Effects of Hypnotic Drugs on Driving Performance

Chapter 46

Joris C. Verster; Aurora J.A.E. van de Loo; Thomas Roth

Chapter Highlights

- There are a variety of methodologies to examine whether it is safe to drive a car the day after being treated with hypnotic drugs. This chapter discusses epidemiologic evidence and explains the experimental methodology and results of the standardized on-the-road highway driving test to determine the effects of hypnotic drugs on driving ability.
- Most classic benzodiazepine hypnotics and zopiclone, when administered at bedtime, significantly impair next-morning driving ability. The magnitude of driving impairment depends on variables such as gender and age, drug dosage, half-life, and the time between drug intake and driving. Depending on dose and half-life, impairment of some benzodiazepines may last until the afternoon, that is, 16 to 17 hours after bedtime administration.
- When allowing a full night of sleep, next-morning driving ability was not impaired after bedtime administration of zolpidem (10 mg) and zaleplon (10 mg). Middle-of-the-night administration of zolpidem (10 mg), however, significantly impaired driving performance 4 hours after that time.
- Currently the only drugs that showed no significant driving impairment 4 hours after middle-of-the-night administration are zaleplon (10 and 20 mg) and sublingual zolpidem tartrate (3.5 mg).
- Despite its short half-life, the melatonin receptor agonist hypnotic ramelteon impairs next-day driving performance. Hence the development of safer yet effective hypnotic drugs is needed.

For most people, driving a car is a daily activity (e.g., to commute to and from work). Typically people with insomnia and other sleep disorders are outpatients; thus it is likely that they routinely drive a car. Driver sleepiness (reduced alertness) accounts for 10% to 30% of accidents.[1] Because a number of patients with insomnia report daytime sleepiness, it is important to determine whether sleep disorders or their pharmacologic treatments negatively affect driving.

Data on driving ability in untreated insomniacs is inconsistent as to whether insomnia impairs driving. The fact that only some insomniacs report daytime sleepiness, and objective assays of sleepiness show them to be alert, probably accounts for the negative findings in insomnia. Surprisingly little research has been conducted to examine the effect of insomnia on driving ability under controlled conditions. One on-the-road driving study found no impairment in patients with insomnia, but these patients used hypnotic drugs infrequently, so they may have benefited from treatment.[2]

To be effective, hypnotic drugs need to put patients to sleep and maintain sleep during the night. However, this induction of sedation needs to dissipate across the night because the patient wants to wake up refreshed without residual daytime sleepiness. The challenge is to find the right balance between efficacy into the later portion of the night and safety of hypnotic drugs. This chapter focuses on the effects of hypnotic drugs on next-day driving.

EPIDEMIOLOGIC EVIDENCE

Several epidemiologic studies examined the effect of hypnotic drug use on driving. Neutel selected 78,070 patients using the benzodiazepine hypnotics triazolam or flurazepam from the Saskatchewan Health Database and compared the risk for traffic accident injury with data from 97,862 "healthy control" subjects.[3] The use of benzodiazepine hypnotics was associated with a significantly increased (3.9 times) risk for traffic accident injury. The data further revealed that the risk for accident injury is highest after treatment initiation and then gradually decreases with continued use. Similarly, Barbone and colleagues reported an increased traffic accident risk for users of benzodiazepine hypnotics (odds ratio [OR] = 1.19; 95% confidence interval [CI], 0.83 to 170).[4] In contrast, McGwin and associates did not find a significant increase in traffic accident risk patients using benzodiazepine hypnotics (OR = 5.2; 95% CI, 0.9 to 30).[5] Importantly, researchers have shown that the risk was, in part, dependent on the half-life of the drug. Surprisingly, whereas classic benzodiazepine hypnotics with a long (>24 hours) or intermediate (6 to 24 hours) half-life showed no significant effect on accident risk, users of other benzodiazepine receptor agonist hypnotics with shorter half-lives (i.e., <8 hours) showed a significantly increased traffic accident risk (OR = 4.00; 95% CI, 1.31 to 12.2). Interestingly, in the latter study 14 drivers were all treated with zopiclone.[4]

