

Zopiclone's Residual Effects on Actual Driving Performance in a Standardized Test: A Pooled Analysis of Age and Sex Effects in 4 Placebo-Controlled Studies[☆]

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ABSTRACT

Background: In many European countries, Canada, and Japan, the nonbenzodiazepine zopiclone is now among the most frequently prescribed hypnotic drugs. This finding can be explained by the growing view among physicians that zopiclone is more effective and safer than conventional benzodiazepines. However, in 4 studies using similar procedures, it has been shown that zopiclone 7.5 mg causes moderate to severe impairment in driving performance.

Objective: The goal of the present article was to review these studies and analyze the pooled data to determine whether the severity of effects is modified by the sex and age of the subjects.

Methods: The driving data of the placebo and zopiclone 7.5 mg evening treatment periods from a total of 4 studies conducted at Maastricht University were included in this pooled analysis. All studies were conducted according to balanced double-blind, cross-over designs. The effects on driving were always measured the next morning, between 10 and 11 hours after administration, by using a standardized highway driving test. A total of 101 healthy volunteers of both sexes in equal proportions (with no reports of insomnia) participated. Subjects comprised young volunteers (age range, 21–45 years) in 3 studies and older volunteers (age range, 55–75 years) in the fourth study.

Results: Results show that zopiclone 7.5 mg has significant and clinically relevant performance-impairing effects on driving in the morning, until 11 hours after bedtime ingestion. The effects did not differ between male and female subjects and did not increase with age, at least until 75 years. The effects of zopiclone 7.5 mg are comparable to the effects of a mean blood alcohol concentration between 0.5 and 0.8 mg/mL, which has

been associated with a 2- to 3-fold increase in the risk of becoming involved in a traffic accident.

Conclusions: We concluded that patients using an evening dose of zopiclone 7.5 mg should avoid activity in skilled work and participation in traffic the morning after intake. General practitioners' beliefs regarding the beneficial safety profile of zopiclone may need adjustment, and patients using zopiclone 7.5 mg should be warned accordingly. There is no need to differentiate warnings about zopiclone's residual impairing effects depending on the sex of the patient. (*Clin Ther.* 2014;36:141–150) © 2014 The Authors. Published by Elsevier, Inc. All rights reserved.

Key words: hypnotics, on-the-road driving, residual effects, zopiclone.

INTRODUCTION

The prescription of newer hypnotic agents such as zopiclone, zolpidem, and zaleplon (the so-called Z drugs) has been steadily rising over the last few years, while prescriptions of benzodiazepines have been falling.¹ In many European countries, Canada, and Japan, the nonbenzodiazepine zopiclone is now among the most frequently prescribed hypnotic drugs.^{2–6} This finding can be explained by the growing view among physicians that these newer hypnotic agents are more effective and safer than conventional benzodiazepines.⁷

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A recent survey comparing primary care physicians' perceptions of benefits and risks of benzodiazepine and Z-drug use found that Z drugs were believed to be more effective than benzodiazepines in terms of patients feeling rested on waking, daytime functioning, and total sleep time.⁸ They were also thought to be safer in terms of tolerance, dependence, residual daytime sedation, and road traffic accidents.

Regarding the risk of next-morning impairment, however, there may be age and sex differences. Such differences became apparent for zolpidem as new dosage forms were developed.⁹ Women were found to clear zolpidem more slowly than men, resulting occasionally in next-morning blood levels associated with significant driving impairment. Consequently, the US Food and Drug Administration required revision to the labels of zolpidem-containing products to recommend lower dosing, particularly for women. It may be that sex-specific labeling revisions will be required for other insomnia drugs as well, including zopiclone, after the US Food and Drug Administration has reviewed all available data.

There is little research into the potential age and sex differences in next-day effects of zopiclone on driving. Our group has conducted a number of experimental studies assessing zopiclone's residual effects on driving, but sample sizes and age ranges in individual studies were too small to analyze age and sex differences. Four studies,¹⁰⁻¹³ however, have used similar designs, with the same driving test and identical procedures, which justifies aggregating the data for analysis of age and sex effects across studies. All studies were conducted according to double-blind, placebo-controlled crossover designs in healthy male and female volunteers. Three studies were conducted in young volunteers¹⁰⁻¹² and one in elderly volunteers.¹³ In all studies, single doses of zopiclone 7.5 mg were administered at bedtime, in the presence of an investigator, and effects on driving were assessed the next morning by using the same on-the-road driving test, between 10 and 11 hours after intake.

