Hypnotics and Driving Safety: Meta-Analyses of Randomized Controlled Trials Applying the on-the-Road Driving Test

Joris C. Verster[*,1], Dieuwke S. Veldhuijzen[1], Alain Patat[2], Berend Olivier[1] and Edmund R. Volkerts[1]

[1]*Utrecht Institute for Pharmaceutical Sciences, Department of Psychopharmacology, University of Utrecht, PO BOX 80082, 3508 TB, Utrecht, The Netherlands*

[2]*Wyeth Research, Clinical Pharmacology, Paris, France*

Abstract: *Background:* Many people who use hypnotics are outpatients and are likely to drive a car the day after drug intake. The purpose of these meta-analyses was to determine whether or not this is safe.

Methods: Placebo-controlled, randomized, double-blind trials were selected if using the on-the-road driving test to determine driving ability the day following one or two nights of treatment administration. Primary outcome measure of the driving test was the Standard Deviation of Lateral Position (SDLP); i.e., the weaving of the car. Fixed effects model meta-analyses were performed. Effect size (ES) was computed using mean standardized (weighted) difference scores between treatment and corresponding placebo SDLP values.

Results: Ten studies, published from 1984 to 2002 (207 subjects), were included in the meta-analyses. 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 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). Zopiclone 7.5 mg also impaired driving in the morning (ES=0.89; CI=0.54 to 1.23). Zaleplon (10 and 20 mg) and zolpidem (10 mg) did not affect driving performance the morning after dosing. Following middle-of-the-night administration, significantly impaired driving performance was found for zopiclone 7.5 mg (ES=1.51, CI=0.85 to 2.17), zolpidem 10 mg (ES=0.66, CI=0.13 to 1.19) and zolpidem 20 mg (ES=1.16, CI=0.60 to 1.72). Zaleplon (10 and 20 mg) did not affect driving performance.

Conclusions: The analyses show that driving a car the morning following nocturnal treatment with benzodiazepines and zopiclone is unsafe, whereas the recommended dose of zolpidem (10 mg) and zaleplon (10 mg) do not affect driving ability.

Keywords: Driving, hypnotics, benzodiazepines, zopiclone, zolpidem, zaleplon.

INTRODUCTION

Insomnia not only comprises sleep initiation problems, but also nightly and early morning awakenings. The majority of patients suffering from insomnia is treated in an outpatient setting and continue their daily activities, including driving a car.

Several surveys illustrate that insomnia must be viewed as a major public health problem. For example, according to the 2002 Sleep in America poll, 37% of adults reported that daytime sleepiness interferes significantly with their daily activities [1]. Also, the National Sleep Foundation Gallup Survey revealed that 63 million adults have sleep levels considered hazardous to their well being, with 6% experiencing severe levels of sleepiness [2-3]. Benzodiazepine hypnotics are still the most commonly used psychoactive drugs to treat insomnia, but the use of so-called z-drugs (zopiclone, zolpidem and zaleplon) is rapidly increasing. This shift was initiated by the observation that benzodiazepines produce residual effects such as daytime sleepiness and reduced alertness, whereas the ideal hypnotic should be devoid of these potentially performance-impairing adverse effects. Since most hypnotics are prescribed to outpatients that fully participate in society, much research has focused to examine the possible residual effects of hypnotics on daily activities such as driving a car.

In the 1980s, the on-the-road driving test was introduced to examine drug effects on driving ability [4]. Since this standardized driving test is conducted on a public highway during normal traffic, it is evident that this test has a high ecological validity relative to driving simulators and laboratory tests [5].

Recently, a systematic review was published summarizing the results from studies that examined the effects of hypnotics on driving ability using the on-the-road driving test [6]. The disadvantage of systematic reviews is that results from individual studies are discussed based upon their statistical significance. This may be misleading, since studies with small sample sizes may present data (drug-versus-placebo differences) that are conflicting with those from larger studies. Nevertheless, these differences may be meaningful, and including small studies in a meta-analysis may change an overall conclusion based upon large studies only. Combining the results from a number of smaller studies in a meta-analysis will take into account the observed

*Address correspondence to this author at the Utrecht Institute for Pharmaceutical Sciences, Department of Psychopharmacology, University of Utrecht, PO BOX 80082, 3508 TB, Utrecht, The Netherlands; Tel: +31 30 253 6909; Fax: +31 30 253 7387; E-mail: j.c.verster@pharm.uu.nl

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effects, weighing them for their effect size, and produce a synthesized effect estimate with considerable power [7].