For a number of reasons it is hard to draw conclusions on fitness to drive of individual patients from these population-based studies. Importantly these studies provide little information on if, when, and to what extent a drug impairs driving.[6] This is because this type of database research only compares medication distribution files with accident records of patients. It is often not possible to verify whether the drug was actually used on the day of the accident, nor are data collected on actual drug dosage, the specific type of hypnotic drug taken, its half-life, the time between intake and driving, and important accident-related issues (e.g., whether the driver was actually at fault of causing the accident or if it was due to other traffic). Also, sometimes it is unclear whether benzodiazepines were being used for hypnotic or anxiolytic purposes.[7-9] This likely has an effect on the risk for traffic accidents because sleep medication is usually taken at bedtime and anxiolytics during the day, causing a large difference between time of drug intake and driving between the two clinical use patterns. Taken together, current epidemiologic data suggest a potentially increased traffic accident risk in patients treated with hypnotic drugs. However, these data provide little information to the user or the clinician about relative risk associated with different drugs, drugs with different half-lives, and dose for a given drug.

THE ON-THE-ROAD DRIVING TEST

Because of possible ethical restrictions and legislation most countries do not allow the investigation of drug effects on driving in normal traffic. An exception is the Netherlands, where a standardized on-the-road driving test has been used over the past 30 years to examine the effects of drugs on driving.[10-12] The 100-km driving test is conducted on a public highway in normal traffic. Subjects are instructed to drive with a steady lateral position of their own choice within the right (slower) traffic lane while maintaining a constant speed of 95 km/hour. This allows them to drive along with the regular traffic flow. A driving instructor with dual controls guards the safety of the subjects, and the investigator in the back seat monitors the recording equipment. Lateral position data and mean speed are recorded two times per second. The mean lateral position (MLP) and mean speed (MS) are control variables, showing whether the subject conducted the test according to the instructions. These data further allow calculating the traditional primary parameter of the driving test, the Standard Deviation of Lateral Position (SDLP). The weaving of the car (i.e., SDLP) has proved to be an excellent measure of vehicle control. Dose-dependent driving impairment (i.e., SDLP increment) has been shown for alcohol and drugs of abuse[13] as well as for pharmacotherapeutic drugs such as antidepressants, hypnotics, anxiolytics, and antihistamines.[14] Alternatively, driving improvement has also been shown, illustrated by a reduction in SDLP, for example, in patients with attention deficit/hyperactivity disorder who were treated with methylphenidate.[15] The effect of driver sleepiness (e.g., that caused by sedative drugs) on vehicle control is illustrated in Figure 46-1.

Drivers are normally capable of keeping the car within the lane boundaries, and loss of vehicle control by drivers after taking a sedative increases SDLP values. This loss of control may also result in having out-of-lane excursions, but these are a poor predictor of vehicle control (SDLP) because they depend in great part on the choice of lateral position within the right traffic lane.[16] Drivers who choose a lateral position close to the lane boundary are much more likely to have excursions out of lane than those driving in the middle of the road,