The aim of the present article was to analyze the data from these 4 studies¹⁰⁻¹³ to determine whether there are clinically relevant age and sex differences in the risk of next-day driving impairment after use of zopiclone 7.5 mg at bedtime. Based on results from pharmacokinetic and pharmacodynamic studies,¹⁴⁻¹⁷ it is expected that impairment effects on driving increases with age, due to the decreased clearance,

prolonged half-lives, and increased sensitivity found in elderly subjects. Because no clinically relevant sex differences in zopiclone kinetics have been reported, it was not expected that impairment effects would differ significantly between men and women.^{14,15}

MATERIALS AND METHODS

Studies

The driving data of the placebo and zopiclone 7.5 mg evening treatment periods from a total of 4 studies conducted at Maastricht University were included in this pooled analysis.¹⁰⁻¹³ All studies were conducted according to balanced, double-blind, crossover designs, including treatment conditions consisting of administration of single oral doses of zopiclone 7.5 mg and placebo at bedtime. The effects on driving were always measured the next morning, between 10 and 11 hours after administration, by using a standardized highway driving test. Subject samples comprised healthy volunteers of both sexes in equal proportions, with no reports of insomnia. Subjects were young volunteers (age range, 21-45 years) in 3 studies and elderly volunteers (age range, 55-75 years) in 1 study. **Table I** summarizes the treatment conditions and characteristics of the subject samples for each study.

Study 1¹⁰ was designed to assess the residual effects of evening and middle-of-the-night doses of zaleplon 10 mg and 20 mg compared with those of zopiclone 7.5 mg and placebo. Subjects included 28 healthy young volunteers (14 female, 14 male) with a mean (SD) age of 31.2 (5.7) years.

Study 2¹¹ was designed to evaluate the residual effects of zopiclone 7.5 mg and zaleplon 10 mg administered at bedtime and to compare them with the effects of a low dose of alcohol. Thirty healthy young volunteers (15 female, 15 male) with a mean age of 31.6 (6.9) years participated in a 2-part crossover study. Part 1 was conducted as a single-blind, 2-way crossover design with afternoon administration of alcohol or alcohol/placebo drinks. Driving performance was assessed when blood alcohol concentrations (BACs) were just below the legal limit for driving (ie, 0.5 mg/mL). Part 2 followed a double-blind, 3-way crossover design. Treatment conditions were zopiclone 7.5 mg, zaleplon 10 mg, and placebo administered at bedtime.

Study 3¹² was designed to assess the residual effects of evening and middle-of-the-night doses of gaboxadol 15 mg compared with those of evening doses of

Table I. Summary of the study designs of the 4 studies included in the pooled analysis. All studies were conducted following a double-blind, crossover design.

Study	Treatments	Subjects	Age* and Range (y)	Weight* (kg)	Duration of Driver's License (y)*	Annual Mileage* (km/y)	Reference
1	Evening and middle-of-the-night doses of: zaleplon 10 mg, zaleplon 20 mg, zopiclone 7.5 mg, and placebo	14 females, 14 males	31.2 (5.7); 23–40	F: 66.1 (6.7) M: 78.7 (14.6)	F: 11.1 (5.7) M: 11.1 (5.1)	F: 12,686 (4584) M: 23,214 (17,660)	Vermeeren et al ¹⁰ (1998)
2	Evening doses of: zaleplon 10 mg, zopiclone 7.5 mg, and placebo	15 females, 15 males	31.6 (6.9); 21–45	F: 60.6 (6.1) M: 80.2 (10.9)	F: 10.2 (7.0) M: 13.3 (6.9)	F: 14,600 (10,614) M: 23,800 (21,415)	Vermeeren et al ¹¹ (2002)
3	Evening doses of: gaboxadol 15 mg, zopiclone 7.5 mg, and placebo Middle-of-the-night doses of: gaboxadol 15 mg, zolpidem 10 mg, and placebo	12 females 13 males	31.4 (7.5); 22–44	F: 66.8 (6.7) M: 77.7 (9.3)	F: 11.2 (8.4) M: 12.1 (5.6)	F: 13,167 (13,704) M: 15,808 (6600)	Leufkens et al ¹² (2009)
4	Evening doses of: temazepam 20 mg, zopiclone 7.5 mg, and placebo	10 females 8 males	64.3 (4.3); 56–73	F: 64.8 (5.6) M: 77.0 (4.9)	F: 34.2 (9.9) M: 43.9 (4.8)	F: 8258 (4207) M: 11,563 (4640)	Leufkens and Vermeeren ¹³ (2009)