Based upon the conclusions from our recent literature review [6], a series of meta-analyses was conducted to test the following hypotheses:

1. Do hypnotics impair driving ability in the morning (10 – 11 hours after bedtime administration)?
2. Do hypnotics impair driving ability in the afternoon (16 – 17 hours after bedtime administration)?
3. Do hypnotics impair driving ability in the morning, (4 – 6 hours after middle-of-the-night administration)?

To address these hypotheses, different meta-analyses were performed for:

1. benzodiazepines (recommended dose, or twice the recommended dose)
2. zopiclone (recommended dose, 7.5 mg)
3. zolpidem (recommended dose, 10 mg, or twice the recommended dose, 20 mg)
4. zaleplon (recommended dose, 10 mg, or twice the recommended dose, 20 mg)

METHODS

Literature Search and Study Selection

A literature search including MEDLINE and EMBASE was performed (key words: *driving*, combined with *hypnotic*, *benzodiazepine*, *zaleplon*, *zopiclone*, *zolpidem*) and cross-references were consulted to determine all studies examining the effects of hypnotics on driving ability. Studies were selected if the following inclusion criteria were met: (1) the on-the-road driving test was used to determine driving ability, (2) the study was placebo controlled, crossover and double-blind, (3) tests were performed the day following one or two nights of treatment administration, (4) treatments were administered at bedtime or during the night, (5) subjects were healthy volunteers (with or without a history of transient insomnia), and (6) subjects did not use hypnotics or other drugs that are known to affect driving ability at the time of study participation.

The on-the-Road Driving Test

All studies used the same standardized on-the-road driving test during normal traffic (see Fig. **1**) [6]. Subjects are instructed to drive a car over a public highway circuit (usually 100-km) with a constant speed (90 - 95 km/h) and a steady lateral position within the right (slower) traffic lane. A licensed driving instructor who is equipped with dual controls accompanies the subject to guard his/her safety. The primary parameter of the test is the Standard Deviation of Lateral Position (SDLP, cm), the weaving of the car.

From Fig. **1** (top), it can be seen that twice a second the lateral position of the car relative to the lane boundary is recorded. Then, over the 100 km test, the overall mean lateral position is computed (Fig.**1**, middle). The standard deviation of the mean lateral position is the SDLP. From Fig. **1** (bottom) it is evident that SDLP represents the amount of vehicle control. Highly elevated SDLP (gross weaving of the car) may result in excursions out of lane, both into the road shoulder and/or the adjacent traffic lane. Hence, high SDLP values represent unsafe driving behavior.

A closed road study to calibrate the on-the-road driving test methodology showed that most participants had an SDLP value between 18 and 22 cm in the placebo condition [8]. For different dosages of alcohol, SDLP increments were observed in a dose-related manner. An SDLP increment of 2.4 cm, found after administration of alcohol to reach a blood alcohol concentration of 0.05% (the legal limit for driving in most countries), is considered as a clinical relevant change from baseline (placebo).

Statistical Analysis

Statistical analyses were performed using *Comprehensive Meta-analysis*, a computer program for research synthesis [9]. The effect size (ES) for each treatment-versus-placebo comparison was calculated, using standardized mean SDLP differences. That is, when computing the effect size, SDLP differences between treatment and placebo were weighted according to the number of subjects that participated in each study. In addition, the ninety-five percent confidence interval (95% CI) was computed for each ES. If the confidence interval does not include zero, the ES is statistically significant.

First, because the unit of analysis in a meta-analysis is the individual research study, in each meta-analysis only one treatment-versus-placebo comparison was included from each study (Comparisons that come from the same study are statistically dependent). Second, the aim was to include a specific treatment-versus-placebo comparison only once in each analysis. Thus, for example, a second lormetazepam-versus-placebo comparison was not included when a unique oxazepam-versus-placebo comparison could be included.

Homogeneity/heterogeneity analyses were performed to determine if all individual ES have the same distribution as the combined overall ES. In a homogenous distribution, the dispersion of effect sizes around their mean is not greater than that expected from sampling error alone. If the Q statistic resulting from this analysis is not significant ($p > 0.05$), a homogenous distribution can be assumed and using a fixed effects model to perform the meta-analysis is justified. However, if the Q statistic is significant ($p < 0.05$), variation in effect size is greater than would be expected from subject-level sampling error alone, and a random effects model should be applied correcting for additional variation between the studies [7].

RESULTS

Selected Studies and Subjects

Ten studies [10-18] (labeled Study 1-10 in the text and Tables) were identified that met all inclusion criteria for the meta-analyses. Study characteristics are summarized in Table **1**.

