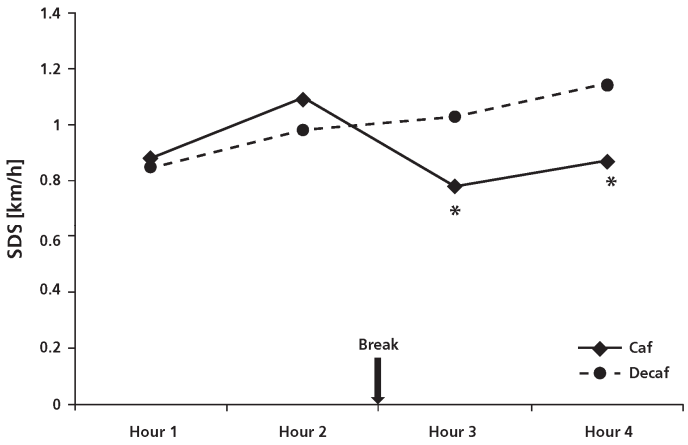

Figure 2. Standard Deviation of Speed (SDS)
* significant difference compared to placebo (p < 0.05)

Subjective driving assessments

Compared to decaffeinated coffee, caffeinated coffee improved subjective driving quality in the third hour of driving ($F_{(1,23)}$=10.5; p=0.004), but not in the fourth ($F_{(1,23)}$=2.6; p=n.s.). Subjects indicated that the mental effort needed to perform the test after caffeinated coffee was significantly reduced in the third ($F_{(1,23)}$=11.4; p=0.003) and fourth hour of driving ($F_{(1,23)}$=5.9;p=0.023). In addition, drivers rated their driving quality as significantly more considerate, responsible, and safer in the caffeinated coffee condition (See Table 1).

Subjective sleepiness

After the break with caffeinated coffee, drivers reported significantly lower sleepiness scores as compared to the break with decaffeinated coffee. This effect was significant both in the third ($F_{(1,23)}$=18.5; p<0.001) and the fourth hour of driving ($F_{(1,23)}$=11.9; p=0.002) (see Figure 3).

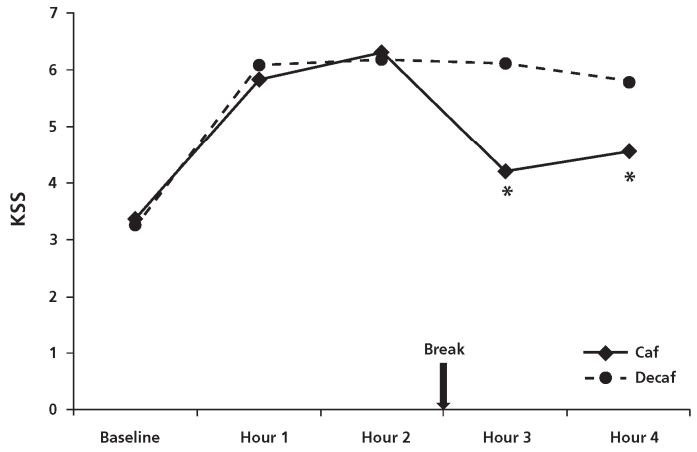

Figure 3. Karolinska Sleepiness Scale
* significant difference compared to placebo (p < 0.05)

DISCUSSION

This study demonstrates that one cup of caffeinated coffee (80 mg caffeine), significantly improves driving performance and reduces driver sleepiness.

Both lane keeping (SDLP) and speed maintenance were improved up to 2 hours after caffeine consumption. The improvement in objective performance was accompanied by improvement in subjective assessments of sleepiness and driving performance. An average decrease of almost 2 points (out of 7) on

the KSS scale was observed after the intake of caffeinated coffee as compared to decaffeinated coffee. The average KSS score was 6 ("some signs of sleepiness") in the decaffeinated coffee condition compared to 4 ("rather alert") in the caffeinated coffee condition.

Up to now, higher dosages of caffeine (150-250 mg, comparable to 2 to 3 cups of regular coffee) have been shown to be effective in counteracting sleep restriction (<5 hours spent in bed), when driving in the early morning (Reyner and Horne, 2000) and in the early afternoon (Horne and Reyner, 1996; Reyner and Horne, 1997). A moderate caffeine dosage (100 mg) decreased drifting out of lane and reduced subjective sleepiness in drivers who had slept for no more than four hours (Biggs et al., 2007). Furthermore, caffeine (3 mg/kg, approximately 225 mg in a 75 kg adult) improved steering accuracy in non-fatigued volunteers (Brice and Smith, 2001). Slow release caffeine capsules (300 mg) had similar effects (De Valck and Cluydts, 2001). Interestingly, caffeine decreased lane drifting both in individuals who had spent 4.5 hours in bed and in those who had spent 7.5 hours in bed, while effects on speed maintenance, fatigue and sleepiness were only observed after 4.5 hours spent in bed (De Valck and Cluydts, 2001). Two on-the-road driving studies on a public highway in France confirmed these findings and showed that relatively high dosages of caffeine (200 mg) improved nighttime driving both in young and in middle-aged drivers (Philip et al., 2006; Sagaspe et al., 2007).

The current results are in agreement with these studies, but further show that lower caffeine content found in one regular cup of coffee, also significantly improves driving performance and reduces driver sleepiness. The importance of this finding is evident, since it can be assumed that in order to refresh, most drivers consume only one cup of coffee during a break, instead of three or four.

Further studies could examine if a low dose of caffeine has similar effects on (professional) drivers who are sleep-restricted or shifted their day-night rhythm, since current studies have only been performed with higher dosages of caffeine.

In conclusion, the present study demonstrates that one cup of caffeinated coffee (80 mg caffeine) has a positive effect on continuous highway driving in non-sleep restricted, healthy volunteers.

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11

POSITIVE EFFECTS OF RED BULL® ENERGY DRINK ON DRIVING PERFORMANCE DURING PROLONGED DRIVING

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ABSTRACT

Background: The purpose of this study was to examine if Red Bull® Energy Drink can counteract sleepiness and driving impairment during prolonged driving.

Methods: Twenty-four healthy volunteers participated in this double-blind placebo-controlled crossover study. After 2 h of highway driving in the STISIM driving simulator, subjects had a 15-min break and consumed Red Bull® Energy Drink (250 ml) or placebo (Red Bull® Energy Drink without the functional ingredients: caffeine, taurine, glucuronolactone, B vitamins (niacin, pantothenic acid, B6, B12), and inositol) before driving for two additional hours. A third condition comprised 4 h of uninterrupted driving. Primary parameter was the standard deviation of lateral position (SDLP), i.e., the weaving of the car. Secondary parameters included SD speed, subjective driving quality, sleepiness, and mental effort to perform the test.

Results: No significant differences were observed during the first 2 h of driving. Red Bull® Energy Drink significantly improved driving relative to placebo: SDLP was significantly reduced during the 3rd ($p<0.046$) and 4th hour of driving ($p<0.011$). Red Bull® Energy Drink significantly reduced the standard deviation of speed ($p<0.004$), improved subjective driving quality ($p<0.0001$), and reduced mental effort to perform the test ($p<0.024$) during the 3rd hour of driving. Subjective sleepiness was significantly decreased during both the 3rd and 4th hour of driving after Red Bull® Energy Drink ($p<0.001$ and $p<0.009$, respectively). Relative to uninterrupted driving, Red Bull® Energy Drink significantly improved each parameter.

Conclusion: Red Bull® Energy Drink significantly improves driving performance and reduces driver sleepiness during prolonged highway driving.

Keywords: Red Bull, Energy drink, Driving, Fatigue, Sleepiness

INTRODUCTION

Sleepiness and fatigue can compromise the ability to drive a car. In several studies, 14.5% to 20% of drivers reported falling asleep while driving (Beirness et al. 2005; National Sleep Foundation 2002; Van Laar et al. 2008). Causal factors of driver sleepiness include sleep restriction, sleep disorders, and circadian factors, but also driving-related factors such as a monotonous environment or low traffic density may contribute to driver sleepiness. A highway is an example of a monotonous driving environment that can increase the likelihood of accidents (Stutts et al. 1999). Studies estimate that sleepiness accounts for 15–23% of all motor vehicle accidents on highways (Horne and Reyner 1995; Maycock 1996).

Highway driving involves two important factors that can lead to driver sleepiness. First, highway driving is associated with monotony: The driving environment is relatively uneventful, predictable, and repetitive. While safe handling of a vehicle requires sustained attention, monotony leads to the opposite: Arousal levels decline and are replaced by inattention and sleepiness resulting in driving impairment (Thiffault and Bergeron 2003). Second, time-of-task effects, i.e., increased time spent behind the wheel, progressively impair driving performance, and may lead to an increase in accident risk (Connor et al. 2001). How these and other factors play a role in highway driving is described in several concepts such as “passive task-related-fatigue”, “highway hypnosis”, or “driving without attention mode”. Situations of mental underload may lead to the driving task become automated. Drivers rely less on feedback from the environment which leads to a reduction of effort to perform the driving task. This leads to a decrease in arousal and alertness and possibly a failure to notice errors and react to sudden changes in traffic (Gimeno et al. 2006; May and Baldwin 2009; Kerr 1991; Wertheim 1991).

To prevent sleep-related vehicle accidents, public campaigns recommend scheduled breaks in between driving sessions. The message of these campaigns is to limit driving time to 2 h followed by a break of at least 15 min before continuing driving. It can be questioned if a 15-min break is sufficient to restore baseline performance. Driving simulator data showed that a 30-min break after an hour of driving was insufficient to normalize driving performance (Horne and Reyner 1996), while an on-the-road study

demonstrated that rested individuals could drive for 10 h without a noteworthy increase in lane crossings when 15-min breaks (prolonged to 30 min at lunchtime) were applied after every 1.75 h of driving (Philip et al. 2005a). Therefore, the general recommendation is always to stop driving if one feels impaired or sleepy. Unfortunately, drivers differ greatly in their ability to sustain attention in monotonous situations (Nilsson et al. 1997). Moreover, recognizing sleepiness and judging its possible impact on one's own driving performance is hard (Schmidt et al. 2009). Therefore, applying suitable countermeasures of driver sleepiness may be an important tool to prevent driving impairment.