F = female; M = male.

*Mean (SD).

zopiclone 7.5 mg, middle-of-the-night doses of zolpidem 10 mg, and placebo. A total of 25 healthy young volunteers (12 female, 13 male; mean age, 31.4 [7.5] years) completed this 5-way crossover study.

Study 4¹³ was conducted to assess the residual effects of evening doses of zopiclone 7.5 mg, temazepam 20 mg, and placebo in healthy elderly volunteers. The 18 subjects (10 female, 8 male) were healthy elderly drivers with a mean age of 64.3 (4.3) years.

Subjects

The complete dataset contained 101 volunteers (51 females, 50 males) in the age range of 21 to 73 years. Participants needed to possess a valid driving license for at least 3 years and have a driving experience over the preceding 3 years of at least 5000 km/year for the young volunteers and at least 3000 km/year for the older volunteers.

All subjects were screened by using a medical history questionnaire, a physical examination including ECG, blood chemistry and hematology assessments, and urinary tests for pregnancy and drugs of abuse. Common exclusion criteria in the studies were any history or current evidence of any clinically significant physical or mental disorders, alcoholism, or drug abuse; acute illness; use of systemic medication except oral contraceptives; use of any psychotropic drug; blood donation or participation in any other clinical trial within the previous 3 months; and consumption of >6 beverages containing caffeine per day, use of >10 cigarettes per day, and drinking >21 alcohol-containing beverages per week.

All studies were conducted in accordance with the code of ethics on human experimentation established by the World Medical Association's Declaration of Helsinki (1964) and its subsequent amendments. The protocols were approved by the medical ethics committee of Maastricht University and University Hospital of Maastricht. Subjects signed a written informed consent form before initiation of any study-related assessments.

Procedure

Subjects were individually trained to perform the driving test. One week before the first treatment period, subjects slept in the same facilities as during treatment periods to overcome possible sleep disturbances associated with sleeping in an unfamiliar environment. On the morning after this habituation,

night subjects rehearsed all tests and procedures, including the driving test.

During treatment periods, zopiclone 7.5 mg and placebo were orally administered at bedtime. Subjects were awakened after 8 hours in bed and served a light breakfast without caffeine. They then underwent a battery of various psychometric tests to assess driving-related behavior. The driving test was always conducted between 10 and 11 hours after bedtime administration.

Highway Driving Test

The driving test used in all studies was developed and standardized by O'Hanlon¹⁸ in the early 1980s. In this test, the subject operates a specially instrumented vehicle over a 100-km (61-mile) primary highway circuit in normal traffic, accompanied by a licensed driving instructor having access to dual controls. The subject's task is to maintain a constant speed of 95 km/h (58 miles/h) and a steady lateral position between the delineated boundaries of the slower traffic lane. Test duration is ~1 hour, during which the vehicle's speed and lateral position are continuously recorded. These signals are edited offline to remove data recorded during overtaking maneuvers or disturbances caused by roadway or traffic situations. The remaining data are then used to calculate means and SDs of lateral position and speed. The pooled lateral position variance is calculated, and its square root, the mean-adjusted SD of lateral position (SDLP in centimeters), is taken as the primary outcome variable. SD of speed (SDSP in kilometers per hour) is measured as a secondary outcome variable and is an index of subjects' ability to maintain a constant speed.