All on-the-road driving studies have been performed in The Netherlands (Universities of Groningen, Maastricht or Utrecht). Six studies [10-14] (Study 1-6) were performed in the 1980s and examined the effects of benzodiazepines and zopiclone after two nights of bedtime administration. Three studies [15-17] (Study 7-9) examined the effects of

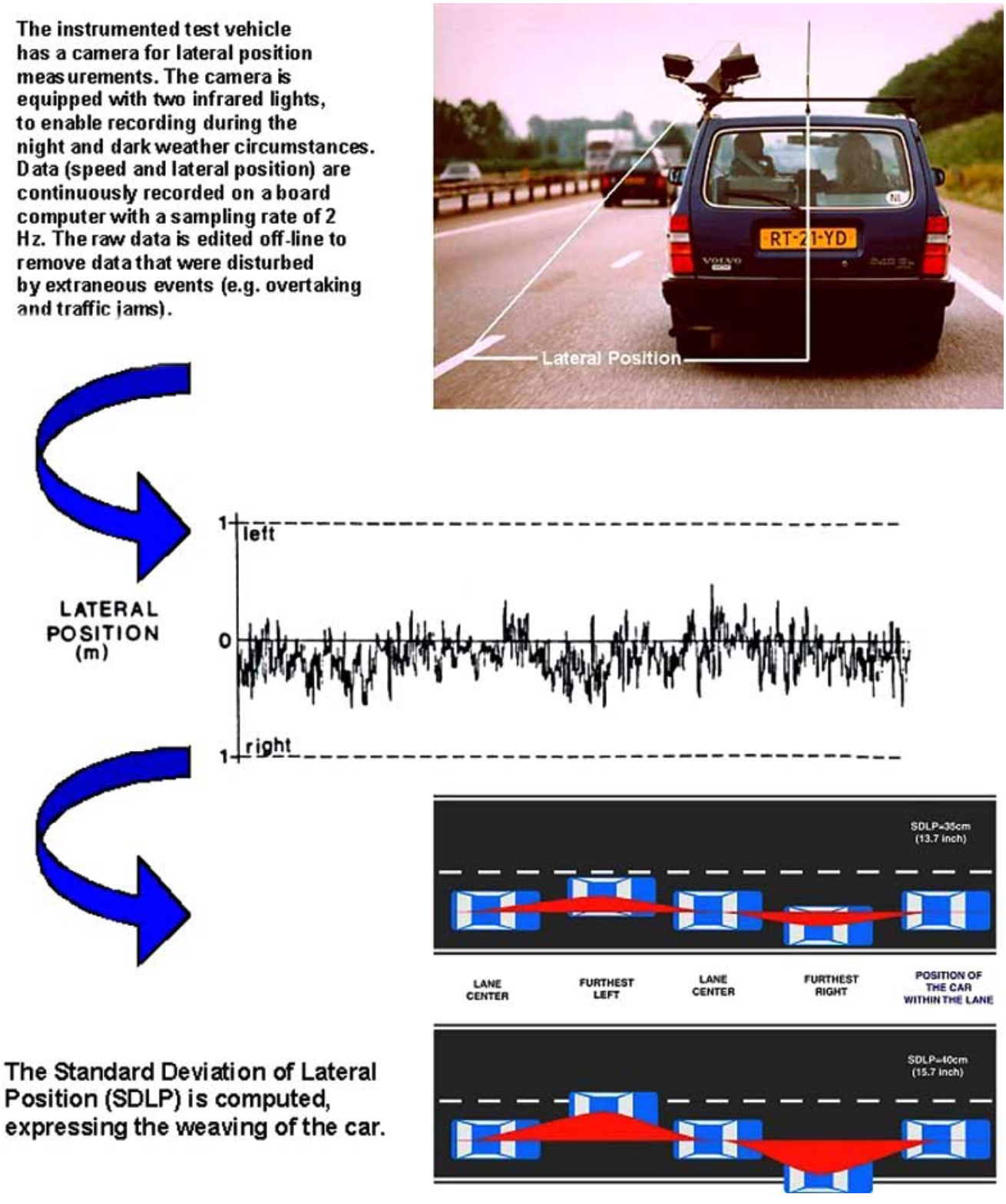


Fig (1). The on-the-road driving test.

