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CLINICAL REVIEW

Residual effects of sleep medication on driving ability

Joris C. Verster*, Dieuwke S. Veldhuijzen, Edmund R. Volkerts

Department of Psychopharmacology, Utrecht Institute for Pharmaceutical Sciences, University of Utrecht, PO Box 80082, 3508 TB, Utrecht, The Netherlands

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Summary Most patients using hypnotics are ambulatory and presumably have a job and drive a car. Since driving a car is one of the most common but potentially dangerous daily activities, hypnotics should act rapidly when needed, but daytime sleepiness and other residual effects that may impair performance are unwanted. This review summarizes the effects of hypnotics on driving ability as determined with the on-the-road driving test during normal traffic. Supportive evidence from epidemiological data, and results from driving simulators and closed-road studies are also considered.

On-the-road studies revealed that benzodiazepine hypnotics significantly impaired driving ability the morning following bedtime administration. Impairment was sometimes also significant in the afternoon (16–17 h after administration). Similar driving impairment was observed with zopiclone. However, the magnitude of impairment depends on various factors including the half-life and dosage of the drug, and the time after administration. The results from on-the-road driving studies are supported by evidence obtained in driving simulators and laboratory tests. Epidemiological data and on-the-road studies show that tolerance develops to the impairing effects of hypnotics. However, this is a slow process, and impairment may persist. Patients treated with benzodiazepine hypnotics or zopiclone should be cautioned when driving a car.

Both zolpidem and zaleplon do not significantly affect driving performance the morning following bedtime administration. Middle-of-the-night administration of zolpidem significantly impairs driving ability in a dose-dependent manner. In contrast, zaleplon did not affect driving ability 4 h after middle-of-the-night administration.

Introduction

Approximately 35% of the population suffers from insomnia. Sleep disturbances result in poor sleep quality that may be reflected in waking up drowsy and impaired daytime functioning. Most commonly reported complaints include sleep initiation problems and nocturnal or early morning awakenings.

Abbreviations: ACE, Angiotensin converting enzyme; BAC, Blood alcohol concentration; CI, Confidence interval; GABA, Gamma amino butyric acid; NSAID, Non-steroid anti-inflammatory drug; OR, Odds ratio; SDLP, Standard deviation of lateral position; SSRI, Selective serotonin reuptake inhibitor; TCA, Tri cyclic antidepressant.

*Corresponding author. Tel.: +30-253-69-09; fax: +30-253-73-87.

E-mail address: j.c.verster@pharm.uu.nl (J.C. Verster).

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Sleep disturbances can be classified according to their duration as either transient (<1 week), short-term (1–3 weeks) or chronic (months). Further, they can be a primary disorder or occur secondary to other disorders such as anxiety and depression. Sleep disturbances are underdiagnosed. The 1991 National Sleep Foundation Survey revealed that only 5% of those suffering from sleep disturbances consult their physician.[1] Instead, most people treat themselves with over-the-counter medication (23%) or alcohol (28%), often in combination with lifestyle adaptation or relaxation techniques. Only 21% use prescription drugs that are specifically approved for the treatment of insomnia. An overview of the most frequently prescribed drugs for the treatment of insomnia is presented in Table 1.

Barbiturates were the first drugs used in the treatment of sleep disturbances. Unfortunately, they produce severe sedation during daytime. Tolerance to their therapeutic effect establishes within 2 weeks after treatment initiation, and their high abuse potential and possible death in case of overdosing limited the use of barbiturates.

Since the barbiturates were abandoned from the clinical area, benzodiazepine drugs became the first-choice pharmacological treatment for the relief of sleep disturbances. All benzodiazepine hypnotics must be administered at bedtime, and have comparable clinical efficacy. Benzodiazepines can be classified according to their half-life as short-acting (<8 h), intermediate (8–24 h) and long-acting (>24 h). They also differ in time of onset (T_{max}), and whether they have active metabolites or not. Benzodiazepines easily cross the blood brain barrier. In the brain, they bind nonselectively and with high affinity to both the α_1 and α_2 subunits of the $GABA_A$ receptor complex. Several subunits have been discovered, including $\alpha_{1-6}, \beta_{1-3}, \varepsilon, \theta$ and γ_{1-3}. Most $GABA_A$ receptors are composed of α, β, and γ subunits. The $GABA_A$ benzodiazepine receptors have been differentiated in Type 1 receptors $(\alpha_1\beta_{1-3}\gamma_2)$ and Type 2 receptors $(\alpha_{2,3,5}\beta_{1-3}\gamma_2)$. It has been shown that the α_1 subunit is related to sedative hypnotic and amnesic effects, whereas the α_2 subunit has been related to anxiolytic effects.[2–3] Binding of benzodiazepines to the $GABA_A$ receptor complex enhances the binding of GABA to the β subunits. The presence of GABA inhibits the activity of various brain structures resulting in reduced alertness and increased sedation.

Table 1 Drugs used in the treatment of insomnia.

	Dose (mg)	$T_{1/2}$ (h)	T_{max} (h)	Active metabolite(s)
Benzodiazepine hypnotics				
Triazolam	0.25	1.5–5.5	1	+
Temazepam	20	7–11	0.8	−
Loprazolam	1	8[a]	2–5	−
Lormetazepam	1	10	1–2.5	−
Flunitrazepam	2	16–35	1.2	+
Nitrazepam	5	18–34	2	+
Flurazepam	30	47–100[a]	0.5–2	+
Benzodiazepine anxiolytics				
Oxazepam	50	4–15	2–3	−
Alprazolam	1	12–15	1–2	−
Diazepam	10	20–100[a]	1–2	+
Lorazepam	2.5	12–16	2	−
Clonazepam	0.5–2	30–40	0.5–1	−
Antidepressants				
Amitriptyline	50–100	12–36[a]	1.5	+
Doxepine	150	33–80[a]	2	+
Trazodone	25–150	8	1–2	+
Non-benzodiazepines				
Zopiclone	7.5	3.5–6.5	1–2	−
Zolpidem	10	2–4	0.5–1	−
Zaleplon	10	1–2	0.5–1	−

+, Active metabolites; −, no active metabolites.
[a] $T(1/2)$ (h) includes those of the active metabolites.

The (wanted) clinical effects of benzodiazepine hypnotics during the night (i.e. sedation and reduced alertness) are essentially the same as the (unwanted) adverse effects during daytime. The ideal hypnotic should have clinical efficacy combined with the absence of residual unwanted effects the following day. In fact, there is a need for rapidly acting agents that can be administered during the night as sleep disturbances occur. This is important, since even patients with most severe chronic insomnia report that their complaints are intermittent. That is, approximately 50% of the nights they do not experience sleep disturbances.[4-5] Daily 'preventive' bedtime use of benzodiazepines is unnecessary and may result in dependency and tolerance to their clinical effects. The accompanying daytime sedation may significantly reduce the patients' quality of life. Hence, aim of research and development was to design new hypnotics that can be used as needed during the night.

This led to the development of non-benzodiazepine hypnotics such as the cyclopyrrolone zopiclone, the imidazopyridine zolpidem, and the pyrazolopyrimidine zaleplon. Zopiclone acts selectively on the α_1 subunit of the $GABA_A$ receptor complex, but its half-life is comparable to those of the short-acting benzodiazepines. Zolpidem and zaleplon also act at the $GABA_A$ receptor complex and are highly selective to the α_1 subunit ($\alpha_1\beta_2\gamma_2$). In addition, the half-life of both zolpidem (2–4 h) and zaleplon (1–2 h) is ultra-short.[6] This high selectivity for the α_1 subunit, combined with their short half-life, made zolpidem and zaleplon promising drugs for meeting the criteria of (1) clinical efficacy, (2) flexible dosing during the night, (3) without producing next-day sedation.