SDLP is an integrated measure of road-tracking error or "weaving." It is an extremely reliable index (test-retest $r = 0.70-0.90$) of individual driving performance and has proven sensitive to many sedating drugs.¹⁹⁻²⁴ The test was calibrated for the effects of alcohol in a closed circuit study in which 24 social drinkers were tested sober and after controlled drinking to raise BACs in steps of 0.3 g/L to a maximum of 1.2 g/L.²⁵ In line with the relation between BAC and accident risk as estimated in a large epidemiologic study by Borkenstein et al.,²⁶ the relation between BAC and SDLP was shown to be an exponential function. Based on this relation, BACs of 0.5, 0.8, and 1.0 g/L were associated with mean changes in SDLP of 2.4, 4.2, and 5.1 cm, respectively. Owens and

Ramaekers²⁷ combined experimental and epidemiologic BAC data and found that there is a very high correlation ($r = 0.99$) between the increase of SDLP relative to placebo and the risk of becoming involved in a traffic accident.

Statistical Analysis

Statistical analyses were performed by using zopiclone – placebo difference scores in SDLP and SDSP as dependent variables (ie, Δ SDLP and Δ SDSP, respectively). Δ SDLP and Δ SDSP were analyzed separately by using 2-way ANOVAs, with study and sex as fixed between-subject factors. The significant main study effects were further analyzed by using 6 simple contrasts between the studies' change scores in elderly and young volunteers; the Tukey A correction was used to adjust for 6 comparisons.

To determine which subject characteristic best predicted zopiclone's effect on driving, a step-wise regression analysis was used, with Δ SDLP as the dependent variable and sex, age, weight, years of driving experience, and annual mileage as predictors.

To compare residual effects on SDLP and SDSP, correlations (Pearson r) and effect sizes (Dunlap's d^{28}) were calculated for studies and sexes separately, and for the total group.

RESULTS

Subjects

There were no significant differences between studies with respect to sex composition, weight, and average annual mileage of the subjects (Table I). Subjects in study 4 were older and had, as can be expected, significantly more years of driving experience compared with subjects in the other studies (all, $P < 0.001$). Overall, male subjects differed from female subjects in terms of body size (height and weight, $P < 0.001$) and in terms of driving experience. They had more years of driving experience ($P = 0.016$) and drove more kilometers per year ($P = 0.015$).

Tests Terminated Prematurely

A total of 4 driving tests were terminated prematurely due to excessive drowsiness. All 4 tests were conducted after use of zopiclone. Two tests were stopped before scheduled completion in study 1: one by the driving instructor and one at the subject's request. The driving instructors also stopped 1 test in study 2 and 1 test in study 4. SDLP scores for these tests

were calculated from the data collected until termination and were included in the statistical analyses.

SD of Lateral Position

Figure 1 shows the individual and mean SDLP scores after administration of placebo and zopiclone 7.5 mg for each study separately.

As reported in the original publications, the mean increases in SDLP after use of zopiclone compared with placebo were significant in each study, varying from 1.94 cm in study 4 with elderly subjects to 4.88 cm in study 1 with young subjects. The overall mean (SD) increase in SDLP after use of zopiclone compared with placebo was 3.33 (3.42) cm, which is highly significant ($F_{1,93} = 87.96$, $P < 0.0001$). Analysis showed an overall difference in Δ SDLP between studies ($F_{3,93} = 3.69$, $P = 0.015$), which was due to a significantly smaller Δ SDLP in study 4 compared with study 1 ($P = 0.025$). There was no overall difference in Δ SDLP between male and female subjects (3.16 vs 3.48 cm, respectively; $F < 1$) or a sex-by-study interaction.

Regression analysis of Δ SDLP with sex, age, weight, years of driving, and annual mileage as independent variables revealed that only age ($F_{1,99} = 5.7$, $P = 0.019$) and years of driving ($F_{1,99} = 8.2$, $P = 0.005$) predicted Δ SDLP, with a β coefficient of -0.23 and -0.27 and adjusted R^2 of 5% and 7%, respectively (Figure 2). Years of driving experience was highly correlated with age ($r = 0.95$).