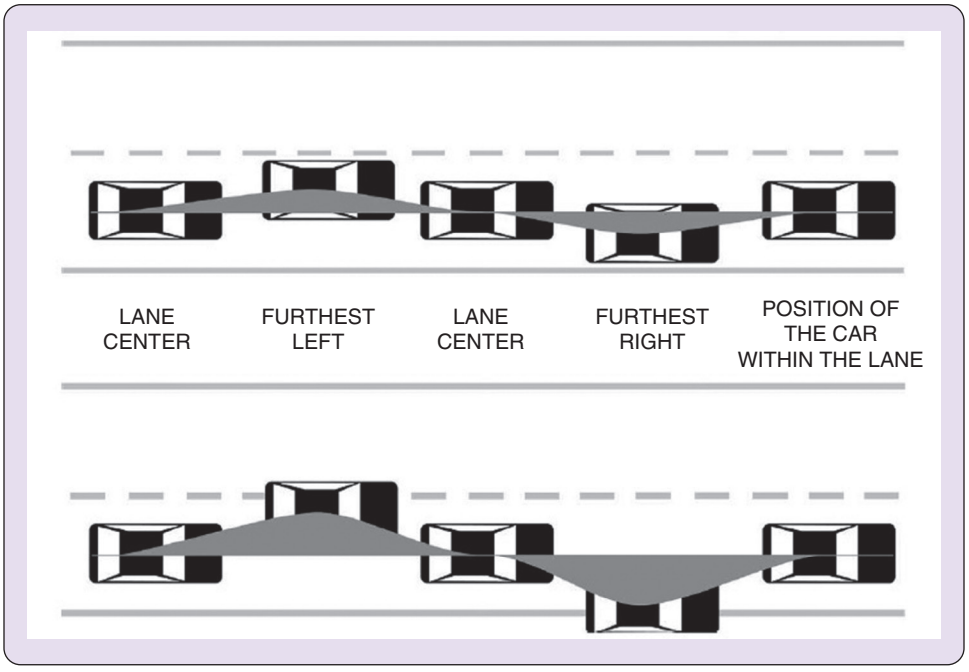

Figure 46-1 Standard Deviation of Lateral Position (SDLP). The *top figure* represents a regular SDLP under placebo condition. If weaving increases (*bottom figure*), the SDLP value becomes higher. (Modified from Verster JC, Veldhuijzen DS, Volkerts ER. Residual effects of sleep medication on driving ability. *Sleep Med Rev* 2004;8:309–25.)

independently from a possible drug effect on driving. A secondary outcome measure of the driving test, the standard deviation of speed, can also provide an indication of loss of vehicle control, but this measure has been shown to be much less sensitive than SDLP.[17]

When interpreting SDLP as an outcome measure it is important to keep in mind that the differences between drug and placebo (ΔSDLP) is the key end point. Absolute SDLP is not as sensitive because values under placebo vary significantly between individual drivers (mean, 18 to 20 cm; range, 10 to 30 cm). However, SDLP values are very stable within individuals (e.g., test-retest reliability above 0.80 have been shown).[12] Aside from demonstrating a significant difference it is also important to determine whether the impairment is clinically relevant as well as how many individuals show a clinically relevant impairment. To determine what should be regarded as clinical relevant impairment, researchers have looked at the ΔSDLP observed after administering alcohol to reach a blood alcohol concentration (BAC) of 0.05%. The driving data indicated that ΔSDLP of greater than 2.4 cm should be regarded as illustrative of clinically relevant driving impairment (Box 46-1).

In many instances in which the driving performance impairment is clinically relevant (i.e., ΔSDLP >2.4 cm), the standard deviation of speed after drug treatment does not differ significantly from placebo.[17] The same is also true for the number of excursions out of lane.[16] Therefore the standard deviation of speed and the number of excursions out of lane are generally not considered as important factors to determine whether driving is safe. Also, the number of collisions and stopped driving tests are poor indicators of a drug's effect on driving (Box 46-2).

An important aspect of the driving test is time on task. The standardized driving test takes about 1 hour to complete. This is necessary to get a good sample of the drug's effect on driving. Research has shown that shortening the driving test makes it less sensitive in showing a true difference between drug and placebo.[21] The latter is caused by the fact that in tests of short duration motivated drivers may successfully counteract impairment by investing more effort to perform the test. Vigilance decrement (i.e., increased performance impairment over distance driven or duration of driving time) is an essential characteristic of the driving test.[21] Hence, on the driving test its gets harder and harder to compensate for drug-induced impairment with increasing time on task. Increased effort sometimes can be effective for short duration (e.g., a 10-minute driving test) but does not last for the full 1 hour.