In addition to these hypnotics, benzodiazepine anxiolytics and antidepressant drugs are also prescribed for the treatment of insomnia (Table 1). Although the latter drugs are generally not approved for hypnotic purposes, they do possess sedative properties that may initiate sleep. In this context, anxious or depressive patients often report sleep disturbances and thus may benefit from their sedative effects.

Although sleep disturbances are a common medical problem, hospitalization of patients suffering from insomnia is rare. On contrary, most of them have regular jobs and drive a car. To enhance overall traffic safety, preclusion of patients using potentially sedative drugs from driving would be favorable. However, serious socioeconomic consequences make this an unrealistic solution, and since patients often perceive that driving is their right[7] this would presumably result in poor therapeutic compliance or illegal driving.

This review will summarize and discuss the effects of hypnotics on driving ability along four lines of evidence: (1) epidemiological data, (2) closed-road studies, (3) driving simulators, and (4) actual on-the-road driving during normal traffic.

Epidemiological evidence

Borkenstein and colleagues[8] conducted a classical epidemiological study in which they clearly established the correlation between blood alcohol concentration (BAC) and the probability of causing a traffic accident. Other studies examined the relationship between the use of psychoactive drugs and the risk for traffic accidents or related injury. For example, Skegg and colleagues[9] reported a significantly increased traffic accident risk (Odds Ratio [OR] = 4.9) for those using benzodiazepine anxiolytics (mostly diazepam). However, this study included only five cases and 32 healthy controls.

A more extensive study by Oster and colleagues[10] examined the risk of traffic accidents and injury of 7271 benzodiazepine users, compared to 65,439 matched controls (nonusers). They showed that the percentage of patients requiring medical attention due to traffic accidents or injury was significantly higher among users of benzodiazepine anxiolytics (24.8%) than among healthy controls (22.0%). Also, the number of accident-related hospital admissions was significantly higher among users of benzodiazepine drugs (3.2%) when compared to nonusers (2.0%). However, the authors also reported that benzodiazepine users had a higher number of hospital admissions in general, which may have interfered with their study outcome.

In a subsequent study,[11] Oster and colleagues examined the risk of traffic accident injury in drivers using benzodiazepine anxiolytics (alprazolam, chlordiazepoxide, chlorazepate, diazepam, lorazepam, oxazepam). Data from 4554 benzodiazepine users was compared to those from 13,662 controls. Three months before treatment initiation, future benzodiazepine users showed increased numbers of accident-related emergency outpatient visits (OR = 2.0; 95% CI = 0.96–4.44), accident-related hospital admissions (OR = 1.7; 95% CI = 1.11–2.61) and accident-related medical encounters of any type (OR = 1.5; 95% CI = 1.29–1.66). Hence, anxiety itself seems to increase the risk of traffic-accident related injury. During a 6-months period of therapy with a benzodiazepine anxiolytic, increased numbers of accident-related emergency outpatient visits

(OR = 2.09;95% CI = 1.27-3.42), accident-related hospital admissions (OR = 1.27; 95% CI = 0.84-1.90) and accident-related medical encounters of any type (OR = 1.15; 95% CI = 1.05-1.26) were found. The use of multiple benzodiazepines (more than three) significantly increased the risk of accident related emergency outpatient visits (OR = 3.7; 95% CI = 2.05-6.68), accident-related hospital admissions (OR = 1.8; 95% CI = 0.99-3.21) and accident-related medical encounters of any type (OR = 1.5; 95% CI = 1.30-1.67).

Ray and colleagues[12] examined the traffic accident risk in elderly drivers (>65 years old) treated with psychoactive drugs. The use of benzodiazepine drugs—including diazepam (38%), lorazepam (29%), chlordiapoxide (16%), and clorazepate (9%)—significantly increased traffic accident risk (OR = 1.5; 95% CI = 1.2-1.9). Higher dosages (comparable to diazepam >20 mg) increased traffic accident risk (OR = 2.4; 95% CI = 1.3-4.4), as did concomitant use of more than one benzodiazepine drug (OR = 4.8; 95% CI = 1.6-14.5). Traffic accident risk was also significantly increased for users of TCAs (Tri Cyclic Antidepressants) (OR = 2.2; 95% CI = 1.3-3.5), which was more profound when higher dosages were administered (OR = 5.5; 95% CI = 2.6-11.6). The use of two or more TCAs also increases traffic accident risks (OR = 9.8; 95% CI = 2.4-39.5), as did combined administration of a benzodiazepine and a TCA (OR = 2.1; 95% CI = 1.1-4.2). In contrast, Ray and colleagues did not find increased traffic accident risks for patients using antihistamines (OR = 1.2; 95% CI = 0.6-2.4) and opioid analgesics (OR = 1.1; 95% CI = 0.5-2.4).

Leveille and colleagues[13] examined traffic accident risk in elderly treated with psychotropic drugs. Benzodiazepine use—including triazolam (50%), flurazepam (27%), diazepam (9%), chlordiazepoxide (5%), and alprazolam (5%)—did not significantly increase traffic accident risk (OR = 0.9; 95% CI = 0.4-2.0). Antihistamine use also produced no significantly increased traffic accident risk (OR = 0.7; 95% CI = 0.3-1.7). In contrast, increased traffic accident risk was found for patients using TCAs (OR = 2.3; 95% CI = 1.1-4.8) and opioid analgesics (OR = 1.8; 95% CI = 1.0-3.4). Leveille and colleagues further reported significantly increased traffic accident risk when using more than one psychotropic drug (OR = 2.0; 95% CI = 1.0-4.0).

Neutel[14] selected 78.070 patients using a benzodiazepine hypnotic (triazolam or flurazepam) from the Saskatchewan Health Database. The risk of becoming injured in a traffic accident was compared with that of 97.862 healthy control subjects. Benzodiazepine users were followed for 8 weeks after treatment initiation. Fig. 1 shows the risk of becoming injured in a traffic accident when treated with a benzodiazepine hypnotic.

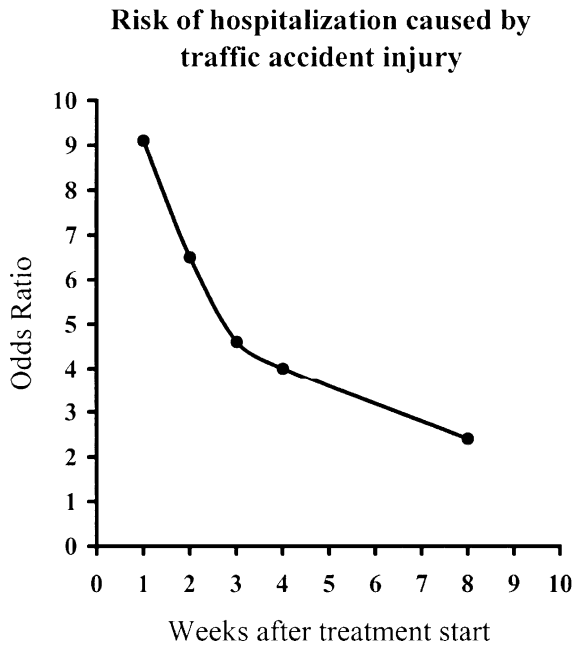

Figure 1 Traffic accident risk during daily treatment with triazolam or flurazepam (data from Ref. 14).

It is evident from Fig. 1 that the risk is highest after treatment initiation and then gradually decreases. Overall, risk of traffic accident injury for patients using benzodiazepine hypnotics was 3.9 times higher than that for the healthy control subjects.