SD of Speed

The ability to keep a constant speed, as measured by using SDSP, differed significantly between placebo and zopiclone ($F_{1,93} = 17.86$, $P < 0.0001$). Overall, the variability in speed was increased by 0.17 km/h after use of zopiclone. Zopiclone's effects on SDSP did not differ between studies and sexes (F 's < 1).

Effect Sizes

Table II shows the effect sizes of changes in SDLP and SDSP for the studies and male and female subjects. Effect sizes on SDLP were large, with a mean of 0.67 and ranging from 0.50 in study 4 with elderly subjects to 0.96 in study 1 with young volunteers. The overall effect size on SDSP (0.35) was smaller than on SDLP, ranging from 0.30 in study 3 to 0.73 in study 4. Effect sizes on SDLP were slightly smaller for male subjects than for female subjects, whereas effect sizes on SDSP were slightly larger for male than for female subjects.

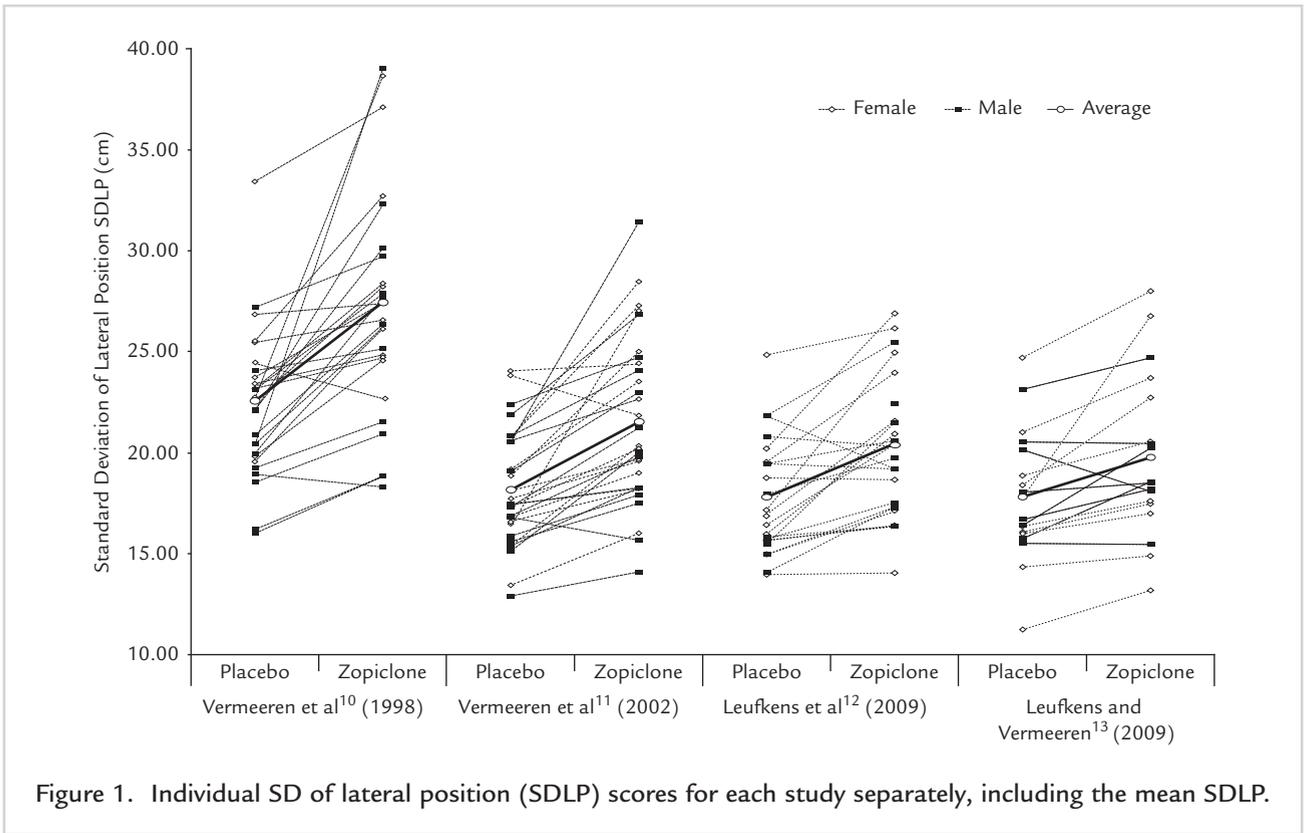


Figure 1. Individual SD of lateral position (SDLP) scores for each study separately, including the mean SDLP.