Countermeasures, such as taking a nap and caffeine, have been proven effective, especially when driving in the early morning, at night, or when sleep-deprived (Biggs et al. 2007; Philip et al. 2006; Reyner and Horne 1997, 2000). In addition, energy drinks are popular to overcome driver fatigue. Worldwide, the most popular energy drink is Red Bull® Energy Drink. Red Bull® Energy Drink contains several ingredients including caffeine, taurine, glucuronolactone, B vitamins, and inositol. The combination of these ingredients is believed to account for the positive effects on cognitive performance, attention, and driving performance. In laboratory tests of mental performance, Red Bull® Energy Drink improved (choice) reaction time, energetic arousal, subjective alertness, concentration, and memory (Alford et al. 2001; Warburton et al. 2001), as well as attention capacity in a stressful situation (Seidl et al. 2000). Driving was improved in all previous studies examining Red Bull® Energy Drink, or drinks with similar ingredients (Gershon et al. 2009; Horne and Reyner 2001; Reyner and Horne 2002). In subjects who were sleep restricted to 5 h, Red Bull® Energy Drink (500 ml) reduced the number of lateral lane crossings and decreased reaction time in a secondary task (Horne and Reyner 2001). Subjects drove for 30 min, had a 30-min break, and then drove for two additional hours. The effects lasted from 0 to 90 min after the break. Similar results were obtained in a subsequent study in which 250 ml was administered (Reyner and Horne 2002): Lateral lane crossings and Karolinska Sleepiness Scale (KSS) sleepiness scores were decreased until 90 min after the break. A similar energy drink (500 ml) led to a more stable lane position (RMS of the standard deviation of lateral position (SDLP)) during 2 h of driving in non-sleep-deprived individuals. Steering

wheel variations, fatigue, and reaction time in a simultaneous reaction time task were also improved (Gershon et al. 2009).

The characteristics of these studies include that subjects were sleep-deprived before taking part in the driving test (Horne and Reyner 2001; Reyner and Horne 2002), consumed 500 ml of Red Bull® Energy Drink (Horne and Reyner 2001), and drove only for half an hour (Horne and Reyner 2001; Reyner and Horne 2002) before Red Bull®Energy Drink was consumed.

To test the impact of Red Bull® EnergyDrink on prolonged highway driving of non-sleep-deprived individuals, a paradigm was developed in which subjects drove in an advanced driving simulator for 2 h, had a 15-min break in which 250 ml of energy drink or placebo was consumed, followed by two more hours of highway driving. In a third condition, they drove for 4 h without a break and without any treatment (in the text referred to as uninterrupted driving or "no break" condition). Based on previous research discussed above, it is hypothesized that after drinking Red Bull® Energy Drink, driving will be significantly improved when compared to placebo or driving without a break.

MATERIALS AND METHODS

This study was a double-blind, randomized, placebocontrolled, crossover study. No formal ethical approval was required by the Medical Ethical Committee of the University Medical Center Utrecht. The study was conducted according to the ICH Guidelines for "Good Clinical Practice" and the Declaration of Helsinki and its latest amendments. Written informed consent was obtained from the participants before taking part in the study.

Subjects

Twenty-four adult healthy volunteers (12 males and 12 females) were recruited by means of public advertisements at and around Utrecht University campus. Subjects were included if they were aged between 21 and 35 years, were regular drivers (>5,000 km/year), had been in the possession of a drivers license for at least 3 years, had a normal body mass index (21<BMI<30; 55–85 kg), were non-smokers, had regular sleeping hours, and were otherwise healthy. Sleep disturbances were assessed with the SLEEP-50 questionnaire (Spoormaker et al. 2005). The Epworth Sleepiness Scale (ESS) was administered to assess general levels of daytime sleepiness (Johns 1991).

Subjects with ESS scores above 10 were excluded from participation. Other inclusion criteria were moderate caffeine consumption (two to four glasses of caffeine-containing beverages per day) and infrequent energy drink consumers (<1 drink per month). On each visit, urine samples were collected to test for drugs of abuse (amphetamines (including 3,4-methylenedioxymethamphetamine), barbiturates, cannabinoids, benzodiazepines, cocaine, and opiates) and a pregnancy test in female subjects (β-human chorionic gonadotropin test). In addition, alcohol use was tested using the Dräger Alcotest 7410 Breath Analyzer. Alcohol consumption was not permitted from 24 h before the start of the test day and on test days. From awakening until the end of the tests, caffeinated beverages and smoking were not allowed.

Study design

The study comprised one training day and three test days. On the training day, participants were screened and familiarized with the test procedures. If subjects met all inclusion and exclusion criteria, a practice session in the STISIM driving simulator was performed. Thereafter, subjects completed the Simulator Sickness Questionnaire (Kennedy et al. 1993) to determine possible simulator sickness. Included subjects were randomly assigned to a treatment order comprising three conditions: (1) Red Bull®Energy Drink + break, (2) placebo + break, and (3) no break + no treatment condition (see Fig. 1).

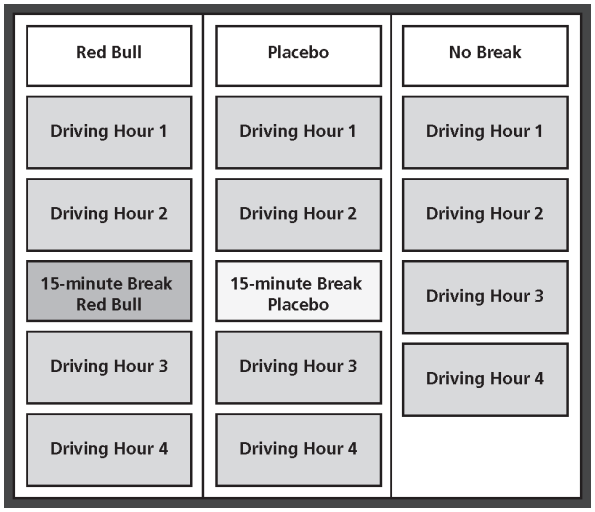

Fig. 1 Overview of the test days

On test days, drug or alcohol use, pregnancy, illness, and medication use were checked after arrival. In addition, quality of sleep was assessed using the 14-item Groningen Sleep Quality Scale (Mulder-Hajonides van der Meulen et al. 1980), in which 0 indicates high quality sleep and 14 ndicates very poor sleep. When subjects met all criteria,they performed a two times 60-min driving session in the STISIM driving simulator. On two test days, a 15-min break was scheduled in which subjects received either of the double-blind treatments. After the break, another driving session of two times 60 min was performed. In the "no break" condition, participants drove for a total of 4 h without a break. In each condition, every 60-min driving session was followed by subjective assessments on driving quality, driving style, mental effort to perform the test, and sleepiness. Test sessions were performed either in the morning (0800–1300 hours) or in the afternoon (1300–1700 hours) in a balanced manner. Each subject started each test day at the same time.

Treatments

Treatments were 250 ml of Red Bull® Energy Drink or placebo, administered during the break. Per 250-ml Red Bull® Energy Drink contains 21 g sucrose, 5 g glucose, 1 g taurine, 80 mg caffeine, 60 mg glucuronolactone, 50 mg inositol, and B vitamins (niacin, pantothenic acid, vitamin B6, vitamin B12). The placebo drink was Red Bull® Energy Drink without taurine, caffeine, glucuronolactone, inositol, and vitamin B complex. The blinded Red Bull® Energy Drink and placebo beverage samples were provided by Red Bull GmbH. Treatment appearance (bottle and color of the beverage) was double-blinded, and a nose clip was worn to enhance treatment blinding. Drinks were consumed within 5 min, starting from 5 min after onset of the break. Subject randomization was conducted at Utrecht University. The treatment code was revealed by Red Bull GmbH after the study was completed and data were analyzed.

STISIM highway driving test

Driving tests were performed using STISIM Drive™ (version M300, Systems Technology, Inc., Hawthorne, CA, USA). The simulator consists of a car unit with adjustable car seats and a dashboard and includes a steering wheel, turn sign indicators, gear lever, clutch, brake, and gas pedals for vehicle control. The system generates a realistic roadway scenery which is projected on a

screen (2.10 × 1.58 m), placed 1.90 m in front of the center of the steering wheel. Speed and gear number are displayed on the dashboard and the screen. Auditory feedback is provided by speakers and included sound of the engine, braking, speeding in curves, and driving off-road. Whenever a collision occurs, a broken windshield and the sound of braking glass are presented. Subsequently, the car is placed back in the middle of the right traffic lane and the test continues.

A 100-km highway driving test scenario was developed by EyeOctopus B.V., tailored to Dutch traffic situations (e.g., Dutch traffic signs, vehicles, buildings, and sceneries). The test scenario aims to resemble the on-the-road driving test in real traffic. The scenario consists of a two-lane highway in each direction with a lane width of 3.5 m. The environment is monotonous and comprised trees, occasional bridges, and hills as well as other traffic (see Fig. 2).

Fig. 2 Highway scenery of the STISIM driving simulator

Subjects were instructed to drive with a steady lateral position in the right (slower) traffic lane while maintaining a steady speed of 95 km/h. Overtaking maneuvers were allowed whenever a subject approached a slower moving car. These events were removed from the data before analysis. Weaving of the car, expressed by the SDLP (centimeters), was the primary outcome measure of this test (see Fig. 3).