In the same study, Neutel examined data from 147.726 users of benzodiazepine anxiolytics (oxazepam, lorazepam, and diazepam). Overall, risk of traffic accident injury for patients using benzodiazepine anxiolytics was 2.5 times higher than that for the healthy control subjects. In contrast, the use of TCAs, anticonvulsants, and antipsychotics did not significantly increase risks for traffic accident injury. When using a psychotropic drug, men were significantly more likely to become injured in a traffic accident than women, both 2 weeks (OR = 4.2; 95% CI = 2.3-7.6) and 4 weeks (OR = 3.5; 95% CI = 2.2-5.5) after treatment initiation.

Hemmelgarn and colleagues[15] examined the risk of traffic accident involvement in elderly (over 65 years old) benzodiazepine users. Those using benzodiazepines with a long half-life (clonazepam, diazepam, clorazepate, chlordiazepoxide, flurazepam, and nitrazepam) showed significantly increased accident risks within the first week after treatment initiation (OR = 1.45;

95% CI = 1.04-2.03). This increased risk was also evident after 1 year of treatment (OR = 1.26; 95% CI = 1.09-1.45). In contrast, for benzodiazepines with a shorter half-life (alprazolam, bromazepam, lorazepam, oxazepam, temazepam, and triazolam), relative risks were not significant within 1 week (OR = 1.04; 95% CI = 0.80-1.34) and after 1 year (OR = 0.91; 95% CI = 0.82-1.01).

Barbone and colleagues[16] also reported an increased traffic accident risk for benzodiazepine hypnotics (OR = 1.19; 95% CI = 0.83-170). Benzodiazepines with a half-life >24 h showed no significant increased risk (OR = 0.88; 95% CI = 0.41-1.87), as did those with an intermediate half-life of 6-24 h (OR = 1.10; 95% CI = 0.73-1.64). In contrast, benzodiazepine hypnotics with a half-life shorter than 6 h (14 cases, all zopiclone users) had a significantly increased traffic accident risk (OR = 4.00; 95% CI = 1.31-12.2). For users of benzodiazepine anxiolytics traffic accident risk was also significantly increased (OR = 2.18; 95% CI = 1.52-3.13). The use of TCAs (OR = 0.93; 95% CI = 0.72-1.21) and SSRIs (Selective Serotonin Reuptake Inhibitors) (OR = 0.85; 95% CI = 0.55-1.33) did not significantly increase traffic accident risk.

McGwin and colleagues[17] reported an increased traffic accident risk in elderly using nonsteroid anti-inflammatory drugs (NSAIDs) (OR = 1.7; 95% CI = 1.0-2.6), and angiotensin converting enzyme (ACE) inhibitors (OR = 2.6; 95% CI = 1.0-7.3). Combined use of NSAIDs and ACE-inhibitors further increased traffic accident risk (OR = 3.4; 95% CI = 1.1-10.9). In contrast, the use of benzodiazepine hypnotics (OR = 5.2; 95% CI = 0.9-30), TCAs (OR = 0.8; 95% CI = 0.2-3.0), and other drugs did not significantly increase traffic accident risk.

In conclusion, increased risk for traffic accident involvement or related injury has been reported for benzodiazepines in both young and elderly patients, but the observed accident risks depend on the specific benzodiazepine drugs that were examined. Risks tend to increase with high dosages, benzodiazepines with a long half-life, and when used in combination with other benzodiazepines or psychoactive drugs.[18] Risks may reduce during continued treatment (i.e. tolerance develops), but significantly increased risks have been reported after daily use up to 1 year in elderly.[15]

Nevertheless, results from epidemiological studies have to be interpreted with caution since they (1) generally do not take into account presumable differences in drug dosages and time after administration, (2) assume that treatments are used on a daily basis according to prescription instructions, (3) often examine hypnotics as a class and do not differentiate between individual drugs, and (4) often do not take the culpability of the driver (i.e. the responsibility for the accident) into account.[19]

This may also explain the seemingly opposite results from studies in elderly showing sometimes significantly increased risks when using benzodiazepine hypnotics[12,15] whereas other studies do not.[13,17] In these studies, benzodiazepines with a long half-life significantly increased traffic accident risks, whereas those with a short half-life did not. Unfortunately, relative risks for specific drugs are not available, except for zopiclone whose use was shown to significantly increase traffic accident risks.[16] Differences in specific drugs that were examined may also explain the opposite results for TCAs, antihistamines and opioid analgesics.

Laboratory tests

Driving is an example of complex behavior, in which many skills and abilities have to be executed simultaneously. Laboratory tests enable studying these driving-related skills under controlled and standardized conditions. Unfortunately, most test batteries comprise an ad hoc collection of not standardized and poorly documented tests that cover many areas of human psychopharmacology.[20] Laboratory tests are often chosen based upon their sensitivity to drug effects. Hence, tests that are easy applicable and of short duration are over-represented.[21] For example, the Digit Symbol Substitution Test (DSST), symbol copying, trial making test, and the Critical Flicker Fusion Test (CFFT) are among those frequently used tests. However, the relationship to driving of these tests is unclear. Other tests with a higher face validity, such as tracking tests or divided attention tests, do not cover all aspects involved in actual driving. As a result, comparative analyses show that the predictive validity to on-the-road driving of laboratory measurements greatly varies.[22-35] Thus, extrapolation of laboratory test results to actual driving ability is problematic. The explanation of this inconsistency is two-fold, and concerns both the unclear relationship between driving and the laboratory tests, as well as inadequate on-road assessments (by means of subjective assessments). Numerous studies have examined the residual effects of hypnotics on memory functioning, cognition, and psychomotor performance. Given the limitations of laboratory tests in predicting actual

driving ability, results from these studies will not be considered in this review.

Self-reports and subjective assessments of driving ability

In several studies assessments of driving ability comprised the outcome of drivers' self-reports, scoring by the experimenter, or judgments of the driving instructors. The scoring methods vary from a simple pass-or-fail judgment to complex scoring of several skills and performances during driving. It has been demonstrated repeatedly, however, that these subjective reports are inaccurate. Young drivers overestimate their driving ability and underestimate the risk of traffic accidents,[36-37] cross-cultural differences have been reported[38-39] and the accuracy of self-assessments is highly dependent on driving experience.[40] Moreover, approximately 80% of all drivers report their driving ability to be above average[41-42] or consider driving performance of others more negatively.[43] Thus, it seems that subjects are not able to judge their own and others driving ability accurately. Therefore, results from these assessments should be interpret with caution.