Table 1. Study Characteristics

Study [ref.]	Subjects	Age (SD)	Nights	Treatment	Outcome
1 [10]	24 women with a history of insomnia and hypnotic treatment	28.6 (4.0)	2	flurazepam 15 en 30 mg secobarbital 200 mg placebo	SDLP was significantly increased after flurazepam (15 and 30 mg) and secobarbital 10-11h and 16-17h after administration.
2 [10,19]	16 women with a history of insomnia and hypnotic treatment	28.7 (4.8)	2	loprazolam 1 and 2 mg flunitrazepam 2 mg placebo	SDLP was significantly increased 10-11h and 16-17h after Flunitrazepam and loprazolam 2 mg administration. Loprazolam 1 mg significantly increased SDLP 10-11h after administration, but not in the afternoon.
3 [11]	16 women with a history of insomnia and hypnotic treatment	29.1 (4.7)	2	zopiclone 7.5 mg nitrazepam 5 mg flunitrazepam 2 mg placebo	SDLP was significantly increased 10-11h and 16-17h after Flunitrazepam 2 mg. SDLP was significantly increased 10-11h after zopiclone 7.5 mg administration, but not in the afternoon. Nitrazepam 5 mg did not impair driving ability.
4 [12,20]	12 women with a history of insomnia and hypnotic treatment	32.9 (3.8)	2	temazepam 20 mg (caps.) nitrazepam 10 mg placebo	Temazepam did not significantly impair driving ability. SDLP was significantly increased after Nitrazepam 10 mg. The effects of Nitrazepam were most pronounced in the afternoon test.
5 [13,21]	16 healthy volunteers with a history of insomnia and hypnotic treatment (6 men and 10 women)	26-41	2	lormetazepam 1 mg and 2 mg (caps.) flurazepam 30 mg placebo	Driving ability was not significantly impaired after lormetazepam 1 mg and 2 mg. Flurazepam 30 mg significantly impaired driving ability.
6 [14,22]	18 male healthy volunteers	26.3 (1.6)	2	lormetazepam 1 mg oxazepam 50 mg placebo	In the morning, SDLP was significantly increased after both lormetazepam 1 mg and oxazepam 50 mg. Driving was not significantly impaired in the afternoon.
7 [15]	17 female subjects with a history of insomnia and hypnotic treatment	40.8 (7.2)	1	zolpidem 10 mg flunitrazepam 2 mg partial sleep deprivation placebo	10-11 hours after bedtime administration, SDLP did not differ significantly from placebo after zolpidem and flunitrazepam. Also, partial sleep deprivation did not affect driving performance.
8 [16]	28 healthy volunteers (14 men and 14 women)	31.0 (5.7)	1	zaleplon 10 mg and 20 mg zopiclone 7.5 mg placebo	Zopiclone significantly increased SDLP and SD speed 5-6h after administration; SDLP was also significantly elevated 11h after administration. Driving performance after both doses of zaleplon matched placebo.
9 [17]	30 healthy volunteers (15 men and 15 women)	31.6 (6.9)	1	zopiclone 7.5 mg zaleplon 10 mg placebo alcohol (BAC<0.05%)	Zopiclone significantly impaired driving ability, 10h after bedtime administration. Alcohol also significantly impaired driving performance. Zaleplon did not affect driving.
10 [18]	30 healthy volunteers (15 men and 15 women)	24.0 (2.4)	1	zaleplon 10 mg and 20 mg zolpidem 10 mg and 20 mg placebo alcohol (BAC<0.05%)	Zolpidem (10 and 20 mg) and alcohol significantly impaired driving ability 4-5h after middle-of-the-night administration. Zaleplon 10 mg and 20 mg did not affect driving ability.

zopiclone, zolpidem and zaleplon after one night of bedtime administration. Two studies [16,18] (Study 8 and 10) also examined zolpidem and zaleplon after middle-of-the-night administration.

The evaluated benzodiazepine hypnotics (recommended dose) were: nitrazepam (5 mg), flurazepam (15 mg), flunitrazepam (2 mg), loprazolam (1 mg), lormetazepam (1 mg), oxazepam (50 mg) and temazepam (20 mg).

In all studies, subjects were trained to become familiar with the vehicle and testing procedures. All studies used the same standardized driving test over a public highway during normal traffic. Tests were performed in the morning, i.e. 10-11 hours after dosing (Study 1-10) [10-18], or in the afternoon, i.e. 16-17 hours after dosing (Study 1-6) [10-14].

A total of 207 healthy volunteers participated in ten on-the-road studies. In studies 1-4 and 7, all subjects were females. In study 6, the subjects were men. In studies 5 and 8-10, both men and women were included. In studies 6 and 8-10, healthy volunteers had no past experience of insomnia or hypnotic drug use. In studies 1-5 and 7, subjects were former users of hypnotic drugs for the treatment of insomnia. They were selected based upon the knowledge that the majority of insomniacs are women. In addition, the investigators wanted to be sure that subjects would be

responsive to hypnotic treatment (as was evident from their successful use in the past). The majority of these women were housewives, who were successfully treated with a benzodiazepine drug (mostly nitrazepam) for transient insomnia caused by unfortunate life events such as divorce. At the time of study participation, these problems and accompanying sleep disturbances were solved and they can thus be regarded as healthy volunteers.