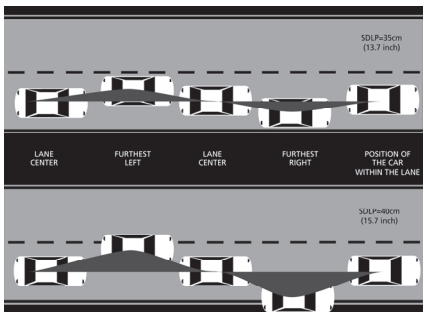

Fig. 3 Meaning of the standard deviation of lateral position (SDLP)

SDLP has been used as primary parameter in standardized on-the-road tests. SDLP showed to be sensitive to dose-dependent impairment after administration of a variety of psychoactive drugs including hypnotics, antidepressants, and antihistamines (Verster and Mets 2009). On-the-road, SDLP increments corresponding to the most common legal limits for driving were +2.4 cm (0.05%), +4.1 cm (0.08%), and +5.3 cm (0.10%; Louwerens et al. 1987). Recent research showed that the highway driving test scenario and its primary parameter SDLP in the STISIM driving simulator also differentiate between impairment produced after consumption of different dosages of alcohol (Mets et al. 2011).

The second outcome measure was the standard deviation of speed (kilometers per hour). Mean lateral position (centimeters) and mean speed (kilometers per hour) were control variables.

Subjective assessments

After each hour of driving, participants made subjective assessments on driving and sleepiness causing a 2-min interruption of the driving task. Subjects indicated their perceived driving quality on a visual analog scale, ranging from 0 (“I drove exceptionally poorly”) to 20 (“I drove exceptionally well”). In addition, mental effort exerted during the driving test was rated on an interval scale (15 cm) ranging from “almost no effort” to “very great effort”. Furthermore, subjects completed a driving style questionnaire (McCormick et al. 1987), which consisted of different bipolar differential scales (10 cm) including foolish-wise, unpredictable–predictable, dangerous-safe, tense-relaxed, inconsiderate–considerate, and irresponsible–responsible. Finally, the KSS was used to rate sleepiness on a scale of 1 to 9, ranging from 1 (very alert) to 9 (very sleepy, an effort to stay awake, fighting sleep; Åkerstedt and

Gillberg 1990). Completion of the subjective assessments took approximately 2 min. Driving was resumed right thereafter.

Statistical analysis

Data were analyzed using ANOVA general linear model for repeated measures (two-tailed, $p \leq 0.05$). For the STISIM driving simulator test, the primary parameter was the SDLP.

RESULTS

Twenty-four healthy subjects participated in the study. Three male subjects were excluded due to protocol violations and resulting statistical outliers. A total of 21 subjects were included in the analysis (nine men and 12 women; age (mean (SD) 22.8 (1.4) years)). They were of normal weight range for height (BMI mean=23.6, SD=2.4), had their driver's license at least 3 years (mean=57.8 months, SD=17.2 months), and were regular drivers (minimum 5,000 km/year, mean=11,976 km/year, SD=10,569 km/year). Overall, subjects reported a normal sleep quality and duration the night before testing, and no significant differences were found between the test days or conditions. Results from the study are summarized in Table 1.

Driving test

For the primary parameter (SDLP), the results are shown in Fig. 4. In the first 2 h, driving test parameters did not differ significantly between the treatment conditions. When compared to placebo, Red Bull® Energy Drink significantly reduced SDLP during the 3rd ($p<0.046$) and 4th ($p<0.011$) hour of driving. Similarly, compared to the uninterrupted driving condition, Red Bull significantly reduced SDLP in hour 3 ($p<0.003$) and hour 4 ($p<0.013$).

Table 1 Effects of Red Bull® Energy Drink in comparison to a placebo drink and uninterrupted driving (no break) on driving performance and subjective sleepiness

	Time	Placebo	Red Bull	No break
Driving Test Results				
SDLP	Hour 1	22.95 (3.98)	22.44 (4.17)	23.12 (4.72)
	Hour 2	26.30 (6.51)	25.63 (5.33)	27.52 (7.10)
	Hour 3	24.69 (5.73)	22.35 (3.95)*	26.91 (7.79)
	Hour 4	26.82 (5.86)	23.76 (4.43)*	26.23 (5.85)
SDS	Hour 1	1.01 (0.35)	1.05 (0.60)	1.06 (0.53)
	Hour 2	1.15 (0.54)	1.21 (0.72)	1.40 (1.01)
	Hour 3	1.15 (0.59)	0.91 (0.48)*	1.27 (0.76)
	Hour 4	1.18 (0.54)	1.02 (0.54)**	1.24 (0.64)
MLP	Hour 1	-15.46 (7.81)	-15.68 (8.84)	-15.94 (8.16)
	Hour 2	-14.79 (8.54)	-15.96 (7.48)	-13.17 (9.74)
	Hour 3	-15.39 (6.57)	-16.58 (7.00)	-13.08 (10.06)
	Hour 4	-14.28 (6.81)	-16.73 (7.36)	-14.19 (9.19)
MS	Hour 1	95.42 (0.28)	95.45 (0.27)	95.49 (0.25)
	Hour 2	95.44 (0.27)	95.55 (0.31)	95.50 (0.40)
	Hour 3	95.54 (0.28)	95.59 (0.28)	95.53 (0.39)
	Hour 4	95.48 (0.28)	95.61 (0.24)	95.58 (0.31)
Subjective Sleepiness Scores				
KSS	Baseline	3.38 (1.43)	3.24 (0.77)	3.33 (1.20)
	Hour 1	5.19 (2.06)	5.62 (1.91)	5.95 (1.86)
	Hour 2	6.14 (2.08)	6.14 (2.10)	6.71 (2.15)
	Hour 3	6.00 (2.14)	3.86 (1.49)*	6.10 (2.02)
	Hour 4	5.57 (1.69)	4.33 (1.28)*	5.67 (2.11)

Mean (SD) are shown for each parameter

SDLP standard deviation of the lateral position, *SDS* standard deviation of speed, *MLP* mean lateral position, *MS* mean speed, *KSS* Karolinska Sleepiness Scale, *SD* standard deviation

* $p<0.05$ compared to placebo and "no break"; ** $p<0.05$ compared to "no break"

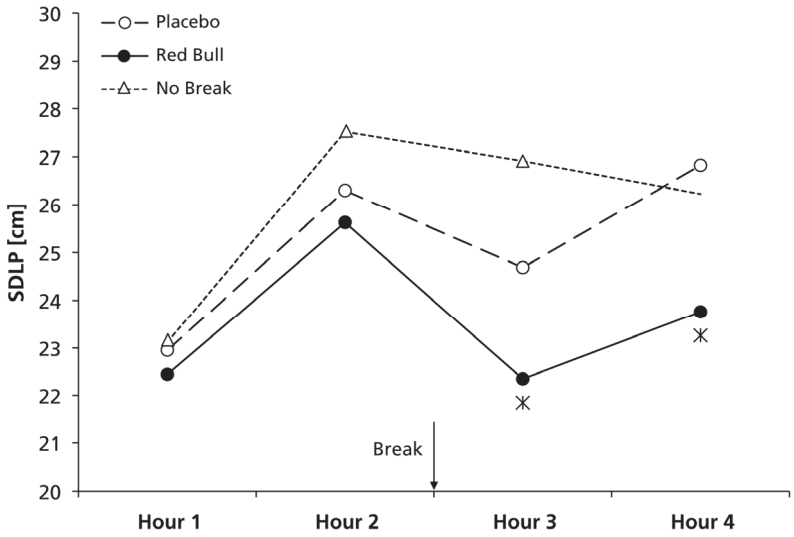

Fig. 4 Standard deviation of lateral position (SDLP). *p<0.05, significant difference compared to placebo

Although in the placebo condition driving improvement (i.e., reduced SDLP) is seen after the break, there were no significant differences between the placebo and the "no break" condition. Gender and time-of-day effects were not significant.

A post hoc analysis of the effects per 50 km, or approximately 30 min, showed that SDLP values in the Red Bull® condition were significant lower compared to placebo. This effect was seen from half an hour after the break, until the end of the test (250–300 km: $p<0.028$; 300–350 km: $p<0.010$; 350–400 km: $p < 0.024$). Prolonged driving compared to placebo gave no significant results. Figure 5 shows that Red Bull® Energy Drink significantly reduced speed variability compared to placebo and uninterrupted driving in the 3rd hour ($p<0.004$ and $p<0.0001$, respectively). In the 4th hour, standard deviation of speed differed significantly between Red Bull® Energy Drink and uninterrupted driving ($p<0.003$).

No effects were found on the mean lateral position and mean speed, confirming that subjects performed the driving test according to the instructions.

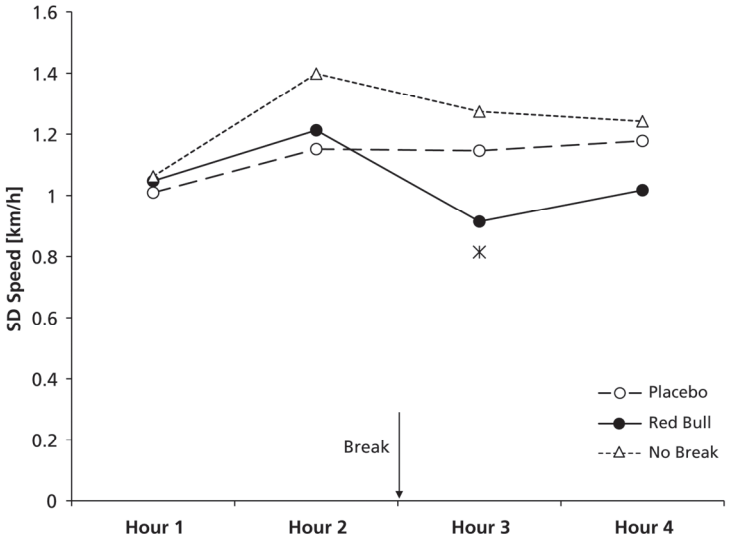

Fig. 5 Standard deviation of speed (SDS). *p<0.05, significant difference compared to placebo

Subjective driving assessments

Relative to placebo and uninterrupted driving, Red Bull® Energy Drink significantly improved subjective driving quality during the 3rd hour of driving ($p<0.0001$). Similarly, mental effort during driving was decreased after the intake of Red Bull® Energy Drink after 3 h of driving compared to placebo ($p<0.024$) and uninterrupted driving ($p<0.005$). In accordance with these results, after 3 h, each aspect of driving style was found to be improved in the Red Bull® Energy Drink condition when compared to the other conditions ($p<0.05$). That is, subjects rated their driving as more wise, safe, responsible, relaxed, predictable, and considerate in the first hour after the intake of Red Bull® Energy Drink. In the 4th hour of driving, no significant differences were reported except for the fact that subjects judged their driving as significantly more safe after intake of Red Bull® Energy Drink when compared to uninterrupted driving ($p<0.026$).