Closed-road driving tests and driving simulators

Driving simulators become more and more sophisticated and are often regarded as a safe alternative to test driving ability during normal traffic. Moreover, driving simulator experiments allow specific manipulations (e.g. weather conditions) to be examined during highly controlled circumstances in a similar fashion in all subjects. However, an important part of real driving is the interaction with other drivers in sometimes unexpected or even risky situations. Since both driving simulators and closed-road tests lack these elements, the validity of test results may be doubtful. Further, the tasks on closed-road circuits (e.g. maneuvering along a pilot circuit) often do not represent normal driving. It is therefore not surprising that results from closed-road studies and driving simulators are sometimes contradictory. In this context, a comparative study showed that

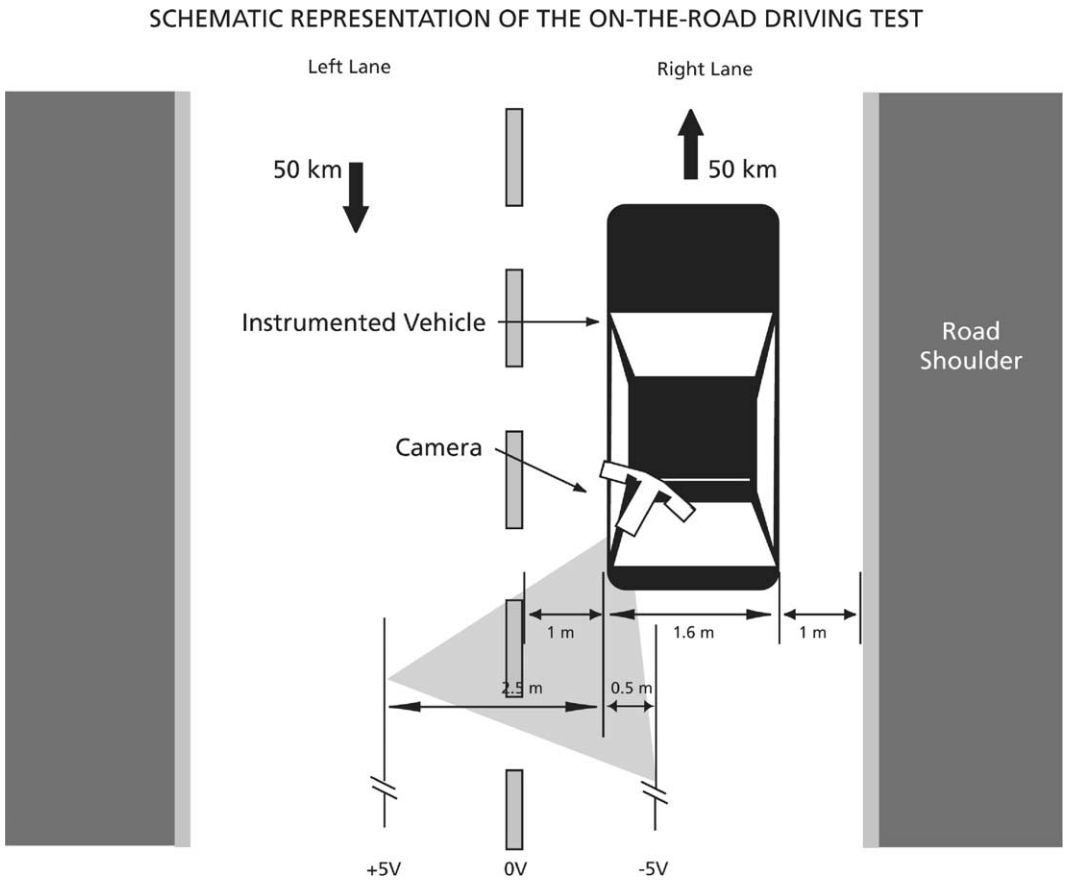

Figure 2 Schematic representation of the test vehicle. All data are continuously recorded on a board computer with a sampling rate of 2 Hz and edited off-line to remove data that were disturbed by extraneous events (e.g. overtaking, traffic jams, road maintenance).

simulator tests are not as sensitive as actual driving during normal traffic.[44] Thus, the presence of other traffic and the occurrence of unexpected events, which are sometimes regarded as problematic, in fact are necessary components of a driving test, and a prerequisite of its ecological validity. Results from simulator tests and closed-road studies should therefore be viewed primarily as supportive evidence.

On-the-road driving test

The on-the-road driving test during normal traffic,[45-46] developed in the 1980s, is the golden standard method to determine the effects of psychoactive drugs on driving ability and has been applied in over 50 studies including both healthy volunteers and patients.

Subjects are instructed to operate the instrumented vehicle with a constant speed and steady lateral position within the right (slower) traffic lane over a 100 km highway track. In the right front seat, a licensed driving instructor accompanies the subject. His job is to guard safety during the driving test. He is equipped with a brake and clutch system to intervene with the subject's driving actions if necessary.

A camera, mounted on the roof of the car, continuously records the actual position of the car within the traffic lane, by tracking the relative distance of the car from the delineated stripe in the middle of the road. This is illustrated in Fig. 2. Primary parameter is the Standard Deviation of Lateral Position (SDLP), i.e. the amount of weaving of the car. In placebo conditions, SDLP generally ranges between 18 and 22 cm. Psychoactive drug effects can elevate SDLP values to 35 cm or more. This excessive weaving results in repeated excursions out-of-lane into both the road shoulder and the adjacent traffic lane. As illustrated by Fig. 3, SDLP can thus be regarded as an index of driving safety.

The on-the-road driving test was calibrated in a study with four doses of alcohol (BAC 0.24, 0.60, 0.85 and 1.22 mg/ml) and placebo on a 25 km highway circuit.[47] According to Dutch legislative regulations that forbid driving with BAC $\geq$0.05%, the highway was closed for other traffic. Participants were instructed to drive with a steady lateral position within the right traffic lane, while maintaining a constant speed of 90 km/h. The major conclusion from this study was that SDLP is sensitive to alcohol-induced impairment in a dose-related manner. SDLP increments relative to placebo corresponding to the most commonly used BAC levels at which driving is prohibited were +2.6 cm (BAC 0.05%), +4.1 cm (BAC 0.08%) and +5.3 cm

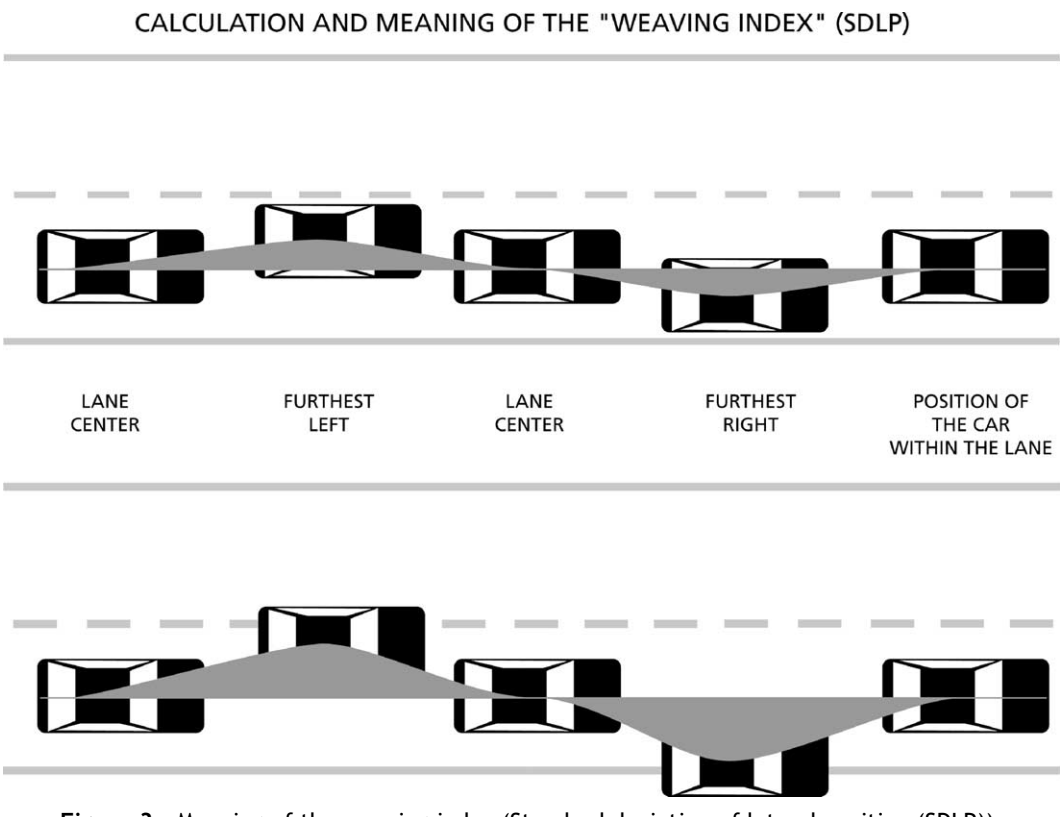

Figure 3 Meaning of the weaving index (Standard deviation of lateral position (SDLP)).