Correlations

The overall correlation between Δ SDLP and Δ SDSP was 0.41 ($P < 0.001$), and it ranged between 0.30 (NS) in study 3 and 0.73 ($P < 0.01$) in study 4 (Table II).

DISCUSSION

The present article was intended to determine age and sex influences on residual effects of zopiclone 7.5 mg on driving performance as measured by using a

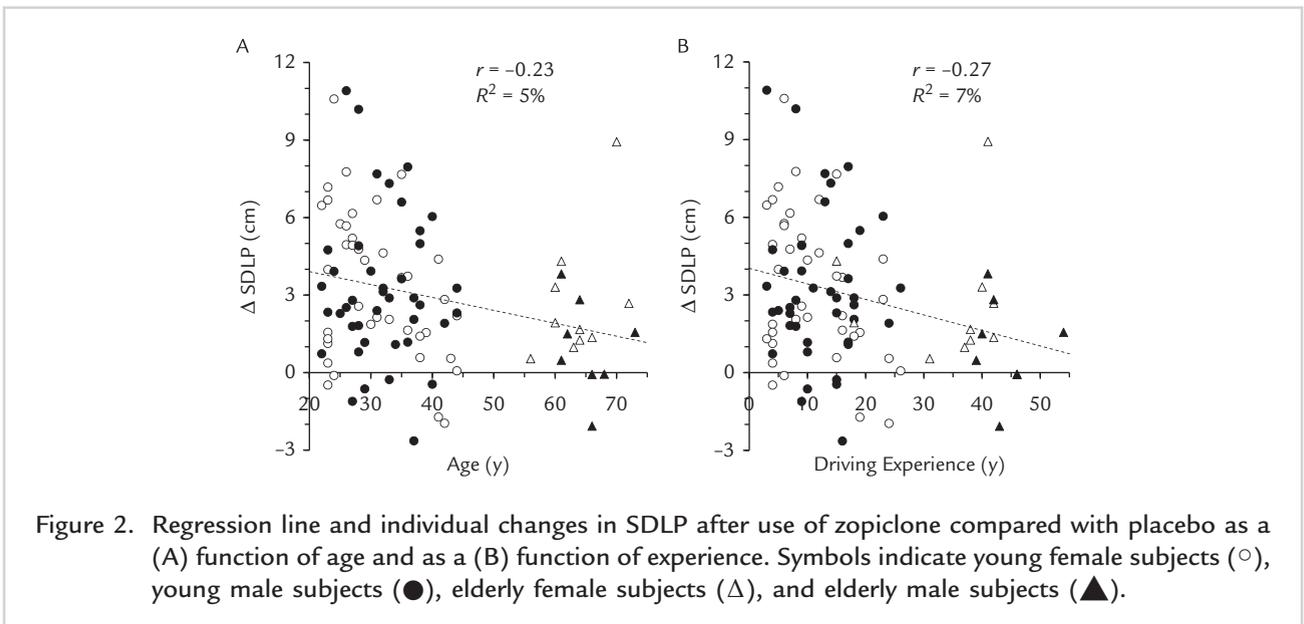


Figure 2. Regression line and individual changes in SDLP after use of zopiclone compared with placebo as a (A) function of age and as a (B) function of experience. Symbols indicate young female subjects (○), young male subjects (●), elderly female subjects (△), and elderly male subjects (▲).

Table II. Mean (SD) change scores (Δ), effect sizes, and correlations between changes in mean-adjusted SD of lateral position (SDLP) and SD of speed (SDSP) for each study and sex separately, and overall.