To confirm if drivers were aware of changes in driving performance, we computed the correlation between difference scores for SDLP and subjective driving quality (3rd hour scores−2nd hour scores). In the Red Bull condition, the correlation was significant ($r=-0.548$, $p<0.010$) as well as in placebo condition ($r=-0.517$, $p<0.016$), but not in the prolonged driving condition. This indicates that whereas subjects acknowledged objective driving

improvement after having a break (with or without Red Bull), they were not aware of driving impairment in the prolonged driving condition.

Subjective sleepiness

After the third and fourth hour, sleepiness scores were significantly lower in the Red Bull® Energy Drink condition when compared to placebo ($p<0.001$ and $p<0.009$, respectively) and uninterrupted driving ($p<0.0001$ and $p<0.026$, respectively). Surprisingly, a break without Red Bull® Energy Drink did not significantly reduce sleepiness levels when compared to uninterrupted driving (see Fig. 6).

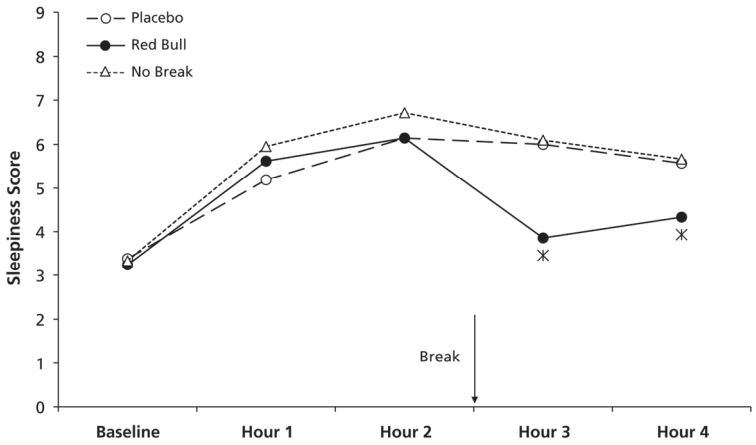

Fig. 6 Karolinska Sleepiness Scale. *p < 0.05, significant difference compared to placebo

DISCUSSION

This study shows that Red Bull® Energy Drink significantly improves driving performance and reduced subjective sleepiness during subsequent driving. The effects of Red Bull® Energy Drink were supported by assessments of subjective driving quality and driving style and were in accordance with the effects observed in previous studies (Horne and Reyner 2001; Reyner and Horne 2002; Gershon et al. 2009). In addition to previous studies, the present study demonstrates that Red Bull® Energy Drink improves driving ability in healthy non-sleep-deprived individuals when consuming a standard 250-ml can of Red Bull® Energy Drink.

Interestingly, while rested individuals would be expected to benefit from breaks, the 15-min break in our design did not lead to significantly lower SDLP values in hours 3 and 4 when compared to the uninterrupted driving condition, nor did it lead to a decrease in sleepiness levels. We have no clear explanation for this finding, and it is in contrast to previous studies (e.g., Philip et al. 2005a; Sagaspe et al. 2008). Further studies should be conducted into the effectiveness of scheduling breaks during prolonged highway driving.

The average difference in SDLP between the placebo and Red Bull condition was 2.3 cm in the third hour and 3.1 cm in the fourth hour. This difference is comparable to the effect observed for blood alcohol concentrations higher than 0.05% (Mets et al., submitted for publication), i.e., above the legal limit for driving in most European countries.

It has been suggested that the combination of ingredients produce the beneficial effects of Red Bull® Energy Drink (Reyner and Horne 2002). A post hoc analysis, based on the results per 30 min, showed that Red Bull® Energy Drink significantly reduced SDLP starting from 30 min after the break until 2 h after intake. This is in accordance with the pharmacokinetics of caffeine showing peak plasma concentrations after 30 to 60 min (Roehrs and Roth 2008; Lorist and Tops 2003) and a half-life of 2 to 10 h (Sawyer et al. 1982; Smith 2002). Although higher dosages of caffeine (100–300 mg) have been shown to improve driving performance (Brice and Smith 2001; Regina et al. 1974; Reyner and Horne 2000; Biggs et al. 2007; De Valck and Cluydts 2001; Sagaspe et al. 2007; Philip et al. 2006; Reyner and Horne 1997), it is surprising that the effect of lower caffeine on driving (e.g., one cup of coffee) has not been examined. Some studies did, however, report positive effects of low dosages of caffeine (−75 mg) on driving-related skills such as reaction time, performance, and mood (Childs and De Wit 2006; Durlach 1998; Haskell et al. 2005; Quinlan et al. 2000; Smit and Rogers 2000; Smith et al. 1999).

Taurine's effects on driving have not been studied, but research did show that taurine can alleviate visual fatigue (Zhang et al. 2004). Taurine's peak plasma concentration is reached after about 90 min, and concentrations then decline within 180–270 min (Trautwein and Hayes 1995). The role of taurine in CNS effects is unclear, as animal experiments could not demonstrate effects on brain taurine levels (Sved et al. 2007). Although B vitamins play a role in cognitive functioning (Calvaresi and Bryan 2001; Franchi et al. 1998;

Huskisson et al. 2007), their effects on driving are unknown. As Red Bull® Energy Drink contains relatively low levels of vitamins and was administered only once in this study, it is unlikely that these ingredients play a major role in driving improvement. No scientific evidence is available on the contribution of glucuronolactone (Kim 2003). Finally, glucose is unlikely to produce the beneficial effects of Red Bull® Energy Drink as both the drink and the placebo contained sugar. In conclusion, further studies on the ingredients of Red Bull® Energy Drink are important to elucidate their specific effects on cognitive performance and driving.

One of the limitations of this study was that each hour of driving was followed by subjective assessments, causing a 2-min interruption of the driving task. Although subjects remained seated in the car and were occupied with completing the VAS scales, this may have had an effect. On the other hand, a 2-min break is also seen in real-life driving, for example in conditions such as being stopped by traffic lights or traffic jams. Another limitation is that we did not control previous-night sleep quality using objective measures such as EEG or actigraphy but used a questionnaire. In addition, the development of sleepiness and experiencing monotony may differ between simulated and actual driving. It was suggested that sleepiness develops sooner and is more pronounced in a driving simulator (Anund et al. 2009; Philip et al. 2005b). The absence of actual risk in the driving simulator also differs from on-the-road driving. Preferably, the effect of Red Bull® Energy Drink on driving performance should therefore be replicated in on-the-road studies in normal traffic. Finally, with a mean age of 23, the population of drivers was relatively young. Although energy drinks are popular among this age group, it may be interesting to examine the effects of Red Bull® Energy Drink in older, more experienced drivers.

In conclusion, Red Bull® Energy Drink significantly improved driving ability relative to placebo and uninterrupted driving. For the primary parameter (SDLP), this effect was significant for 2 h after drinking Red Bull® Energy Drink. Subjective assessments consistently confirmed these findings.

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12

SUMMARY AND FUTURE TRENDS

This dissertation focuses on the effects of sleep and sleepiness on daytime functioning. Residual effect of hypnotics, the impact of sleep disturbances, and sleepiness countermeasures are the primary areas of interest. This discussion summarizes the findings of these studies and provides suggestions on how research in this field can be continued in the future.

PART I. SLEEP DISORDERS, HYPNOTICS AND DAYTIME FUNCTIONING

Insomnia and residual effects of benzodiazepine receptor agonists

Chapter 2 presented a review of the most commonly prescribed psychoactive substances and their effects on driving ability. Hypnotic drugs can be divided into benzodiazepines and non-benzodiazepines or z-drugs. Because they all act on the benzodiazepine (BZ) receptors that are part of the γ-aminobutyric acid type A ($GABA_A$) receptor complex, together they are known as benzodiazepine receptor agonists (BZRAs). It was believed that the benzodiazepines bind non-selectively to several types of BZ receptors located in different parts of the brain, affecting not only brain parts involved in sleep and sedation, but also areas involved in cognition, memory, and psychomotor performance, which leads to several undesired effects (Krystal, 2010). Likewise, on-the-road driving studies show that the majority of benzodiazepine hypnotics impair driving ability.

Compared to the older benzodiazepines, the z-drugs were regarded as an improvement because they were developed to selectively bind to the benzodiazepine receptor type involved in sleep and sedation. They were therefore expected to have fewer side effects and potential for abuse (Wagner and Wagner, 2000). However, with respect to traffic safety, zopiclone also significantly impairs driving ability and significantly increases traffic accidents (Barbone et al., 1998). Zopiclone can therefore not be considered as an improvement. Zaleplon and zolpidem have no effect when taken as recommended. Nevertheless, zolpidem does impair performance when taken in the middle-of the night. This makes zaleplon the only drug in the category of BZRAs that has no demonstrated residual effect on driving performance. Still, similar to other BZRAs, patients using zaleplon are warned for sleep-related behaviors, including 'sleep-driving', i.e. driving a car while not fully awake, followed by amnesia (FDA, 2007). These behaviors seem to be most

prominently found in users of z-drugs. However, it is uncertain to what extent presumed sleep-driving can be attributed to misuse of drugs, what the incident of sleep-driving is, and what mechanism lies behind its occurrence (Pressman, 2011).

Chapter 3 provides an overview of BZRAs and their effects on postural balance. Single administration decreases postural stability, which is most pronounced in the middle of the night. However, next-morning residual effects are also observed. Repeated administration leads to partial tolerance. The conclusion is that users, and especially the elderly, are at risk for balance impairments. This chapter also shows that the effects in the morning after intake are rarely studied and that reports of these tests are often minimal.