(BAC 0.10%). These SDLP values are often used as a historical control in order to comprehend the magnitude of an observed drug effect on driving ability.

Evidence from driving studies

Benzodiazepine hypnotics

Six on-the-road driving studies[46,48–51] investigated the residual effects of benzodiazepine hypnotics. The results from these studies are summarized in Table 2. Treatments were administrated at bedtime in a double blind, placebo-controlled crossover design. Driving ability was assessed 10–11 h (in the morning) and 16–17 h after administration (in the afternoon), resembling the time of day that most people travel by car towards their job and back home. An overview of SDLP differences from placebo after 2 days of nocturnal benzodiazepine treatment is shown in Fig. 4. SDLP increments after alcohol[47] are depicted as well. These levels of impairment are included for illustrative purposes, and it must be kept in mind that the SDLP increments for alcohol were found in healthy volunteers, whereas the subjects in on-the-road driving studies examining the effects of hypnotics were insomniacs.

Flurazepam

Study 1 examined the residual effects after two nights of treatment with flurazepam (15 mg and 30 mg), secobarbital (200 mg), or placebo on driving ability in 24 female healthy volunteers with a history of insomnia and hypnotic treatment.[46] All treatments significantly impaired driving performance. Driving impairment was greatest after flurazepam 30 mg and secobarbital 200 mg (a barbiturate), but also significant after flurazepam 15 mg. The magnitude of impairment was illustrated by the fact that some of the subjects were unable to complete their driving test after flurazepam 30 mg (three subjects) and secobarbital 200 mg (two subjects). Performance impairment was most pronounced in the morning session. Four subjects also participated in a sub-chronic experiment comparing flurazepam 30 mg with placebo. After 8 days of treatment, flurazepam 30 mg significantly impaired driving performance. Similar impairment was found for flurazepam 30 mg in Study 5, after two, four and seven subsequent treatment nights.[50] Driving impairment was most pronounced in the morning tests (comparable to BAC $>$ 0.10%), but also seriously impaired in the afternoon (comparable to BAC $>$0.08%).

Performance in a driving simulator was also significantly impaired the morning following bedtime administration of flurazepam (30 mg).[52]

Loprazolam

In Study 2, driving after loprazolam 1 mg was significantly impaired in the morning test, but this effect did not reach significance in the afternoon.[46]

Table 2 Results from on-the-road driving studies with benzodiazepine hypnotics.

	Ref.	Subjects	Nights	Treatment	10–11 h	16–17 h
1	46	24 Females[a]	2	Flurazepam 15 mg	*	*
				Flurazepam 30 mg	*[b]	*[b]
				Secobarbital 200 mg	*	*
2	48	16 Females[a]	2	Loprazolam 1 mg	*	ns
				Loprazolam 2 mg	*	*
				Flunitrazepam 2 mg	*	*
3	48	16 Females[a]	2	Zopiclone 7.5 mg	*	ns
				Nitrazepam 5 mg	ns	ns
				Flunitrazepam 2 mg	*	*
4	49	12 females[a]	2	Temazepam 20 mg (caps.)	ns[b]	ns[b]
				Nitrazepam 10 mg	*[b]	*[b]
5	50	16 Females[a]	2	Lormetazepam 1 mg (caps.)	ns[c]	ns[c]
				Lormetazepam 2 mg (caps.)	ns[c]	ns[c]
				Flurazepam 30 mg	*[d]	*[d]
6	51	18 Males	2	Lormetazepam 1 mg (tabs.)	*	ns
				Oxazepam 50 mg	*	ns

Ref., reference number; *significantly different from placebo ($p < 0.05$); ns, not significant.
[a] Subjects had a history of insomnia and were experienced with benzodiazepine hypnotic treatment.
[b] Also significant after seven treatment nights ($n = 4$).
[c] No significant impairment after four and seven treatment nights.
[d] Significant impairment after four and seven treatment nights.

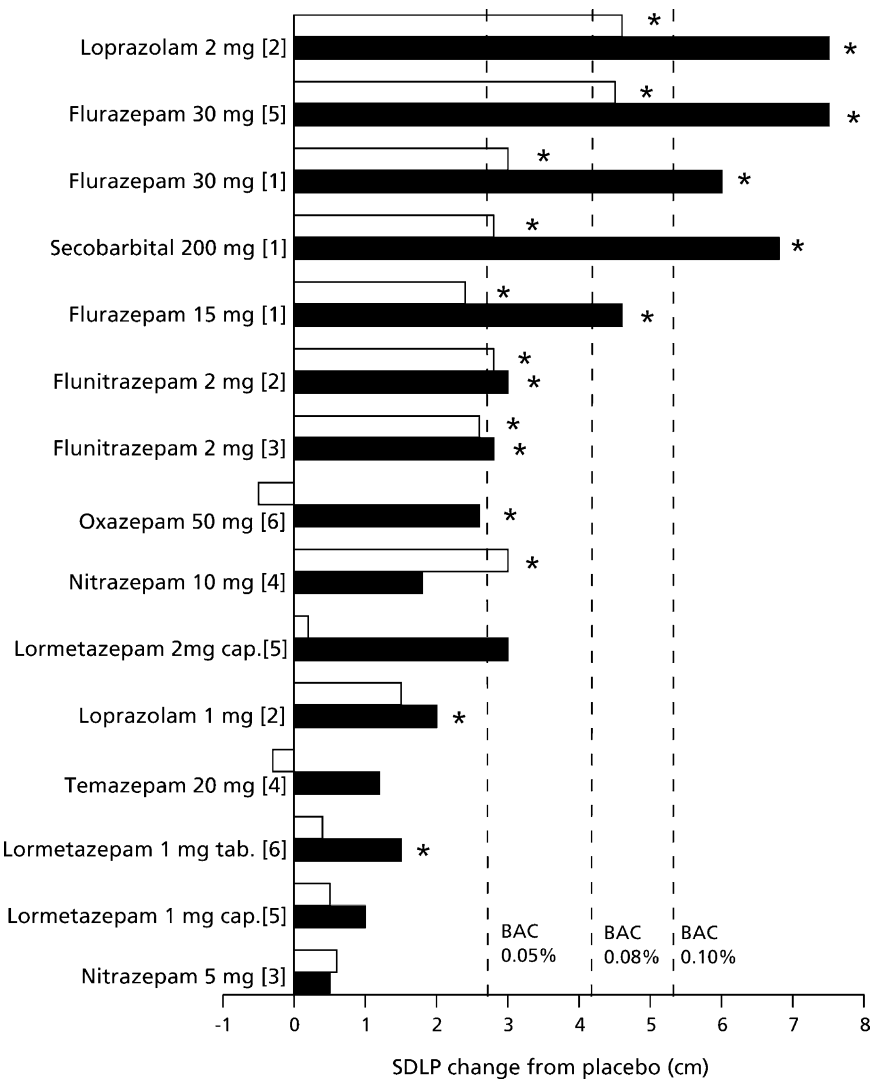

Figure 4 Effects of benzodiazepine hypnotics on actual driving determined after two successive treatment nights. SDLP changes from placebo (cm) are shown for the morning test sessions (10–11 h after bedtime administration; black bars) and the afternoon test sessions (16–17 h after bedtime administration; open bars). Significant differences from placebo are indicated by (*). BAC, blood alcohol concentration, cap., capsules, tab., tablets, Study numbers[1–6] are shown between brackets.