It has been suggested that on-the-road driving tests can be replaced by psychometric tests measuring driving-related skills and abilities or by driving simulators. At first this seems a safer alternative, and it would be less effortful if on-the-road driving performance and fitness to drive could be predicted by a short test battery that could be conducted at any place of choice (e.g., the physician's office). Unfortunately, comparative research showed that cognitive and psychomotor tests poorly predict on-the-road driving performance.[22,23] The primary reason for this poor correlation is the fact that driving-related skills and abilities are tested in isolation, whereas when on the road these are integrated (e.g., judgment, vision, reaction time). Importantly, overall driving performance is not simply the sum of its components (e.g., tracking, reaction speed, attention) but rather is the integration of these various skills to produce optimal safe driving. Driving simulators attempt to mimic actual driving, and these machines have become more sophisticated over the years. Whereas in the past, driving simulators were often simple computerized divided-attention tasks using a steering wheel instead of a respond box,

Box 46-1 CLINICALLY RELEVANT STANDARD DEVIATION OF LATERAL POSITION INCREMENT

There is only indirect evidence that Standard Deviation of Lateral Position (SDLP) is related to the risk for having car crashes.[18] Hence, to determine whether the magnitude of driving impairment has clinical relevance, often the comparison with impairment seen after different dosages of alcohol is made. Louwerens and colleagues examined driving performance after different dosages of alcohol.[19] The results are depicted in Figure 46-2 and show a clear dose-dependent relationship between SDLP and blood alcohol concentration (BAC).

From these historical data, it was inferred that the cutoff for clinically relevant impairment is an SDLP increment relative to placebo of +2.4 cm, corresponding to a BAC of 0.05%, which is the most commonly reported legal limit for driving a car.

Box 46-2 CRASHES AND STOPPED DRIVING TESTS

At first, the occurrence of crashes may be regarded as the ultimate evidence that a drug negatively affects driving; however, this premise can be debated. First, crashes can be caused by many factors; the effect of hypnotic drugs is only one. For example, a crash may be caused by another driver without any blame to the patient. In the on-the-road driving test, crashes do not occur because the driver is accompanied by a licensed driving instructor. If safety becomes compromised, the driving instructor intervenes and prevents a crash from happening. In driving simulators, crashes are more commonly seen. This likely has to do with increased sleepiness scores and the fact that participants know that having a crash has no real-life consequences in terms of injury or death. Crashes are infrequent and uncommon events during normal driving. Even when driving is significantly impaired, usually crashes do not occur. Therefore counting the number of crashes as an indicator of drug-induced driving impairment is not useful.

Driving tests can be stopped for many reasons. For example, the driver experiences adverse events such as stomach pain or drowsiness and requests to stop the test before completion. Alternatively, the driving instructor may abort the test if he or she feels it is unsafe to continue. In both instances, these are subjective decisions that by no means imply that driving is actually impaired. A comparative analysis of more than 7000 driving tests revealed that stopped driving tests occur both after drug treatment (4.1%) and, although to a lesser extent, in placebo conditions (0.7%).[20] Further analyses revealed that 39.6% of stopped drivers had a lower and 60.4% had a higher SDLP than 35 cm, a cutoff sometimes used to indicate unsafe driving. Because SDLP values of stopped and completed driving tests often do not significantly differ, the number of stopped tests should be regarded as a poor predictor of a drug's effect on driving performance.