It can be concluded that BZRAs should be taken with caution because they can lead to impaired functioning, both acute and next-day.

Sleep disorders

Chapter 4 provided an overview of narcolepsy and its impact on traffic safety. The symptoms of narcolepsy, most importantly excessive daytime sleepiness, have a significant impact on the patients' quality of life and mobility. Most striking is the fact that the effects of currently used therapies have not been studied in these patients. A study to assess the effect of currently applied narcolepsy treatment on driving ability is therefore highly desirable.

In Chapter 5 reviews circadian rhythm disturbances related to work schedules. Apart from the discussion whether shift work sleep disorder is an actual disease, or simply the consequence of being awake while an individual is programmed to sleep, the fact remains that shift work is often necessary in modern society, and certain individuals experience severe consequences. The interplay between sleep loss, circadian disruption, social and family life, work demands, and driving times in the case of professional drivers, the multitude of work schedules that exist, and personal psychological and biological characteristics, makes this a complicated issue. One of the most notable observations is that a small proportion of drivers causes the majority of accidents. A multidisciplinary approach combining insights from sleep specialists and geneticists, driving researchers, and advanced statistical methods, may shed more light on these oversensitive subjects.

Chapter 6 presents the results of a survey among sleep specialists. When comparing their ideas with some of the information provided in earlier chapters, it becomes clear that their views are not always in line with scientific evidence. Although this was a relative small survey, its results illustrate that continuous education of sleep specialists is important to update them on the important issue of traffic safety and its relationship to sleep disturbances and its treatment.

PART II. RAMELTEON

Relatively new pharmacological treatment options for insomnia are the melatonin receptor agonists, including endogenous melatonin, prolonged-release melatonin, ramelteon, and other melatonin analogues such as agomelatine or tasimelteon. As opposed to the BZRAs, melatonin agonists exert their effects by acting at the melatonin I and II receptors, instead of the $GABA_A$ receptor complex.

As outlined in chapter 7, ramelteon is a novel prescription hypnotic that does not belong to the class of BZRAs. This chapter shows that neither the mechanism of action, e.g. absence of affinity for most receptors associated with adverse effects, nor any previous study have given rise to concerns regarding next-morning residual effects. There are, however, concerns regarding its efficacy (EMA).

Chapter 8 presents a study on the residual effects of ramelteon the morning after bedtime intake. This study showed that ramelteon impairs driving performance, delayed memory recall, and psychomotor functioning. Based on the review in chapter 7, these results were unexpected. However, unlike the BZRAs, ramelteon did not lead to balance disturbances at peak plasma levels, which is in accordance with previous studies. The effects of ramelteon on postural balance in the morning after intake should be incorporated in future studies.

Cohen et al. (2010) examined ramelteon in the context of using it as a method to improve napping in the evening in a simulated night shift protocol. To test for impairments, a neurobehavioral test battery was used. Ramelteon (8 mg) administered 30 minutes prior to a 2 hour evening nap led to deteriorations in subjective alertness and sleepiness, DSST scores and performance in the Psychomotor Vigilance Task. Worsening of performance

was observed shortly after the nap and was most pronounced in the second half of the night. The authors suggested that the nadir of the circadian rhythm in combination with high homeostatic sleep pressure may be accountable for the effects. However, this cannot explain the findings of impairment in our driving study. Instead, it seems more likely that our findings support the idea that a more elaborate way of testing may be able to detect impairments, which go unnoticed when simpler tests are used. Still, the mechanism leading to the impairments demonstrated in chapter 8 is has yet to be elucidated and is an important aim of future research. Against the background of currently available drug treatments of insomnia, this dissertation shows that ramelteon is not the much hoped for therapy without residual effects on daily activities such as driving a car.

Melatonin receptor agonists

Ramelteon's mother compound, endogenous melatonin, is available in two forms, regular release and prolonged release. Prolonged-release melatonin (6 mg) did not cause any impairments in healthy adults on a test battery examining information processing skills related to flight performance, whereas zaleplon, zopiclone, and temazepam did (Paul et al., 2003). Similarly, melatonin (prolonged-release; 2 mg) did not cause impairments on a test battery in elderly insomnia patients, but instead improved performance the morning after bedtime intake (Luthringer et al., 2009). More important in the context of this dissertation, prolonged-release melatonin (2 mg) did not affect simulated driving performance one and four hours after intake, and in the morning, whereas zolpidem (10 mg) in the same study did (Otmani et al., 2008). The effects of regular release melatonin are more controversial, but may be attributable to the time of intake in that impairments are usually found after daytime intake (Otmani et al., 2008). A driving-skill related test battery showed no impairments after exogenous melatonin (5 mg) when taken in the afternoon and tested 90 minutes thereafter. Because regular melatonin is not a prescription drug, there is much less research conducted on its effectiveness and adverse effects, and the efficacy of melatonin remains controversial (Van den Heuvel et al., 2005; Zhdanova, 2005). Melatonin, in low dosages, is freely available in a number of countries including the Netherlands. Because of its potential use as a chronobiotic, shift workers and individuals

experiencing jet lag may be using melatonin, perhaps even for a prolonged period of time. In the context of traffic safety, examining the effects of melatonin on driving ability in an on-the-road study is therefore warranted.

Agomelatine is registered as an antidepressant, while tasimelteon, intended for use as a hypnotic, is currently under development (Spadoni et al., 2010). Whether or not these drugs have residual effects on driving is unknown.

Future developments

It can be concluded that to date there is no prescription drug in the treatment of insomnia that is completely devoid of residual adverse effects. Insomnia and transient sleeplessness are relatively common and many individuals who therefore use hypnotic drugs can be expected to have a job and drive a car. Therefore, there is a large population potentially at risk for accidents due to residual drug effects. This makes the development of new drug treatments desirable.

Hypnotic drugs with a new mechanism of action are currently under development. Firstly, the hypocretin/orexin antagonists may be interesting, because they have a direct influence on the sleep mechanism. However, they may lead to other side-effect because they also influence non-sleep related functions (Ruoff et al., 2011). Secondly, serotonin receptor antagonists may be promising (Landolt and Wehrle, 2009). On-the-road driving studies into selective serotonin reuptake inhibitors (SSRIs) did not find noteworthy deteriorations in driving performance in healthy volunteers (Ramaekers 2003). Nevertheless, this does not mean that this is also the case for the serotonin-related hypnotics, so this should be determined in future driving studies. Finally, new insights into $GABA_A$ modulating agents show that the way in which BZRAs affect different receptor subtypes may be more complex than believed up until recently (Krystal, 2010). This may lead to the development of very specific types of BZRAs, which may increase effectiveness of insomnia treatment, and hopefully also have fewer side-effects.

PART III. DRIVING RESEARCH METHODOLOGY

Another objective of this dissertation was to develop a highway driving test scenario to be used in the STISIM driving simulator. Simulator testing has benefits over testing on a real road in terms of costs, standardization of test conditions and ethical concerns with regard to risks involved in the task. However, it remains an artificial testing environment which may have consequences in terms of ecological validity.

The primary objective of the development of the STISIM highway driving test was to apply it in pharmacological studies. The test should be able to assess the extent to which a certain condition affects driving performance. On the one hand, drugs can be tested to see if they impair driving. Depending on the magnitude of the effect, patients using these drugs can be warned and in the worst case be prevented from driving when using the specific drug. On the other hand, treatments may improve driving performance compared to untreated patients. An example of a condition in which this may be relevant is narcolepsy. The driving simulator provides a safe environment to test this. However, the test methodology should be sensitive enough to actually detect relevant differences from placebo.

For this purpose, a calibration study was conducted, which is presented in chapter 9. Historical data of driving impairment seen after different alcohol levels is often used to interpret the magnitude of a drug effect on driving ability (Louwerens et al. 1987). Performance at the legal BAC limit for driving (0.05% or 0.08%) is often used as a comparator to draw conclusions regarding the clinical relevance of outcomes. The results of our study showed a dose-dependent impairment after the intake of alcohol. Firstly, this confirms that the highway driving test scenario is sensitive to alcohol-induced impairments, and as such suitable for future pharmacological research. Secondly, the differences compared to placebo that are obtained can serve as reference values for impairment seen with other drugs.

Another aspect that is of importance in simulator testing is validity: does the test measure what it claims to measure in terms of the test itself and how it is used? Ideally, a direct comparison of the highway test on the road and in the simulator should be conducted. However, due to legal constraints, it is not possible to use relative changes compared to placebo for alcohol dosages above 0.05%. An alternative method to test the validity would be to use a

commonly used drug such as zopiclone (hypnotic) or diazepam (anxiolytic), which have demonstrated impairing effects on driving performance. A direct comparison of its effect in an on-the-road test with the effect in the STISIM highway driving test could provide more insight into the validity of the STISIM driving simulator test.

Because the highway driving test was found to be sensitive for alcohol-induced driving impairments, it was used in two following experiments to test the effect of prolonged highway driving on driving ability and subjective sleepiness.

As explained in the introduction, sleep-related accidents often occur on highways. This is probably due to the monotonous driving environment combined with long hours behind the wheel. Following common advice from traffic safety organizations, i.e. "two hours of driving, fifteen minutes rest", a sleepy-driver paradigm was developed. In this paradigm, subjects drive for two hours, then have a fifteen minute break in which the countermeasures is given, followed by two subsequent driving hours. The results are discussed in the following section.

PART IV. DROWSY DRIVING COUNTERMEASURES

Caffeinated drinks

When having a break during prolonged driving, drivers can be expected to drink one cup of coffee before continuing driving. However, the effects of a single cup of coffee on driving performance have not been studied before. Instead, previous studies examined the effects on driving of much higher dosages of caffeine. It is unlikely that in real life, drivers consume 3 to 6 cups of coffee during a short break. Therefore, the objective of the study presented in chapter 10 was to test one standard cup of coffee (80 mg of caffeine) as a sleepiness countermeasure in non-sleep deprived individuals. It was shown that coffee had a positive effect on reported sleepiness and driving performance. All objective and subjective measures in these studies pointed in the same direction.