On both occasions driving impairment was less than that observed with BAC 0.05%. Loprazolam 2 mg (twice the recommended dose) significantly impaired driving performance during both morning and afternoon driving tests. The magnitude of impairment in the morning was comparable to a BAC well above 0.10%, and in the afternoon impairment was still at a magnitude comparable to that observed with a BAC of 0.10%.

Flunitrazepam

Flunitrazepam (2 mg) significantly impaired driving performance during both morning and afternoon driving tests, comparable to BACs between 0.05 and 0.08% (Study 2).[46] These results were replicated in a subsequent study (Study 3),[48] which was also performed in healthy female volunteers with a history of insomnia and benzodiazepine treatment. In contrast, in Study 7, after one treatment night no significantly impaired driving performance was found 10–11 h after bedtime administration of flunitrazepam 2 mg. SDLP increment relative to placebo was only 0.3 cm.[53] According to the authors, driving impairment after two treatment nights may be more pronounced because of the presence of accumulated active metabolites of flunitrazepam. However, a driving simulator study[54] and an on-road study examining speed, lateral acceleration and steering velocity[55] all reported significant impairment the morning

following bedtime administration of flunitrazepam (1–2 mg).

Lormetazepam

Study 5 investigated the repeated dose effects of lormetazepam (1 and 2 mg soft gelatine capsules) in 16 healthy women with a history of insomnia and benzodiazepine treatment.[50] Lormetazepam did not significantly impair driving ability after two, four and seven treatment nights, but individual SDLP increments were reported comparable to those observed with BACs higher than 0.05% (+4.6 cm for the 1 mg dose) and 0.08% (+10.3 cm for the 2 mg dose). There were no differences with placebo in the afternoon driving test. In 18 healthy male volunteers after one and two nights of lometazepam administration (1 mg tablets) driving impairment was significant in the morning sessions (comparable to BAC <0.05%), but not in the afternoon (Study 6).[51] However, in this study the impairing effects were not observed in the driving simulator. The different results obtained in Studies 5 and 6 presumably reflect the differences in formulation (capsules versus tablets) and study population (women versus men).

A recent driving simulator study failed to find significant impairment the morning following three nights of lormetazepam (1 mg) treatment in 12 healthy volunteers.[56] Additional tests assessing memory, attention, and simple and complex reaction speed also showed no significant performance impairment. This showed to be different when testing takes place immediately after administration. For example, a daytime study examining the acute effects of lormetazepam (2 mg) in a driving simulator within 3 h after administration reported significant performance impairment.[57] Performance was further worsened by co-administration of alcohol.

Nitrazepam

Nitrazepam (5 mg) did not significantly impair driving ability in 16 females with a history of insomnia and benzodiazepine treatment (Study 3).[48] After two nights of nitrazepam 10 mg driving was significantly impaired, comparable to that observed with BACs between 0.05 and 0.08% (Study 4).[49] However, after four and seven nights of nitrazepam (10 mg), driving performance was not significantly impaired. This illustrates that driving impairment depends both on the administered dosage and the duration of treatment. Interestingly, in contrast to common observations that driving performance is most impaired in the morning session in both studies driving impairment was most pronounced during the afternoon driving tests.

In 18 healthy volunteers, performance on a monotonous driving simulator test was significantly impaired the morning following one night of nitrazepam (5 mg) administration.[58–59] Auditory reaction speed was significantly slowed, whereas 'time outside the road' was not. After three nights of treatment performance impairment did not reach significance. In a closed-road driving test (obstacle avoidance maneuvers) performed by the same subjects after one and three nights, performance impairment did not reach significance.[59]

Temazepam

Driving performance was not significantly impaired after two, four and seven successive nights of temazepam 20 mg administration (Study 4).[49] In line, another on-the-road study[55] in 16 outpatients with insomnia reported improved driving performance after one and seven nights of temazepam treatment (20 mg). In a closed road study in 12 healthy female subjects, performance was tested 12 h after bedtime administration of temazepam 20 mg. Weaving between bollards was not significantly impaired, but maneuvering along a circuit with passable and non-passable gaps resulted in a significantly increased number of side-hits.[60]

Triazolam

Triazolam has not been studied on-the-road during normal traffic. In a driving simulator and a closed-road test, triazolam (0.25 mg) did not significantly impair performance the morning following one and three nights of bedtime administration in healthy volunteers.[59] However, triazolam has been found in blood samples from drivers involved in traffic accidents.[61]

Brotizolam

Brotizolam has not been tested on-the-road during normal traffic. In a monotonous simulated driving test, the morning following three nights of administration of brotizolam (0.25 mg), performance (reaction speed and time outside the road) was not significantly impaired.[58] Immediately after acute intake on the first night, brotizolam significantly reduced reaction speed, but time outside the road did not differ from placebo.

Benzodiazepine anxiolytics

Experimental research on benzodiazepine anxiolytics is generally limited to daytime administration. Studies examining their residual effects after bedtime administration are scarce or absent.

Diazepam

On-the-road driving performance was significantly impaired in 10 professional drivers, 1–2 h after administration of diazepam (10 mg), comparable to impairment observed with a BAC above 0.15%.[45] In anxious outpatients, daily administration of diazepam (5 mg tid) showed similar impairment in week 1. Tolerance to driving impairment developed slowly and driving was significantly impaired after 3–4 weeks of daily treatment.[62]

Alprazolam

On-the-road driving performance was significantly impaired in 20 healthy volunteers 1 h after acute administration of alprazolam (1 mg).[63] Serious loss of vehicle control was expressed in both significantly increased SDLP and speed variability. Impairment in six of these subjects resulted in unsafe driving behavior including repeated excursions out-of-lane into both the adjacent traffic lane and the road shoulder. During their test they fell asleep, and their driving test was terminated before completion.

Lorazepam

In anxious outpatients, driving performance was seriously impaired when treated with lorazepam (2 mg bid). SDLP increments, relative to placebo, were +18 cm on day 1 and +10 cm on day 8.[64] Similar impairment was reported in 18 healthy male volunteers after 7 days of lorazepam treatment (1.5 mg bid).[65]

Oxazepam

In 18 healthy male volunteers, oxazepam (50 mg) significantly impaired on-the-road driving performance after one treatment night (Study 6).[51] Similar driving impairment was found in the morning test session after two treatment nights; comparable to impairment found with BACs between 0.05 and 0.08%. The same subjects also performed a test in a driving simulator. No impairment was found on this test. In the afternoon tests driving performance was not affected by oxazepam.

Antidepressants

Doxepine, amitriptyline and trazodone are sedative antidepressants. When taken at bedtime they successfully initiate sleep. Doxepine (25 mg t.i.d.) significantly impaired on-the-road driving performance on day 1. After 8 days of treatment, these depressive patients showed no significant driving impairment.[66] Amitriptyline (25 mg in the morning and 50 mg at bedtime for 8 days) produced significant driving impairment 1.5 h after administration of the morning dosage on Day 1. After 8 days of treatment, driving performance was not significantly impaired.[67]

No on-the-road driving studies have been performed with trazodone. Since trazodone is often used for hypnotic purposes, future studies should determine its effects on driving ability.