Study	No. of Subjects	Tests Terminated Prematurely No. (%)	Δ SDLP* (cm)	Δ SDLP Effect Size (Dunlap's d)	Δ SDSP* (km/h)	Δ SDSP Effect size (Dunlap's d)	Correlation Δ SDLP - Δ SDSP (Pearson's <i>r</i>)
By study							
Study 1: Vermeeren et al ¹⁰ (1998)	28	2 (7.1)	4.88 (4.50)	0.96	0.15 (0.38)	0.35	0.58
Study 2: Vermeeren et al ¹¹ (2002)	30	1 (3.3)	3.38 (2.88)	0.89	0.11 (0.39)	0.24	0.34
Study 3: Leufkens et al ¹² (2009)	25	0	2.53 (2.65)	0.82	0.25 (0.30)	0.54	0.30
Study 4: Leufkens and Vermeeren ¹³ (2009)	18	1 (5.6)	1.94 (2.32)	0.50	0.21 (0.59)	0.37	0.73
By sex							
Female	51	3 (5.9)	3.49 (3.27)	0.70	0.16 (0.45)	0.30	0.51
Male	50	1 (2.0)	3.17 (3.59)	0.62	0.19 (0.37)	0.41	0.31
Overall	101	4 (4.0)	3.33 (3.42)	0.67	0.17 (0.41)	0.35	0.41

*Mean (SD).

standardized on-the-road driving test in normal traffic. Data from 101 subjects of 4 separate placebo-controlled, double-blind crossover studies using the same procedures were pooled and analyzed to determine whether zopiclone's impairment effects depend on age or sex or on associated differences in weight or driving experience of the subjects.

Zopiclone impaired subjects' control over the vehicle's lateral position on the road (ie, weaving) and driving speed. Weaving as measured by using SDLP increased on average by 3.3 cm, which represents a moderate to large effect size (Dunlap's $d = 0.67$). Compared with the effects of alcohol in the same test,²⁵ a 3.3-cm mean increase in SDLP is comparable to the effects of a mean BAC between 0.5 and 0.8 mg/mL, which is associated with a 2- to 3-fold increased risk of becoming involved in a traffic accident.²⁹ According to the International Council on Alcohol, Drugs and Traffic Safety, such effects can be classified as moderately severe impairment of driving performance.³⁰

Zopiclone's effects on variance in driving speed (SDSP) were also significant but considerably less pronounced compared with those on SDLP in terms of effect sizes (Dunlap's d of 0.35 vs 0.67, respectively). The overall correlation between zopiclone's effects on SDLP and SDSP was moderate ($r = 0.41$). This finding supports the idea that these factors measure different processes and indicates that subjects' control of the

vehicle's lateral position is most sensitive to the residual effects of zopiclone. This finding is supported by results from studies by Bocca et al³¹ and Berthelon et al^{32,33} using various scenarios in driving simulators for assessing the residual effects of zopiclone 7.5 mg. These investigators found that zopiclone significantly impaired control of lateral position but not control of speed,³¹ collision anticipation,³² or processing of visual information in a driving context.³³ Moreover, an epidemiologic study of unsafe driving actions by crash-involved drivers showed that "failure to stay in proper lane/running of road" was the most frequently reported unsafe driving action by benzodiazepine users.³⁴ This finding supports the validity of SDLP for measuring safe driving and its impairment by sedating drugs such as benzodiazepines.

Importantly, no sex differences were found in the effects of zopiclone on SDLP and SDSP. This is in line with findings from a previous review of effects of sleep medication, including zopiclone, on driving performance in men and women separately.³⁵ In that review, results may have suffered from increased variance, however, because the data were combined from 6 experimental studies conducted over a large time period by different centers and with differences in design, study population, and setting. Nevertheless, other studies have found that the subject's sex does not seem to have important effects on the kinetics of zopiclone and other substrates of the cytochrome P-450

3A system.^{17,36} On the one hand, drugs have been found to produce larger pharmacologic responses in female subjects than in male subjects,^{37,38} which can usually be explained by their lower weight. Conversely, it has been found that total clearance of drugs metabolized by the cytochrome P-450 3A4 system, such as zopiclone, is slightly faster in women compared with men, although results were not consistent.^{16,39,40} The combination of these effects may explain the lack of sex differences in the residual effects of zopiclone.