Red Bull® Energy Drink is another popular caffeinated drink that is believed to increase alertness and enhance performance. On their website, Red Bull states the following:

"Red Bull shows its effects when you drink it at times of increased mental and physical strain, for example, during intensive working days, on long sleep-inducing motorways, prior to demanding athletic activities or before tests and exams." (Underlining added).

Chapter 11 confirmed that Red Bull® Energy Drink (250 ml) alleviates subjective sleepiness and improves driving performance in non-sleep deprived individuals. The effects of Red Bull® Energy Drink and coffee on driving performance were of comparable magnitude, although the effect of Red Bull® Energy Drink seemed to be somewhat more pronounced. In this context it is important to know that the administered coffee and Red Bull® Energy Drink both contained the same amount of caffeine (80 mg). It would be interesting to further study the ingredients of Red Bull® Energy Drink, such as by repeating the experiment with different combinations of ingredients, in a properly controlled repeated measures study.

In the current studies, healthy subjects who were regular drivers and moderate caffeine drinkers were tested in a crossover design. None of the subjects were shift workers or had sleeping problems. The objective was to mimic real-life conditions in which individuals take a rest when driving for a longer period of time. It should therefore be noted that the results presented here are confined to the ordinary driver. Furthermore, these findings cannot be extended to driving times of more than two hours.

It is likely that different tasks are differently affected by caffeine (Nehlig, 2010). In addition, sleepiness and fatigue and their differential causes may add to these differences. The same may hold true for patterns of consumption (Smit and Rogers, 2000). This has consequences for traffic safety research. For example, a person who drinks one cup of coffee after a full night of sleep and drives to work, and a shift-working truck driver who spends long hours behind the wheel and consumes large amounts of coffee, greatly differ on all these accounts. Studying drivers who appear to be most at risk, such as shift workers, truck drivers and individuals with sleep disturbances is therefore of importance. In addition, more complex tasks and the effect on for example risk taking behavior in traffic can be included.

Counteracting residual effects of hypnotics

To prevent driving impairment due to residual effects of hypnotic drugs, one could look at new treatment options, e.g. novel hypnotics, but also at methods or substances to counteract these effects. The question that arises here is whether consumption of coffee in the morning could be advised to these patients in order to counteract residual drug effects by the stimulating effects of caffeine. There is currently no scientific evidence that supports giving such an advice. Some studies indicate that caffeine might aid in counteracting the effects of hypnotics (Klopping et al., 2005). Whether this is the case for all types of hypnotics, and if this also holds true for residual effects on driving, is unknown. Therefore, it would be interesting to examine this application of caffeine and other sleepiness countermeasures.

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SAMENVATTING

Slaperigheid en vermoeidheid achter het stuur zijn belangrijke oorzaken van verkeersongelukken. De belangrijkste factoren die hierbij een rol spelen zijn slaaponthouding, slaapstoornissen, circadiane factoren zoals de tijd van de dag en verstoringen van het slaap-waak ritme, gebruik van medicatie of drugs, een monotone omgeving en de tijd die aan de rij-taak besteed wordt (time-on-task). Deze condities kunnen onder andere leiden tot een afname in alertheid, concentratieverlies, vermindering van het cognitieve functioneren en een afname van de reactiesnelheid. Dit kan tot gevolg hebben dat een bestuurder niet meer in staat is het voertuig naar behoren te besturen en adequaat te reageren op verkeerssituaties, en uiteindelijk het risico loopt achter het stuur in slaap te vallen.

Het is niet duidelijk hoe groot het probleem van slaperige en vermoeide bestuurders is, omdat vermoeidheid niet altijd als oorzaak van verkeersongevallen aan te duiden is. Ten eerste is er tot op heden geen eenduidige test om vermoeidheid in het verkeer te meten. Er zijn momenteel geen geschikte biologische markers. Wel zijn er systemen (in-vehicle devices) die mogelijkheden kunnen bieden, maar deze worden nog niet op grote schaal gebruikt en zijn deels nog in ontwikkeling. Ten tweede compromitteren de omstandigheden waarin dergelijke ongevallen zich voordoen een correcte analyse: ongevallen gebeuren vaak ’s nachts, mensen zijn meestal alleen in het voertuig, de impact van een botsing maakt slaperige bestuurders weer alert en bestuurders zijn zich vaak niet bewust van de oorzaak of willen deze niet toegeven in verband met mogelijke juridische consequenties. Hierdoor ontbreekt slaap als oorzakelijke factor dikwijls in ongevalregistraties. Schattingen van het percentage verkeersongevallen waarin slaap een factor is, lopen daarom uiteen van 2 tot 25%.

Psychoactieve stoffen kunnen hierbij een belangrijke rol spelen. Enerzijds kan de behandeling van slaapstoornissen er voor zorgen dat mensen beter in staat zijn een voertuig te besturen en anderzijds kunnen bijwerkingen of residuele effecten leiden tot een verminderde rijvaardigheid. De belangrijkste categorieën geneesmiddelen die in deze context een rol spelen zijn stimulantia, welke vermoeidheid tegengaan, en hypnotica: middelen die de slaap bevorderen. Om patiënten en behandelaars optimaal te informeren over het gebruik en de eventuele risico's is het van belang de effecten van deze middelen op rijvaardigheid en verkeersveiligheid te meten.

Het besturen van een voertuig is een complexe taak. Daardoor is er een grote verscheidenheid aan theorieën en modellen die de verschillende aspecten van rijvaardigheid trachten weer te geven. Informatieverwerkingsmodellen verklaren en beschrijven de rijvaardigheid op meerdere niveaus van informatieverwerking. Enerzijds wordt er gekeken naar de ervaring van de bestuurder en anderzijds naar de vertrouwdheid met en de complexiteit van de omstandigheden waarin de taak wordt uitgevoerd. De gestandaardiseerde rijvaardigheidstest in het normale verkeer op de snelweg wordt momenteel beschouwd als de gouden standaard voor het objectief bepalen van rijvaardigheid. Door middel van deze test wordt primaire voertuigbeheersing gemeten. Tijdens deze test legt een proefpersoon een traject af van 100 km op een openbare snelweg tussen Arnhem en Utrecht. Deze test vindt plaats in een auto die is uitgerust met apparatuur om de snelheid en de positie binnen de rijbaan te meten.

Bij deze test is een rij-instructeur aanwezig die de beschikking heeft over dubbele bediening om de veiligheid te garanderen. Tevens is een onderzoeker aanwezig die de apparatuur bedient en kan registreren of er bijzonderheden optreden. Dit kunnen verkeerssituaties zijn, maar ook gedragingen van de proefpersoon zelf. De onderzoeker instrueert de proefpersoon volgens een vast protocol. Met in achtneming van de verkeersveiligheid, dient de proefpersoon een vaste positie binnen de rechterrijstrook aan te houden met een constante snelheid van 95 km/uur. Inhaalmanoeuvres en andere onregelmatigheden, zoals files, worden uit de data verwijderd voor de analyse.

Het doel van dit proefschrift was om de invloed van slaap en slaperigheid op het dagelijkse functioneren te onderzoeken. De studies die hiervoor zijn uitgevoerd maken gebruik van bovengenoemde methodologie. De uitkomstmaten die gehanteerd worden zijn de mate van slingering, ofwel de standaard deviatie van de laterale positie binnen de rijbaan (SDLP), de standaard deviatie van de snelheid (SDS), de gemiddelde positie binnen de rijbaan (MLP) en de gemiddelde snelheid (MS). De twee laatstgenoemde zijn controlematen om te verifiëren of de proefpersoon de instructies correct heeft opgevolgd. De mate van slingering is de primaire uitkomstmaat bij dit type onderzoek. In de afgelopen decennia is in een groot aantal studies aangetoond dat de SDLP gevoelig is voor effecten van alcohol, drugs en geneesmiddelen, maar ook voor verminderd functioneren tengevolge van slaperigheid.

Omdat rijsimulatoren voordelen hebben betreffende kostenbesparing, standaardisering van testcondities en veiligheid, worden deze steeds vaker ingezet om rijvaardigheid te meten. Hierbij dient echter wel aangetoond te worden dat deze ook daadwerkelijk geschikt zijn voor het meten van effecten van geneesmiddelen. In dit proefschrift wordt een onderzoek naar de gevoeligheid van een rijtest in de rijsimulator beschreven. Vervolgens zijn er twee onderzoeken uitgevoerd die deze methode toepassen. Bij alle onderzoeken was de mate van slingering de voornaamste uitkomstmaat. Daarnaast zijn er ook andere testen uitgevoerd die de invloed van een geneesmiddel op psychomotorisch functioneren, geheugen en gemoedstoestand bepalen.

DEEL I. SLAAPSTOORNISSEN, HYPNOTICA EN FUNCTIONEREN OVERDAG

In hoofdstuk 2 wordt ingegaan op de literatuur betreffende psychoactieve stoffen en de invloed op verkeersveiligheid. Hierbij ligt de nadruk op het gebruik van slaapmiddelen. Farmacotherapie bij patiënten die lijden aan slapeloosheid is momenteel voornamelijk gericht op het gebruik van de zogenaamde benzodiazepine receptor agonisten. Deze groep slaapmiddelen omvat de benzodiazepinen en de Z-drugs (zaleplon, zolpidem en zopiclone). De benzodiazepinen hebben niet alleen invloed op slaap en sedatie, maar ook op hersengebieden die verantwoordelijk zijn voor onder andere geheugen en psychomotorisch functioneren. Meerdere studies tonen aan dat het gebruik van dit type slaapmiddelen leidt tot een verminderde rijvaardigheid en een toename van ongevallen.