Non benzodiazepine hypnotics

Zopiclone

After two nights of nocturnal treatment in sixteen female healthy volunteers with a history of insomnia zopiclone (7.5 mg) significantly impaired driving performance during the morning session, but not in the afternoon (Study 3).[48] Driving impairment 10–11 h after administration was comparable to that observed with BACs between 0.05 and 0.08%. In 28 healthy volunteers driving impairment was also pronounced after one night of treatment administration (Study 8): 11 and 6 h after bedtime administration zopiclone (7.5 mg) produced significant SDLP increments of +5.0 and +8.25 cm, respectively, corresponding to BACs of 0.10% and higher.[68] A subsequent study (Study 9) in 30 healthy volunteers found similar impairment 10 h after bedtime administration of zopiclone (7.5 mg).[69] In comparison to an afternoon driving test to examine the effects of alcohol (BAC <0.05%) mean SDLP elevation after zopiclone was twice the magnitude of that observed with alcohol.

In a driving simulator, 16 healthy volunteers performed a 90 min test, 10 and 12 h after bedtime administration of zopiclone (7.5 mg).[54] They were instructed to drive with a steady lateral position, and as quickly as possible along the virtual road. SDLP and speed variability were determined. SDLP was significantly increased 10 h after intake, but speed variability was not. Twelve hours after zopiclone administration, these effects were not significant.

Zolpidem and zaleplon

Design and results from on-the-road driving studies examining zolpidem and zaleplon are summarized in Table 3.

Zolpidem

In 17 female subjects with a history of insomnia and benzodiazepine use, driving was not significantly impaired 10–11 h after one night of bedtime treatment with zolpidem 10 mg (Study 7).[53] Also, the morning following bedtime administration no significant performance impairment has been reported in a driving simulator.[54] Thus, in contrast to the benzodiazepine hypnotics and zopiclone, driving the morning following bedtime administration of the recommended dose of zolpidem seems safe.

Table 3 Results from on-the-road driving studies with zaleplon and zolpidem.

Study	Ref.	Subjects	Nights	Treatment	4–5 h	5–6 h	10–11 h
7	53	17 Females[a]	1	Zolpidem 10 mg	-	-	ns
				Flunitrazepam 2 mg	-	-	ns
				Partial sleep deprivation	-	-	ns
8	68	28 Male/female	1	Zaleplon 10 mg	-	ns	ns
				Zaleplon 20 mg	-	ns	ns
				Zopiclone 7.5 mg	-	*	*
9	69	30 Male/female	1	Zaleplon 10 mg	-	-	ns
				Zopiclone 7.5 mg	-	-	*
10	70	30 Male/female	1	Zaleplon 10 mg	ns	-	-
				Zaleplon 20 mg	ns	-	-
				Zolpidem 10 mg	*	-	-
				Zolpidem 20 mg	*	-	-

Ref., reference number; *significantly different from placebo ($p < 0.05$); ns, not significant; -, not tested.
[a] Subjects had a history of insomnia and were experienced with benzodiazepine hypnotic treatment.

However, middle-of-the-night administration of zolpidem produced significant and dose-dependent driving impairment (Study 10).[70] In 30 healthy volunteers, SDLP was significantly elevated after both zolpidem 10 mg (+4 cm) and zolpidem 20 mg (+11 cm), comparable to BACs exceeding 0.08 and 0.10%, respectively. Three female subjects had to terminate their driving test before completion after zolpidem (20 mg). Thus, middle-of-the-night administration of zolpidem is not recommended.

Zaleplon

In 28 healthy volunteers, driving performance was not significantly impaired 6 and 11 h after a single night administration of zaleplon 10 mg (the recommended dose) and zaleplon 20 mg (Study 8).[68] A subsequent study by these authors again showed no significant driving impairment 10 h after bedtime administration of zaleplon 10 mg (Study 9).[69] Thus, driving the day following bedtime administration of zaleplon can be regarded safe.

In addition, zaleplon 10 and 20 mg did not significantly impair driving ability 4 h after middle-of-the night administration in 30 healthy volunteers (Study 10).[70]

Discussion

Knowledge of the residual effects of hypnotics on driving ability is of great importance, since these drugs are among the most frequently used psychoactive medications. Moreover, driving is a common daily activity. Unfortunately, residual effects of hypnotics such as sleepiness and reduced alertness may limit the capability of operating a vehicle. The primary evidence presented in this review comes from on-the-road driving tests. The fact that these standardized tests are conducted during normal traffic greatly enhances their ecological validity. Supportive evidence was obtained from epidemiological studies, driving simulators and closed-road driving studies.

The results from these different lines of evidence showed that all benzodiazepine hypnotics produced next-day sedative effects. On-the-road driving studies revealed that they may impair driving performance during the day up to 17 h after bedtime administration, whereas other benzodiazepines produced significant driving impairment only in the morning session (Table 2).

Half-life

Benzodiazepines with a long half-life (>24 h) showed the most pronounced impairment during on-the-road driving studies. When compared to observations made with different levels of blood alcohol, SDLP increments found with these hypnotics often exceed these most common legal limits for driving. The magnitude of impairment was greatest during the morning hours following bedtime administration, but also present in the afternoon. Results from laboratory tests were consistent with the observations during actual driving. Also, epidemiological data revealed that in both young and elderly users of benzodiazepine hypnotics with a long half-life traffic accident risks were significantly increased.

In contrast, traffic accident risks were not significantly increased for benzodiazepines with a short half life (<8 h). This was also expressed by the results from on-the-road driving studies: SDLP increments were less pronounced, and differences from placebo did not always reach significance. In laboratory tests it often depended on the specific

memory or psychomotor tests that were conducted whether impairment reached significance or not.

Dosage

Performance impairment (both on-the-road as well as in the laboratory) showed to be dose-depended. That is, performance worsens in a dose-dependent manner. Whereas the recommended dose may not significantly impair driving ability, administration of twice the recommended dose may show severe driving impairment. For example, note the difference between the effects of 5 and 10 mg nitrazepam on driving performance.

The impact of dosage on the magnitude and duration of impairment is important to address since in real life, many patients use higher dosages than recommended. In this context it has been shown that substantial number of arrested drivers or those involved in traffic accidents show high blood concentrations of benzodiazepines.[71–72] In addition, in the blood of drivers arrested for showing dangerous or impaired driving behavior high concentrations (multiple times the recommended dose) of zaleplon[73] and zolpidem[74] have been detected as well. Thus, patients that do not comply with treatment instructions are at increased risk of becoming involved in traffic accidents.

Time after administration

On-the-road driving research showed that performance impairment becomes less pronounced during the day following administration. Driving was often not significantly affected during the afternoon driving tests (16–17 h after administration), whereas in the morning driving was unsafe and significantly impaired (Fig. 4). However, not all hypnotics show this pattern of impairment. For example, impairment with nitrazepam was more pronounced in the afternoon than during the morning tests.

Tolerance

Impairment was most pronounced after treatment initiation. During repeated daily use, tolerance develops to the performance impairing effects of hypnotics. Driving studies show that impairment is most pronounced after one or two nights of administration. Thereafter, impairment is less pronounced or may not reach statistical significance. However, tolerance develops slowly, and significantly impaired driving performance has been reported up to several weeks after treatment initiation.[63] Epidemiological evidence also point at the persistent increased risk of becoming involved in traffic accidents when treated with benzodiazepine hypnotics. Even 1 year after treatment initiation, the risk was found to be significantly increased for benzodiazepines with a long half-life.[15] The latter observation suggests that although driving impairment becomes less pronounced during chronic treatment, tolerance is only partial. When patients use hypnotics as needed (e.g. not on a daily basis), it may be expected that tolerance to their residual effects will develop even slower, if at all.