In conclusion, all subjects that participated in these ten studies did not use hypnotics or other psychoactive medication at the time of study participation and were free from sleep disturbances. They possessed a valid drivers license for at least 3 years, and drove at least 5000 km yearly.

Effect Sizes and Significance

Effect size, 95% CI, and statistical significance were computed for each treatment-versus-placebo comparison. To calculate the effect size, mean, standard deviation and sample size were obtained from the publication [15,17,18] (Studies 7, 9 and 10), accompanying technical reports [11,19-22] (Studies 2 – 6), raw data files (Study 1), or were obtained from the study sponsor (Study 8, Wyeth Research). The effect size, 95% CI, and the statistical significance for each treatment-versus-placebo comparison is summarized in Table **2**.

Data Selection

In the meta-analysis for benzodiazepines (recommended dose), regarding Study 6, a choice had to be made whether to include data of lormetazepam or oxazepam. The oxazepam condition was chosen, since lormetazepam was already included from Study 5. In line, in the analysis for benzodiazepines (twice the recommended dose) loprazolam from Study 2 and lormetazepam from study 5 were chosen.

For all meta-analyses, the Q statistic from the homogeneity analysis was not significant ($p > 0.05$). Therefore, a homogenous distribution can be assumed and a fixed effects model was used. Results from the meta-analyses are summarized in Fig. **2**.

Driving Performance in the Morning (10-11 Hours After Bedtime Administration)

Benzodiazepine hypnotics administered at bedtime cause significant driving impairment the following morning, both after intake of the recommended dose (ES = 0.42; CI = 0.14 to 0.71) and twice the recommended dose (ES = 0.68;CI = 0.39 to 0.97). Significant driving impairment was also observed the morning following bedtime administration of the recommended dose of zopiclone (ES = 0.89;CI = 0.54 to 1.23). In contrast, driving performance after the recommended dose (10 mg) of zolpidem (ES = 0.08;CI = -0.62 to 0.77) and zaleplon (ES = 0.07,CI = -0.31 to 0.45) was not significantly different from placebo. Also, the morning following twice the recommended dose of zaleplon (20 mg), driving performance did not differ from placebo (ES = -0.23,CI = -0.82 to 0.35). Zolpidem 20 mg, twice the recommended dose, has not been tested the morning following bedtime administration.

Driving Performance in the Afternoon (16-17 Hours After Bedtime Administration)

Benzodiazepine hypnotics administered at bedtime produce significant driving impairment in the afternoon after taking twice the recommended dose (ES = 0.57, CI = 0.26 to 0.88), but not after intake of the recommended dose (ES = 0.14, CI = -0.14 to 0.41). Also, zopiclone (7.5 mg) does not significantly impair driving performance in the afternoon (ES = 0.25, CI = -0.47 to 0.98). Zolpidem and zaleplon have not been tested in the afternoon.

Driving Performance After Middle-of-the-Night Administration

In the morning, significant driving impairment was found after middle-of-the-night intake of the recommended dose of zopiclone (ES = 1.51, CI = 0.85 to 2.17). Also, both the recommended dose of zolpidem (ES = 0.66, CI = 0.13 to 1.19) and twice the recommended dose of zolpidem (ES = 1.16, CI = 0.60 to 1.72) significantly impaired driving performance. In contrast, driving performance after both the recommended dose of zaleplon (ES = -0.03, CI = -0.40 to 0.35) and twice the recommended dose of zaleplon (ES = 0.10, CI = -0.29 to 0.48) did not significantly differ from placebo. Benzodiazepine hypnotics have not been tested the morning following middle-of-the-night administration.

DISCUSSION

The meta-analyses confirm previous claims [6,23,24] that benzodiazepine hypnotics significantly impair driving ability. With twice the recommended dose of benzodiazepines, this impairment is still significant in the afternoon. Zopiclone also significantly impaired driving performance the morning following bedtime afdministration, but not in the afternoon. In contrast, zolpidem and zaleplon do not impair driving performance the morning following 1 night of treatment. Zaleplon is the only hypnotic that did not produce driving impairment after middle-of-the-night administration.

The analyses further show that dosage and time after administration determine the magnitude of driving impairment observed for benzodiazepine hypnotics.

Roadside surveys reported that a substantial number of patients use higher drug dosages than recommended, and a significant relationship has been demonstrated between culpability of traffic accidents and benzodiazepine concentrations found in the blood [25]. Hence, the observation that the administered dosage significantly correlates with the magnitude of driving impairment is rather worrisome. Taking into account that driving ability is already significantly impaired when using the recommended dose of benzodiazepines, physicians should caution their patients not to use higher dosages than recommended.