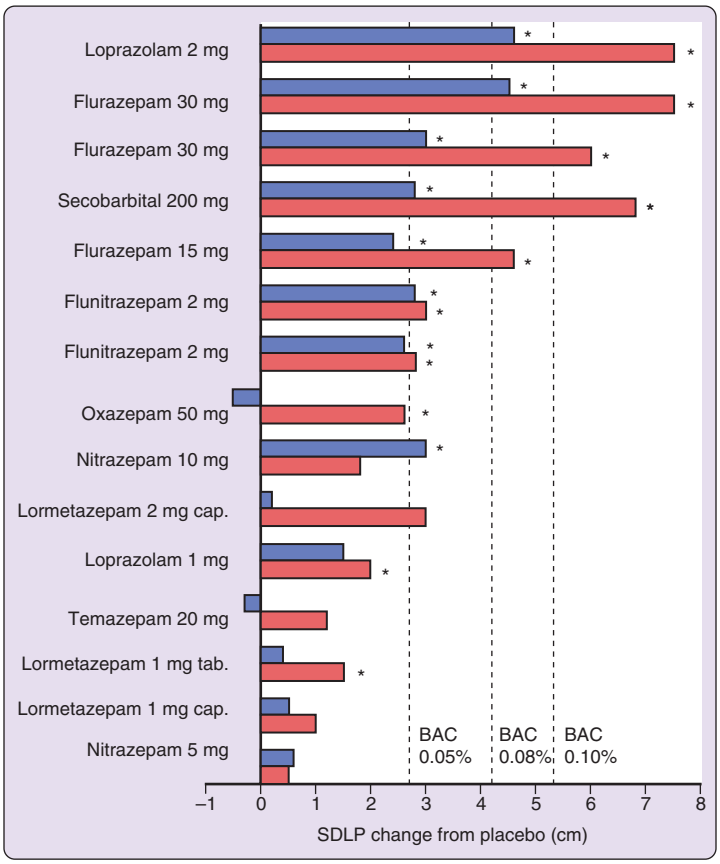

Figure 46-2 Effects of benzodiazepine hypnotics on driving. All treatments were administered at bedtime. Driving tests were performed in the morning, 9 to 10 hours after intake (*red bars*), and the afternoon, 16 to 17 hours after intake (*blue bars*), representing the times many people drive to and from work. Significant differences from placebo ($P < .05$) are indicated by an asterisk (*). (Modified from Verster JC, Veldhuijzen DS, Volkerts ER. Residual effects of sleep medication on driving ability. *Sleep Med Rev* 2004;8:309–25.)

nowadays real cars including car motion and sound are used with realistic scenery projected on a large surrounding screen, including other traffic. Few researchers have directly compared on-the-road and simulated driving. These studies found that SDLP values and sleepiness scores are generally significantly higher in driving simulators.[24] The difference between driving simulator environments and actual driving in terms of risks for having an accident is essential and may account for the observed differences. In many simulators, number of accidents is used as an end point. However, having an accident in a simulator has no consequences in terms of injury or death, whereas these risks are evident during on-the-road driving. Hence a number of people may regard driving in the simulator as a game and thus have a different mindset compared with on-the-road driving. Nevertheless, driving simulators and psychometric tests are useful to determine fitness to drive in general and to examine performance impairment. The decision about whether driving is safe should always be based on the overall available evidence gathered with different research methodologies and thus should include performance on both cognitive and psychomotor tests, driving simulators, and an on-the-road driving test.

The purpose of hypnotic drugs is to make you fall asleep and maintain sleep. It is critical, however, that after waking up 7 to 8 hours later, people who use these drugs are not sedated and can participate safely in activities of daily living such as driving. The next sections of this chapter summarize findings from on-the-road driving studies examining the effects of hypnotic drugs on driving.

EFFECTS OF HYPNOTICS ON DRIVING

The usual design of studies examining the effects of hypnotic drugs on driving performance is a double-blind placebo- and active drug–controlled trial. Treatments are administered at bedtime, and driving tests are typically conducted the following morning and sometimes afternoon (about 9 and 16 hours after intake), occasions that are coincidental with the times people usually drive to and from work. Since the 1980s, the effects on driving of a great number of benzodiazepine and nonbenzodiazepine hypnotic drugs have been examined by applying the standardized on-the-road driving test.[25,26] An overview of the results for benzodiazepine hypnotics is given in Figure 46-3.

It is evident from Figure 46-3 that benzodiazepine hypnotics significantly impair next-morning driving. In the afternoon, impairment is less pronounced, but for several drugs the magnitude of impairment (SDLP increment relative to placebo) still is higher than that seen with a BAC of 0.05%. A recent meta-analysis of these data revealed that driving