Omdat de Z-drugs selectiever zijn voor receptortypen die een rol spelen bij slaap, werd verwacht dat deze ook minder bijwerkingen zouden hebben. Zopiclone blijkt echter vergelijkbare nadelige gevolgen te hebben voor de rijvaardigheid als de benzodiazepinen. Hoewel bij langdurig gebruik tolerantie optreedt, is deze niet volledig en moet patiënten worden aangeraden voorzichtigheid te betrachten bij het besturen van een voertuig. Een categorisatie van geneesmiddelen die mogelijk de rijvaardigheid kunnen verminderen, ontwikkeld door ICADTS (International Council on Alcohol, Drugs and Traffic Safety), kan artsen helpen om een optimale behandeling te kiezen voor patiënten die deelnemen aan het verkeer.

Een ander effect dat kan optreden bij het gebruik van slaapmiddelen is een verstoring van het evenwicht. In hoofdstuk 3 wordt een overzicht gegeven van studies waarin het effect van hypnotica op balans is gemeten. De resultaten laten zien dat er een correlatie is tussen plasmaconcentraties en de mate van evenwichtsverstoringen. Ook in de ochtend na inname kan de balans verstoord zijn. Het gebruik van alcohol in combinatie met slaapmiddelen leidt tot een versterking en een langere tijdsduur van dit effect. Tevens blijkt dat de uitwerking op het evenwicht sterker optreedt bij ouderen. Omdat zij gevoeliger zijn voor botbreuken, lopen zij een verhoogd risico.

Hoofdstuk 4 behandelt de neurologische aandoening narcolepsie. De belangrijkste symptomen zijn excessieve slaperigheid overdag en een verminderde vigilantie. Daarnaast kunnen ook cataplexie, slaapverlamming, hypnagogische hallucinaties en slaapverstoringen optreden. Dit leidt er toe dat patiënten verminderd presteren bij taken die een rol spelen bij rijvaardigheid. Er zijn relatief weinig studies die de invloed van deze aandoening op verkeersveiligheid onderzocht hebben. Studies in onbehandelde patiënten wijzen echter uit dat zij waarschijnlijk een verhoogd risico op ongevallen hebben. Er zijn evenwel grote individuele verschillen gevonden in de mate waarin narcolepsie het functioneren vermindert. Ook is er geen consensus onder artsen voor wat betreft rijgeschiktheid van narcolepsiepatiënten. Het is daarom noodzakelijk om het effect van behandeling op rijvaardigheid te onderzoeken.

In hoofdstuk 5 wordt de invloed van verstoringen van het circadiane ritme besproken, zoals gezien bij ploegendiensten en wisselende werktijden. Het circadiane ritme heeft betrekking op cycli van 24 uur van verschillende biologische processen waaronder de regulatie van slaap en waakzaamheid. De interne biologische klok, gelokaliseerd in een hersengebied genaamd de suprachiasmatische nucleus, genereert cycli van ongeveer 24 uur. Onder invloed van de omgeving, met name (dag)licht, wordt de klok dagelijks bijgesteld, zodat mensen in staat zijn hun activiteiten aan te passen aan dag en nacht. Wanneer er echter een conflict ontstaat tussen deze processen en werktijden, kunnen mensen hier negatieve consequenties van ondervinden. Als deze medewerkers last hebben van slapeloosheid als ze overdag willen slapen en excessieve slaperigheid gedurende hun werktijd die overlapt met hun normale slaaptijd, spreekt met van ‘shift work disorder'. In verschillende

onderzoeken is naar voren gekomen dat het werken in ploegendienst bijdraagt aan verkeersongevallen. Ploegendienstmedewerkers hebben een groter risico om slaperig achter het stuur te zitten, daadwerkelijk achter het stuur in slaap te vallen, en betrokken te zijn bij ongevallen. Ook lijkt het er op dat er een bepaalde groep gevoeliger is, omdat een klein deel van de onderzochte proefpersonen vaak verantwoordelijk is voor een relatief groot deel van de ongelukken. Maatregelen tegen overmatige slaperigheid bij deze medewerkers zijn daarom noodzakelijk. Hierbij valt te denken aan stimulantia om de waakzaamheid te bevorderen en hypnotica om slaap te stimuleren. Naast het optreden van mogelijke bijwerkingen wordt de kern van het probleem hiermee echter niet behandeld. Afzien van werk in ploegendienst is vaak niet mogelijk. Wel zou men ploegendienstschema's kunnen optimaliseren zodat mensen zich beter kunnen aanpassen. Ook kan geprobeerd worden de verstoring in het circadiane ritme aan te pakken door middel van lichttherapie en het gebruik van chronobiotica zoals melatonine, die kunnen helpen bij het verschuiven van het interne slaap-waak-ritme zodat dit aansluit bij de werktijden. Ten slotte kunnen schema's gebruikt worden om de slaap gedurende de dag op een optimaal moment te plannen.

Hoofdstuk 6 behandelt een belangrijk praktisch thema: dat van het bepalen van rijgeschiktheid in patiënten met slaapstoornissen. Er heerst onduidelijkheid over welke patiënten in staat zijn veilig een voertuig te besturen en wie dit moet bepalen. Om inzicht te krijgen in de mening van slaapspecialisten is er een enquête uitgevoerd tijdens een internationaal congres, waarin gevraagd werd naar hun opinie over patiënten met slaapapneu (een slaapstoornis gekenmerkt door belemmering van de ademhaling tijdens de slaap), insomnia (slapeloosheid) en narcolepsie. De totale respons onder de 1000 deelnemers was 11%.

66% van de ondervraagden gaf aan dat insomniapatienten binnen een aantal dagen of weken na de start van een behandeling in staat zijn om te gaan rijden, terwijl 44% vond dat, afhankelijk van de mate van slaperigheid overdag, onbehandelde patiënten niet zouden moeten rijden. Bijna de helft (49%) vond dat onbehandelde slaapapneu patiënten niet mogen rijden. De meerderheid (66%) was van mening dat ze dat wel konden als ze adequaat behandeld werden door middel van een CPAP (Continuous Positive Airway Pressure) apparaat, maar de mate van overmatige slaperigheid overdag bleef

een belangrijke rol spelen. Onbehandelde narcolepsiepatienten werden door de meerderheid van respondenten (77%) ook niet geschikt bevonden om deel te nemen aan het verkeer, maar wel als ze behandeld werden. Dit was wel onder voorbehoud van de mate van slaperigheid. Ook werd onderkend dat de rijvaardigheid van risicogroepen getest zou moeten worden, maar dit is erg kostbaar en tijdsintensief. Op sommige punten komt de mening van de specialisten niet overeen met de literatuur. Ook is het effect van behandeling vaak niet duidelijk, omdat daar onvoldoende onderzoek naar is gedaan. Het blijft daarom van belang om patiënten en specialisten te informeren op het gebied van slaapstoornissen, behandeling, en verkeersrisico's.

DEEL II. RAMELTEON

Ramelteon is een slaapmiddel dat afwijkt van de eerder besproken hypnotica omdat het niet bindt aan de benzodiazepine receptoren, maar aan de melatonine I en II receptoren. Melatonine is een hormoon dat onder andere een rol speelt bij de regulering van het slaap-waak ritme. Ramelteon heeft als indicatie het verkorten van de inslaaptijd.

Hoofdstuk 7 geeft een overzicht van de studies die zijn uitgevoerd naar de effectiviteit en veiligheid van ramelteon. Voor wat betreft het effect op slaap, blijkt ramelteon voornamelijk effectief te zijn in het verkorten van de slaaplatentietijd, zoals deze wordt gemeten in een polysomnografietest. Zowel in kortdurende insomnia als in chronische insomnia werd de slaaplatentietijd verkort met gemiddeld 13 minuten ten opzichte van placebo. Dit beeld was minder eenduidig voor de andere objectieve criteria, zoals totale slaaptijd. Subjectieve slaapscores laten wisselende resultaten zien, waarbij er geen effect is gevonden op slaapkwaliteit. Voor slaapmiddelen wordt een subjectieve verbetering van de slaap als een belangrijk criterium beschouwd, omdat slapeloosheid gezien wordt als een subjectieve slaapstoornis. Het voordeel van ramelteon is dat er geen aanwijzingen zijn voor het ontwikkelen van tolerantie of afhankelijkheid. Tevens laten studies geen effecten op geheugen of op het functioneren overdag zien. Een andere indicatie voor ramelteon zou de regulatie van het circadiane ritme kunnen zijn.

Op basis van deze gegevens zou men verwachten dat ramelteon ook geen effect op rijvaardigheid heeft. Dit werd onderzocht in de studie die werd beschreven in hoofdstuk 8. De effecten van ramelteon (8 mg), zopiclone (7.5

mg) en placebo werden vergeleken in een gerandomiseerd, dubbel-blind, placebo-gecontroleerd onderzoek. Zopiclone werd gebruikt als actieve controle, omdat bekend is dat gebruik van dit middel de rijvaardigheid verslechtert. De medicatie werd 's nachts toegediend en in de ochtend werden de residuele effecten gemeten in gezonde vrijwilligers. Tevens werd er 's nachts een balanstest uitgevoerd. Het effect op rijvaardigheid werd bepaald door middel van de rijtest in het normale verkeer. Daarnaast werd er een testbatterij gebruikt die bestaat uit een woordentest en de Sternberg memory scanning test, die beide geheugen meten, een tracking test en een verdeelde aandachtstaak die uit een combinatie van de twee laatstgenoemde testen bestaat.

De mate van slingeren (SDLP) nam significant toe na inname van ramelteon (+2.2 cm) en zopiclone (+2.9 cm). Beide middelen lieten een toename van reactietijd zien bij de Sternberg memory scanning test, tracking, en reactie tijd en tracking bij de verdeelde aandachtstaak. Het vermogen om woorden te reproduceren die enige tijd daarvoor getoond werden (delayed memory recall) was ook verminderd. In tegenstelling tot zopiclone had ramelteon geen invloed op de digit symbol substitution test (DSST) en ook niet op de balanstest midden in de nacht. Het is echter niet duidelijk waardoor de waargenomen effecten optreden. Mogelijkerwijs is de actieve metaboliet M-II hiervoor verantwoordelijk. Dit is echter geen verklaring voor het feit dat eerdere testen dit effect niet laten zien. Wellicht is door het toepassen van een uitvoerigere testmethode, waaronder de rijtest en de testbatterij, een vermindering van het functioneren aan het licht gekomen, dat in eerdere, eenvoudigere, testen niet opgemerkt kon worden.