Possible explanations for the differences in impairment found with hypnotics may be found at the $GABA_A$ receptor level. Benzodiazepines and zopiclone bind nonselective to benzodiazepine receptor subtypes α_1 and α_2, whereas zolpidem and zaleplon prefer binding to the type α_1-$GABA_A$

Table 2. Summary of the Study Results

Tested 10-11 hours after bedtime administration

Study [ref.]	Treatment	Placebo			Treatment			Outcome		
		N	Mean	SD	N	Mean	SD	*p*	*ES*	*95% CI*
Study 1 [10]	Flurazepam 15 mg	24	19.91	4.78	24	23.38	5.71	0.03	0.65	0.05;1.25
	Flurazepam 30 mg	24	19.91	4.78	24	27.11	8.01	0.0E+01	1.07	0.45;1.70
Study 2 [10,19]	Loprazolam 1 mg	16	18.92	4.62	16	20.96	5.12	0.25	0.41	-0.32;1.14
	Loprazolam 2 mg	16	18.92	4.62	16	26.09	6.78	0.0E+01	1.21	0.41;2.00
	Flunitrazepam 2 mg	16	18.92	4.62	16	21.04	4.94	0.22	0.43	-0.30;1.16
Study 3 [11]	Nitrazepam 5 mg	16	20.54	3.33	16	20.96	4.16	0.76	0.11	-0.61;0.83
	Flunitrazepam 2 mg	16	20.54	3.33	16	23.27	5.22	0.09	0.61	-0.13;1.35
	Zopiclone 7.5 mg	16	20.54	3.33	16	23.19	4.26	0.06	0.68	-0.07;1.42
Study 4 [12,20]	Temazepam 20 mg	12	22.42	3.99	12	23.14	5.76	0.73	0.14	-0.71;0.99
	Nitrazepam 10 mg	12	22.42	3.99	12	24.39	5	0.21	0.51	-0.35;1.38
Study 5 [13,21]	Lormetazepam 1 mg	14	18.5	3.61	14	19.1	3.71	0.67	0.16	-0.62;0.94
	Lormetazepam 2 mg	14	17.6	3.87	14	20	4.7	0.15	0.54	-0.25;1.34
	Flurazepam 30 mg	15	18.5	3.92	15	21.4	5.54	0.11	0.59	-0.18;1.35
Study 6 [14,22]	Oxazepam 50 mg	18	17.1	2.27	18	19.75	3.46	0.01	0.89	0.17;1.60
	Lormetazepam 1 mg	18	17.1	2.27	18	18.76	2.53	0.05	0.68	-0.02;1.37
Study 7 [15]	Flunitrazepam 2 mg	17	21.9	4	17	22.2	3.6	0.82	0.08	-0.62;0.78
	Zolpidem 10 mg	17	21.9	4	17	22	4	0.94	0.02	-0.67;0.72
Study 8 [16]	Zaleplon 10 mg	25	22.03	3.78	25	21.6	2.96	0.66	-0.13	-0.69;0.45
	Zaleplon 20 mg	25	22.03	3.78	23	21.2	3.08	0.41	0.24	-0.82;0.35
	Zopiclone 7.5 mg	25	22.03	3.78	24	26.86	5.72	0.0E+01	0.99	0.37;1.60
Study 9 [17]	Zaleplon 10 mg	30	18.2	2.69	30	18.9	3.23	0.37	0.23	-0.29;0.75
	Zopiclone 7.5 mg	30	18.2	2.69	30	21.6	4.31	0.0E+01	0.93	0.39;1.48

Tested 16-17 hours after bedtime administration

Study [ref.]	Treatment	Placebo			Treatment			Outcome		
		N	Mean	SD	N	Mean	SD	*p*	*ES*	*95% CI*
Study 1 [10]	Flurazepam 15 mg	24	20.51	4.48	24	22.95	4.88	0.08	0.51	-0.08;1.10
	Flurazepam 30 mg	24	20.51	4.48	24	24.84	7.05	0.02	0.72	0.12;1.32
Study 2 [10,19]	Loprazolam 1 mg	16	19.17	4.23	16	20.79	5.83	0.38	0.31	-0.42;1.04
	Loprazolam 2 mg	16	19.17	4.23	16	23.77	6.59	0.03	0.81	0.06;1.57
	Flunitrazepam 2 mg	16	19.17	4.23	16	20.99	5	0.28	0.38	-0.35;1.11
Study 3 [11]	Nitrazepam 5 mg	16	20.91	3.75	16	21.36	4.64	0.77	0.1	-0.62;0.83
	Flunitrazepam 2 mg	16	20.91	3.75	16	23.53	5.07	0.11	0.57	-0.17;1.31
	Zopiclone 7.5 mg	16	20.91	3.75	16	21.95	4.12	0.46	0.26	-0.47;0.98
Study 4 [12,20]	Temazepam 20 mg	12	22.29	3.81	12	22.11	3.5	0.91	-0.05	-0.89;0.80
	Nitrazepam 10 mg	12	22.29	3.81	12	25.72	4.33	0.05	0.81	-0.08;1.69
Study 5 [13,21]	Lormetazepam 1 mg	16	18.5	3.5	16	18.2	4.06	0.82	-0.08	-0.80;0.65
	Lormetazepam 2 mg	15	19.2	3.98	15	19	5.27	0.91	-0.04	-0.79;0.71
	Flurazepam 30 mg	15	18.2	3.59	15	20.6	6.94	0.24	0.42	-0.34;1.18
Study 6 [14,22]	Oxazepam 50 mg	18	17.56	2.82	18	17.13	2.83	0.65	-0.15	-0.83;0.53
	Lormetazepam 1 mg	18	17.56	2.82	18	17.76	2.73	0.83	0.07	-0.61;0.75