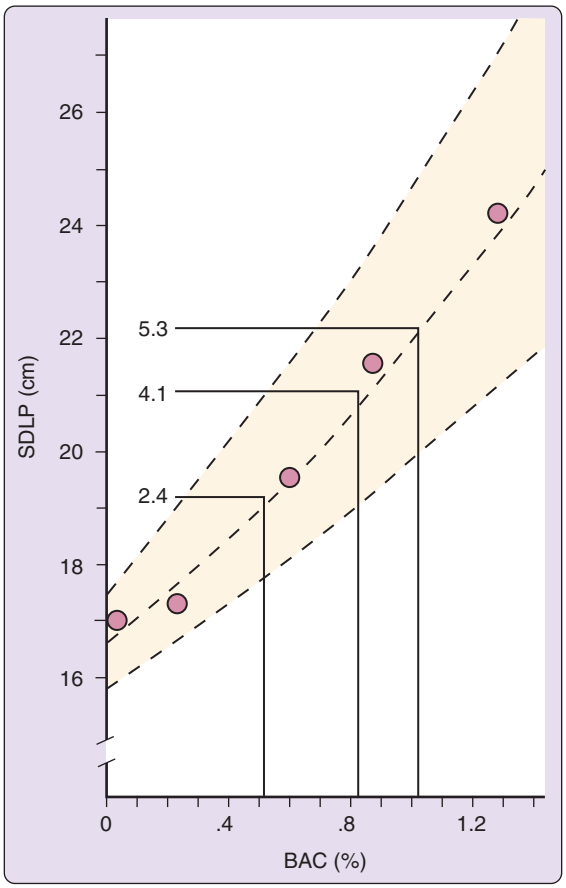

Figure 46-3 Standard Deviation of Lateral Position (SDLP) relative to baseline (no alcohol) at different breath alcohol concentration (BAC) levels.

impairment is dose dependent and is more pronounced with drugs with a longer half-life and when the time between drug intake and driving is shortened.[26] Both intermediate- (6 to 12 hours) and long-acting (>12 hours) drugs cause significant impairment the morning after bedtime administration, whereas short-acting hypnotics (<6 hours) generally do not. Interestingly, interindividual blood drug concentrations at a given time point correlate poorly with an individual's driving impairment.[27] For some benzodiazepine hypnotics, sex differences were seen in the magnitude of driving impairment,[28] emphasizing the importance of including both male and female participants in driving studies. It should be noted that the effects shown in Figure 46-3 were all found after one or two nights of treatment. Up to now, long-term effects of the use of benzodiazepine hypnotics on driving performance have not been extensively examined using the on-the-road driving test. However, given the epidemiologic evidence discussed in this chapter and driving data from studies examining long-term benzodiazepine anxiolytics use (e.g., diazepam for 4 weeks),[29] it can be assumed that at least partial tolerance to the impairing effects can be expected if the drugs are used on a nightly basis over a period of time. However, the rate the development of this tolerance is not currently defined. Importantly, the mechanism that mediates this tolerance has not been investigated. For drugs with a half-life greater than 15 hours, impairment may worsen because of drug accumulation. As a result of the lack of clear data, there is currently no consensus among sleep experts as to whether and when driving is safe after initiating treatment with medications known to impair driving acutely.[30]

The "z-drugs" (i.e., zopiclone, eszopiclone, zolpidem, and zaleplon) also act at the benzodiazepine receptor of the gamma-aminobutyric acid A ($GABA_A$) complex but do so more specifically and have a relatively shorter half-life. Hence, it was anticipated at their introduction that these drugs would be devoid of the next-morning adverse effects seen with benzodiazepine hypnotics. Zopiclone, the first of the z-drugs introduced and commonly prescribed in Europe, is one of the most frequently studied drugs used in hypnotic clinical studies. Bedtime administration of zopiclone (7.5 mg) consistently results in next-morning driving impairment. The magnitude of impairment is about +2 to +3 cm, roughly comparable to that seen with a BAC of 0.05%.[31] For this reason, zopiclone is typically used as positive control in on-the-road hypnotic driving studies. In the afternoon, however, driving after zopiclone (7.5 mg) is not impaired. In contrast, bedtime administration of zolpidem (10 mg) or zaleplon (10 mg) does not impair next-morning driving.[32,33] This is attributable to the short (<3 hours) half-life of these two drugs.