DEEL III. METHODEN VAN RIJVAARDIGHEIDSONDERZOEK

De STISIM rijsimulator is een interactief systeem dat veelvuldig wordt gebruikt. Universiteit Utrecht heeft een snelweg scenario laten ontwikkelen dat is gebaseerd op de rijtest in het normale verkeer. In hoofdstuk 9 wordt een kalibratiestudie besproken die is uitgevoerd om te bepalen of dit scenario in deze rijsimulator geschikt is voor het uitvoeren van farmacologische studies. De vergelijking met de invloed van alcohol wordt regelmatig toegepast in rijvaardigheidsstudies, omdat dit inzicht biedt in de klinische relevantie van testresultaten. Placebo en verschillende alcoholdoseringen die leiden tot een

bloed alcohol concentratie (BAC) van respectievelijk 0.05%, 0.08% en 0.11% werden toegediend aan 27 gezonde vrijwilligers. Nadat de juiste BAC-waarde was bereikt, legden de proefpersonen een afstand van 100 km af in de rijsimulator. De instructies waren hetzelfde als tijdens de snelwegrit in het normale verkeer. De mate van slingering (SDLP) was de belangrijkste parameter. Vergeleken met placebo leidde alcohol tot een significante toename van slingering, waarbij er meer slingering te zien was bij hogere doseringen. Ook werd er een toename van de standaard deviatie van de snelheid geobserveerd in de hoogste doseringen (0.08% en 0.11%), wat betekent dat proefpersonen meer moeite hadden een constante snelheid te rijden. Er werden geen verschillen gevonden voor gemiddelde snelheid en gemiddelde positie op de weg.

Er werd een correlatie gevonden tussen het verschil in SDLP ten opzichte van placebo en de alcoholconcentratie. Omdat proefpersonen kunnen verschillen in de mate van slingering tijdens basiscondities, wordt het verschil ten opzichte van placebo doorgaans gebruikt om effecten aan te duiden.

Bij toenemende BAC-niveaus beoordeelden de proefpersonen hun rijkwaliteit als slechter en hun rijstijl als gevaarlijker, meer gespannen, onverstandiger, minder voorspelbaar, minder doordacht en minder verantwoordelijk. Dit onderzoek laat zien dat de snelwegtest gevoelig is voor verschillende alcoholniveaus en geschikt is om de effecten van psychoactieve stoffen op rijvaardigheid te meten.

DEEL IV. MAATREGELEN TEGEN SLAPERIGHEID VAN BESTUURDERS

Een conditie die slaperigheid kan opwekken of verergeren is rijden in een monotone omgeving. Daarnaast treedt er vermoeidheid op als mensen langere tijd dezelfde taak uitvoeren. Deze combinatie van factoren is waarschijnlijk een van de redenen waarom er meer slaapgerelateerde ongevallen voorkomen op snelwegen.

Om dit soort omstandigheden te onderzoeken in de STISIM rijsimulator is er een protocol ontwikkeld, waarbij gebruik wordt gemaakt van het snelwegscenario dat in hoofdstuk 9 werd beschreven. Proefpersonen voeren gedurende ongeveer 2 uur (2x100 km) de rijtest uit, waarna ze een kwartier pauze krijgen. Gedurende de pauze wordt een middel toegediend. Na afloop

van de pauze rijden mensen wederom 2 uur in de simulator, en worden de effecten van het middel gemeten.

In hoofdstuk 10 worden de effecten van koffie met cafeïne (80 mg) vergeleken met decafé. Cafeïne kan beschouwd worden als de meest gebruikte psychoactieve stof en daarnaast wordt koffie regelmatig geconsumeerd door bestuurders tijdens een onderbreking van het rijden. In het verleden zijn er enkele onderzoeken uitgevoerd die hebben laten zien dat koffie de rijvaardigheid verbetert. Deze onderzoeken zijn echter meestal verricht in mensen met gedeeltelijke slaaponthouding, of in doseringen die vergelijkbaar zijn met meerdere koppen koffie. Het doel van het huidige onderzoek was om te bepalen of een meer gebruikelijke hoeveelheid van 1 kop koffie (80 mg) bij mensen die uitgerust waren ook een effect heeft. In vergelijking met decafé waren proefpersonen in het eerste en tweede uur na de pauze beter in staat een vaste positie binnen de rijbaan aan te houden (verminderde SDLP). Daarbij was er ook sprake van een meer gelijkmatige snelheid dan in de decafé conditie. De subjectieve testen lieten een vermindering van mentale inspanning en subjectieve slaperigheid zien en een verbetering van de subjectieve rijkwaliteit na de inname van koffie. De conclusie is dan ook dat de consumptie van koffie (80 mg cafeïne) gedurende een pauze leidt tot een significante verbetering van rijvaardigheid ten opzichte van decafé tijdens een monotone snelwegrit in de STISIM rijsimulator.

Hoofdstuk 11 laat de resultaten zien van een soortgelijk experiment met Red Bull® Energy Drink. Dit is een energiedrankje dat naast cafeïne (80 mg), ook taurine, glucuronolactone, B vitamines, en inositol bevat. Deze combinatie van stoffen zou volgens de producent leiden tot verbeterde prestaties, onder andere tijdens monotone snelwegritten. Red Bull® Energy Drink werd vergeleken met placebo dat identiek was aan Red Bull® Energy Drink, maar zonder de eerdergenoemde ingrediënten, en met een conditie waarin mensen geen pauze hadden na 2 uur, maar bleven doorrijden. Vergeleken met placebo leidde Red Bull® Energy Drink tot een afname van slingering (SDLP) en een afname van subjectieve slaperigheid in het eerste en tweede uur na inname. Snelheidsbeheersing (SDS), subjectieve rijkwaliteit, en mentale inspanning gedurende de test werden positief beïnvloed in het eerste uur na de pauze. Vergeleken met de conditie zonder pauze, verbeterde Red Bull® Energy Drink de prestaties op alle parameters.

CONCLUSIES EN AANBEVELINGEN

De slaapmiddelen die momenteel worden gebruikt, kunnen leiden tot een verminderde rijvaardigheid. Men had gehoopt dat ramelteon de oplossing zou zijn voor dit probleem, maar dit blijkt niet het geval te zijn. Omdat het niet duidelijk is waarom deze effecten van ramelteon optreden, zou toekomstig onderzoek hier op gericht moeten zijn. Een rijvaardigheidsonderzoek naar de effecten van melatonine, waar ramelteon van is afgeleid en dat in lage doseringen vrij verkrijgbaar is, is aanbevelenswaardig. Samenvattend kan gesteld worden dat het ontwikkelen van een slaapmiddel dat deze nadelige effecten niet heeft, nog steeds wenselijk is.

Rijvaardigheidstesten zoals beschreven in dit proefschrift zijn gevoelig voor de invloed van psychoactieve stoffen, maar richten zich voornamelijk op basale voertuigbeheersing. Om een indicatie te geven over hogere informatieverwerkingsprocessen, worden daarnaast vaak computertesten uitgevoerd. Geavanceerde systemen maken het mogelijk andere aspecten van rijvaardigheid te meten. Het probleem is echter om een objectieve maat te vinden die de invloed van psychoactieve stoffen betrouwbaar weergeeft. Verder zou er meer informatie verkregen kunnen worden over de validiteit van de snelwegrit in de rijsimulator, door een directe vergelijking te maken tussen deze rijtest en dezelfde test in het normale verkeer met behulp van een middel waarvan bewezen is dat het de rijvaardigheid beïnvloedt, zoals het anxiolyticum diazepam of het slaapmiddel zopiclone.

Relatief lage doseringen cafeïne laten een positief effect zijn op rijvaardigheid in monotone omstandigheden. De effecten van Red Bull® Energy Drink en koffie zijn van vergelijkbare grootte, hoewel het verschil van Red Bull® Energy Drink ten opzichte van placebo iets groter lijkt. Verder onderzoek naar de ingrediënten van dit energiedrankje zou daarom interessant kunnen zijn. Verschillende taken en de mate van slaperigheid of vermoeidheid kunnen een uiteenlopend effect hebben op de werkzaamheid van cafeïne. In de huidige studies zijn normale bestuurders onderzocht, die gemiddelde hoeveelheden cafeïne consumeren zonder dat er sprake is van slaapdeprivatie of verstoringen in het slaap/waakritme. Onderzoek in complexere omstandigheden en in andere gebruikersgroepen, zoals mensen die onregelmatige werktijden hebben, medicatie gebruiken, of die veel tijd

achter het stuur doorbrengen, zou kunnen uitwijzen welke condities worden beïnvloed door cafeïne en welke mensen baat hebben bij het gebruik.

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CURRICULUM VITAE

Monique A.J. Mets was born on June 6th 1980 in Geleen, The Netherlands. After graduating from Sint Michiel in Geleen in 1998, she studied Animal Sciences at Wageningen University, The Netherlands. During this study, she did her major MSc thesis on the influence of environmental enrichtment on the welfare of laboratory rats at Utrecht University and Nijmegen University, The Netherlands. Her minor MSc thesis was on communication strategies and was carried out at Wageningen University. For her internship, she studied the behavior of wolves and clinical ethology at the veterinary department of the Universitat Autònoma de Barcelona in Spain. After her graduation, she followed the masterprogram Experimental and Clinical Neuroscience at Utrecht University. As part of the Management profile: business and economics for science students, she studied market opportunities for diagnostics tools at Crossbeta Biosciences at UMC Utrecht. Her internship was carried out at the department of Psychopharmacology of the Utrecht Institute for Pharmaceutical Sciences. After her graduation in August 2007, she started as a PhD candidate at the same department under the supervision of Dr. Verster and Prof. Dr. Olivier. During her PhD project, she was a board member of PrOUt, the PhD network of Utrecht University.
Results obtained during this project are presented in this dissertation.