Individual differences

It should be taken into account that the results from all studies discussed in this review concern differences between average performance scores of groups of subjects. However, individual performance may differ significantly from the group average. For example, all driving studies with benzodiazepine hypnotics reported individual differences in driving performance. That is, driving ability of some subjects showed only slight differences from placebo after treatment with a benzodiazepine drug, whereas others showed marked driving impairment sometimes resulting in termination of a driving test before completion. Individuals that experience serious performance impairment are not clearly reflected by the group average. For example, lormetazepam 2 mg showed only moderate non-significant SDLP increment relative to placebo (overall SDLP increment of 2–3 cm), whereas some individuals showed SDLP elevations up to 10 cm (Study 5).[50]

Patients versus healthy volunteers

Driving studies do not show great differences in performance effects observed in patients of healthy volunteers. However, it has been suggested that effects of insomnia itself (i.e. reduced daytime alertness) may impair skills related to driving. Hence, it may be expected that efficient hypnotics should have a beneficial effect on daytime performance since sleep quality is significantly improved during treatment. This beneficial effect may then (partly) counteract the performance impairment observed in healthy volunteers.

For example, shift working may benefit from hypnotics to promote sleep during daytime. Without the aid of hypnotics, reduced sleep quality and sleep duration have been reported that may affect performance after awakening. Relative to placebo, improved daytime sleep duration, sleep quality and psychomotor performance was reported for

temazepam,[75-77] zopiclone[78-79] and zolpidem.[80] Also, in people traveling across time zones, psychomotor performance was not significantly affected by temazepam, whereas sleep quality and duration was significantly improved.[81-82] No on-the-road driving studies have been performed after daytime sleeping, with or without the aid of hypnotic drugs.

Gender differences

It has been shown repeatedly that women are more sensitive to the effects of benzodiazepine hypnotics than men. Differences in sensitivity between men and women were also found for zolpidem.[83]

As illustrated by Fig. 5, zolpidem produced large individual differences in driving performance. Especially women drove worse after zolpidem, and three driving tests were terminated before completion since subjects fell asleep while driving.[70] These findings illustrate the importance of including both men and women in future driving studies.

Age

In contrast to the fact that most people that suffer from insomnia are elderly, the majority of experimental studies are conducted in healthy young volunteers. When compared to young healthy volunteers, in elderly the residual effects of hypnotic drugs are generally more pronounced. Up to now, no direct comparisons between young and elderly have been made examining the effects of hypnotics on on-the-road driving performance. On first sight, epidemiological evidence seems to suggest increased traffic accident risks in elderly using benzodiazepine hypnotics. However, not all studies in elderly reported significantly increased traffic accident risks,[13,17] and differences between young and elderly drivers may be caused by differences in the examined drugs (long versus short half-life) in these studies.

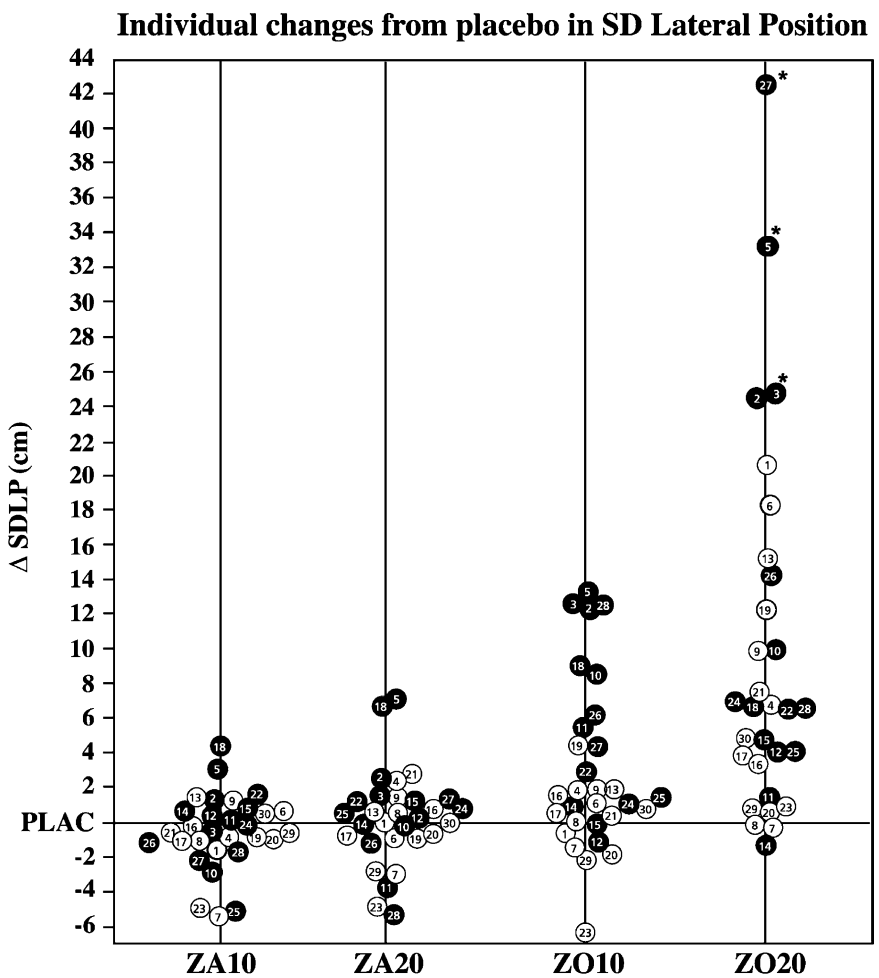

Figure 5 Individual SDLP (differences from placebo, ΔSDLP) for each subject in each condition. ((○) men, (●) women, (*) terminated before completion of the driving test). PLAC, Placebo; ZA10, Zaleplon 10 mg; ZA20, Zaleplon 20 mg; ZO10, Zolpidem 10 mg; ZO20, Zolpidem 20 mg.

Zopiclone

From the point of view of driving safety, the introduction of zopiclone as a hypnotic was not a relevant step forwards. Like benzodiazepines, the use of zopiclone must be limited to bedtime administration. Epidemiological evidence showed that patients using zopiclone have a significantly increased traffic accident risk.[16] Further, three on-the-road driving studies[48,68-69] and a driving simulator study[54] consistently showed significant driving impairment the morning following bedtime administration of zopiclone. Patients using zopiclone should therefore be cautioned not to drive a car, especially during morning hours.

Zolpidem and zaleplon

On-the-road driving studies showed that both zolpidem and zaleplon produce no significant performance impairment the morning following bedtime administration. In contrast to benzodiazepines and zopiclone, driving seems safe the morning following bedtime administration of the recommended dose of zolpidem and zaleplon. In addition, driving a car was also safe as shortly as 4 h after middle-of-the-night administration of zaleplon, but not after zolpidem.[70]

Currently, there is no epidemiological data available to support the experimental findings with zolpidem and zaleplon. However, based upon the consistent test results showing the absence of significant driving impairment, and the fact that both hypnotics possess a relatively short half-life, increased traffic accident risks are unlikely when used as recommended.

Practice points

- All benzodiazepines impair driving performance, but the magnitude of impairment depends on the administered dosage, half-life, and time after administration
- Regarding driving safety, zopiclone has no advantages over the benzodiazepines
- Driving after zolpidem 10 mg is safe when administered at bedtime
- Driving after zaleplon (10 and 20 mg) is safe after bedtime and middle-of-the-night administration (as shortly as 4 h before driving)

Research agenda

- Future studies should focus on individually tailored dosages administered on an as-needed basis when symptoms occur during the night
- Long-term effects on driving ability of daily use of zolpidem and zaleplon should be studied in the patient population
- The effects of zaleplon and zolpidem should be confirmed in the intended patient population (elderly)
- Gender differences of hypnotics on driving performance should be studied in more detail

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