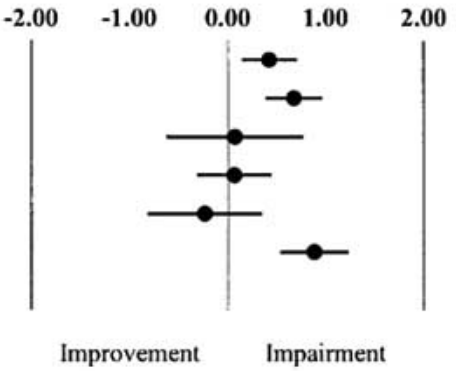
Tested 4-6 hours after middle-of-the-night administration

Study [ref.]	Treatment	Placebo			Treatment			Outcome		
		N	Mean	SD	N	Mean	SD	*p*	*ES*	*95% CI*
Study 8 [16]	Zaleplon 10 mg	25	22.03	3.78	26	22.14	3.85	0.92	-0.03	-0.54;0.59
	Zaleplon 20 mg	25	22.03	3.78	22	22.26	4.78	0.86	-0.05	-0.54;0.64
	Zopiclone 7.5 mg	25	22.03	3.78	24	30.93	7.19	0.0E+01	1.53	0.87;2.19
Study 10 [18]	Zaleplon 10 mg	30	17.5	4.2	30	17.2	4.1	0.78	-0.07	-0.59;0.45
	Zaleplon 20 mg	30	17.5	4.2	30	18.1	4.6	0.6	0.13	-0.38;0.65
	Zolpidem 10 mg	30	17.5	4.2	30	2.3	6.7	0.01	0.67	0.14;1.20
	Zolpidem 20 mg	30	17.5	4.2	30	28.1	11.9	0.0E+01	1.17	0.61;1.74

Ref. = reference, N= Number of subjects, SD = Standard Deviation, ES = Effect size, 95%CI = ninety-five percent confidence interval.

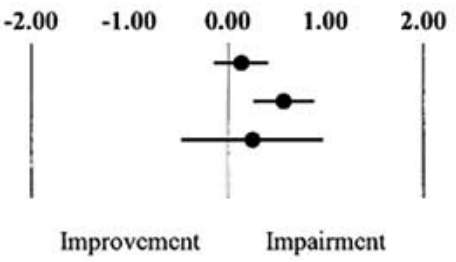
10 - 11 hours after bedtime administration

	N1	N2	Effect	Lower	Upper	PValue
Benzodiazepines - SD	100	100	.42	.14	.71	.00
Benzodiazepines - DD	99	99	.68	.39	.97	.00
Zolpidem 10 mg	17	17	.08	-.62	.77	.82
Zaleplon 10 mg	55	55	.07	-.31	.45	.71
Zaleplon 20 mg	23	25	-.23	-.82	.35	.42
Zopiclone 7.5 mg	70	71	.89	.54	1.23	.00



16 - 17 hours after bedtime administration

	N1	N2	Effect	Lower	Upper	PValue
Benzodiazepines - SD	102	102	.14	-.14	.41	.33
Benzodiazepines - DD	83	83	.57	.26	.88	.00
Zopiclone 7.5 mg	16	16	.25	-.47	.98	.47



4 - 6 hours after middle-of-the night administration

	N1	N2	Effect	Lower	Upper	PValue
Zaleplon 10 mg	56	55	-.03	-.40	.35	.89
Zaleplon 20 mg	52	55	.10	-.29	.48	.61
Zolpidem 10 mg	30	30	.66	.13	1.19	.01
Zolpidem 20 mg	30	30	1.16	.60	1.72	.00
Zopliclone 7.5 mg	24	25	1.51	.85	2.17	.00

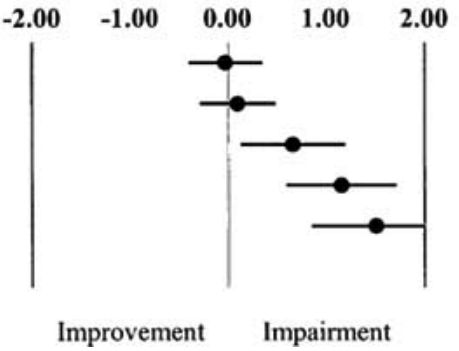


Fig (2). Meta-analysis results.