The effects of age were surprising. Contrary to the expectation that impairment effects would increase with age, the effect on driving in our older sample was generally less than that found in the studies with younger volunteers. The difference was significant for only 1 of 3 studies, however.¹⁰ Several factors may have contributed to this finding. First, our older subjects were all younger than 75 years. Only 2 participants were older than 70 years. In addition, they were selected to be healthy and having normal liver and kidney function. A study by Gaillot et al¹⁵ found that age-related increases of zopiclone's half-life were significant only in the older subjects (ie, those aged >75 years). Second, increased drug effects in elderly subjects may also be due to age-related reductions in body size and body fat.⁴¹ In our studies, there were no significant differences in weight between subject samples. Finally, our elderly subjects had significantly more years of driving experience and were still regular drivers. Their driving performance after placebo administration was generally similar or even better in terms of SDLP compared with younger drivers. Nevertheless, both age and driving experience predicted only 5% to 7% of the variation in effects, indicating that the relation is weak.

Although the protective effects of age or driving experience seemed low, the results are supported by other experimental and epidemiologic studies suggesting that younger and less experienced drivers are more sensitive to drug effects. A number of epidemiologic studies have found that risks for traffic accidents associated with use of benzodiazepines increase most for young male subjects.²² In addition, a recent on-the-road driving study found that the effects of low doses of alcohol on weaving were more severe in novice drivers than in experienced drivers.⁴² Novice drivers are thought to make use of more cognitive resources than experienced drivers. The sedative properties of hypnotic agents may influence more

cognitive skills in relatively inexperienced drivers and, as a consequence, impair performance to a larger extent than in experienced drivers. Age-related increases in driving experience may therefore have protective effects on drug-induced driving impairment.

It should be noted that the effects shown were found in medication-naïve drivers after single use. Insomnia patients often use hypnotic agents repeatedly, which may induce the development of tolerance.⁴³ Tolerance toward the sedative effects of these agents may result in less severe driving impairment. Epidemiologic studies have shown, however, that the relative risk of becoming involved in a traffic accident is still significantly increased after 1 month of treatment.⁴⁴ This finding suggests that the development of tolerance is limited and will not be full-scale. In addition, patients today are recommended to use hypnotic agents on an as-needed basis, hampering the development of tolerance. An inconvenient consequence of that recommendation is that patients are more likely to remain susceptible to the sedative residual effects of these drugs.

It is important to note that subjects affected by impairment after taking zopiclone frequently do not recognize their impaired state. In all 4 studies, subjects were asked to indicate their subjective alertness in the morning after evening administration by using a visual analog scale.⁴⁵ Subjects reported no differences in feelings of alertness between placebo and zopiclone administration. In the study by Vermeeren et al,¹¹ however, subjects were able to detect the impairment effects of alcohol on their alertness when BAC values were 0.4 mg/mL. In contrast, the effects on driving performance after alcohol were less impairing than the effects of zopiclone 7.5 mg, showing that the subjects' alertness does not correctly predict their driving performance. This finding stresses the importance of providing clear and comprehensive information by general practitioners and pharmacists to their patients about the potentially hazardous effects of zopiclone 7.5 mg on driving performance. It also stresses the need to consider lowering the dose, not only for elderly subjects or women, but also for younger patients and men.

Whether the S-enantiomer of zopiclone, eszopiclone, is safer with respect to residual effects is unknown. Assuming dose equivalence with respect to hypnotic effects and comparing the pharmacokinetic profiles of both hypnotic agents, there is no reason to assume that eszopiclone will not have effects on driving the morning after evening administration.⁴⁶

However, to the best of our knowledge, a study investigating eszopiclone's residual effects on actual driving performance has not been conducted.

CONCLUSIONS

The results of the present study found that zopiclone 7.5 mg had significant impairment effects on driving performance at least until 11 hours after hypnotic agent intake. The effects did not differ between male and female subjects and did not increase with age, at least until 75 years. Patients should be warned about the potential hazards of using zopiclone 7.5 mg when they have to engage in morning traffic, and they should be advised to refrain from driving or engaging in any activity that requires full alertness the morning after use. There seems to be no need for differentiating warnings based on sex or age of the user.

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Both authors contributed equally to the literature search, data interpretation, figure creation, and writing of the manuscript.

CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest regarding the content of this article.

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