Observed effect sizes (ranging from –2.00 to + 2.00) and 95% confidence intervals. Significant driving impairment is found if Pvalue < 0.05. In that case, the 95% confidence interval is greater than 0. Abbreviations: SD = Single dose, DD = Double dose, N1= treatment, N2=placebo, Effect = Effect size, Lower = lower limit of the 95% confidence interval, Upper = upper limit of the 95% confidence interval, Pvalue is significant if $p < 0.05$.

receptor. However, they do with a different affinity and at different subtypes of the $GABA_A$ receptor complex [26]. Zolpidem binds with high sensitivity to α_1-$GABA_A$ receptors, an intermediate affinity for α_2- and α_3-$GABA_A$ receptors, but has no affinity for α_5-$GABA_A$ receptors [27]. Zaleplon also possesses high affinity for α_1-$GABA_A$ receptors ($\alpha_1\beta_2\gamma_2$), but is less potent that zolpidem at the α_1-, α_2-, and α_3-$GABA_A$ receptors. In addition, zaleplon binds with greater sensitivity to γ_3- and α_5-$GABA_A$ receptors than zolpidem [28]. The impact of these differences in activity at different receptor subtypes on the magnitude and duration of (residual) drug activity needs to be addressed by future research.

The observed driving impairment with benzodiazepines is in line with the significantly increased risk of traffic accidents reported by the majority [29-31], but not all [32,33] epidemiological studies examining benzodiazepine used for hypnotic purposes. A significantly increased risk of traffic accidents has also been reported for zopiclone [31].

Higher blood concentrations of benzodiazepines, either used for hypnotic [31] or anxiolytic purposes [34], produce significantly higher traffic accident risks when compared to the risks observed when administering the recommended dose. Although not found in elderly [30], recent epidemiological evidence confirmed that the blood concentration of benzodiazepines was significantly related to impairment in apprehended drivers [35].

Epidemiological data on zolpidem and zaleplon is currently lacking.

Limitations of Current Research and Future Aims

A first limitation of the presented analyses is that the driving tests were performed after 1 or 2 nights of administration. It can therefore be argued that the presented results do not take into account that tolerance to the performance impairing effects may develop after repeated use of hypnotics. However, tolerance to the effects of benzodiazepines develops slowly: significantly increased traffic accident risks have been reported to last from several weeks [29] up to 1 year after treatment initiation [30]. Future driving studies should aim to determine the effects of long-term use of hypnotics on driving performance and whether tolerance develops to the impairing effects of benzodiazepines and zopiclone.

Secondly, all on-the-road studies were performed in healthy adults. In real life, elderly patients are the most frequent users of hypnotics. Taking into account that elderly are the fast-growing segment of the general population who increasingly depend on the ability to drive a car to maintain their independence, future driving studies should aim at studying the effects of hypnotics in elderly patients.The on-the-road driving test is performed on a public highway. Although this test is regarded as the 'gold standard' method to determine driving ability during normal traffic, other on-the-road tests have been developed over the years, including car-following tests and city driving. Studies applying these tests are limited and were not included in the meta-analysis, since the latter two tests examine different driving skills (and have different outcome measures than SDLP) when compared to highway driving. For example, highway driving is a relatively monotonous vigilance task using SDLP as primary parameter, whereas city driving requires higher attentional demands to ensure vehicle control and has a subjective driving performance score as outcome measure.

Limitations of the meta-analysis include the relatively low number of driving studies that were available for statistical analysis. In addition, because meta-analysis does not allow including more than one treatment-versus-placebo condition from each study, for some analyses, a choice had to be made between different treatment-versus-placebo conditions. However, additional analyses replacing the used conditions by those conditions that were left out showed that this did not affect the overall results of the meta-analyses.

CONCLUSION

The clinical implications resulting from these meta-analyses are that patients should be warned that their driving ability may be impaired when using benzodiazepine hypnotics or zopiclone. With regard to traffic safety, zolpidem and especially zaleplon are safe alternatives for patients who want to drive a car.

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