MIDDLE-OF-THE-NIGHT ADMINISTRATION

Because sleep maintenance problems are commonly reported by patients with insomnia, treatments enabling patients to fall asleep more rapidly after middle-of-the-night (MOTN) awakenings have been developed, to be taken in the middle of the night. In addition, many drugs (e.g., zolpidem) are taken off label in the middle of the night. Thus the effects of hypnotics taken in the middle of the night need to be investigated in terms of driving performance the next day. To date, four such on-the-road driving studies have been conducted.[34] In these studies, treatments were administered during the night, 4 to 6 hours before the driving test. Driving performance after MOTN administration of traditional benzodiazepine hypnotics has not been examined, presumably because they already impair next-morning driving after bedtime administration. Zolpidem (10 mg and 20 mg, oral immediate-release tablets) significantly impaired driving in a dose-dependent manner when tested 4 hours after MOTN administration.[35] Also, gaboxadol (15 mg) and zopiclone (7.5 mg) significantly impaired next-morning driving after MOTN administration.[36] In contrast, buffered sublingual zolpidem (3.5 mg) and zaleplon (10 mg and 20 mg) did not significantly affect driving 4 hours after MOTN administration.[36-38]

NON–GAMMA-AMINOBUTYRIC ACID HYPNOTICS

In the search for hypnotic drugs without next-day sedation, development has focused on drugs that do not act at the $GABA_A$ receptor complex. In this context, histamine-1 and orexin receptor antagonists are under investigation. Also, melatonin agonists are considered. For example, the effects on driving of ramelteon (8 mg), a melatonin receptor agonist, have been investigated.[39] Significant driving impairment was observed 8.5 hours after bedtime administration. Significant next-day impairment was also found on reaction time in the Sternberg Memory Scanning Test, reaction speed and

tracking in a divided attention test, and delayed recall in a word learning test. No significant impairment was found on the Digit Symbol Substitution Test and a balance test, which was performed during the night, 2 hours after treatment administration. The magnitude of performance impairment seen with ramelteon (8 mg) was comparable to that of zopiclone (7.5 mg). This is an important finding because ramelteon has a short half-life. Thus the question arises as to the mechanism of this impairment. The two possibilities are that the impairment is due the effect of a long-acting ramelteon metabolite or the effect of ramelteon on shifting circadian phase.

FUTURE DIRECTIONS

Although the effects of drugs on mean SDLP has been the standard measure of impaired driving, the nature of the risk and extent of the risk are not fully defined with this single analytic approach. In the recent past, two modifications to the traditional analysis of on-the-road driving have been investigated. The first is the use of alternate end points to SDLP. Lapses have traditionally been used to assess the impairing effects of sleep deprivation on laboratory-based performance. Recently, lapses have been introduced as an outcome measure of the on-the-road driving test.[40] A lapse in driving is defined as a continuous change in lateral position of greater than 100 cm, lasting for at least 8 seconds. In contrast to weaving (SDLP), a unique feature of lapses is that they occur during short periods of inattention. That is, the presence or absence of lapses may differentiate drivers who are aware of driving impairment from those who are not aware of loss of vehicle control (SDLP increment). If correct, having a lapse may have serious consequences in terms of traffic safety because this period of inattention may increase the risk for having a sleepiness-related accident. Moving forward, research using lapses as an outcome measure is needed to determine the degree of overlap between lapses and SDLP and to what extent lapses and SDLP provide unique information regarding impaired driving and traffic accident risks.

The second innovation involves an alternate method to analyze SDLP data. Although mean SDLP contrasts (drug vs. placebo) provide useful information, they do not address the primary issue of putting individuals at increased risk for having a traffic accident. A large sample size or small variance can lead to statistically significant mean differences that do not correspond to meaningful driver impairment (i.e., nonclinically relevant SDLP increments, less than +2.4 cm). A small sample size or large variance can result in failure to find a difference that in fact corresponds to increased accident risk. Indeed, a large variance may be the result of outlying individuals with impaired driving skills who are the very group of interest. As is the case with all safety data parameters, it is more important to discover whether a treatment produces a large effect in a subset of subjects than whether it produces a relatively clinically meaningless shift across the entire sample. This problem can be addressed by a responder analysis that assesses the proportion of patients on drug versus placebo who exceed a predetermined threshold for clinically meaningful impairment or other thresholds, larger and smaller, that are of interest in understanding the degree of impairment. The statistical test used for such an analysis has been called symmetry analysis because it tests whether the distribution of changes (drug minus placebo) above the threshold and below the threshold is symmetrical around zero.

CLINICAL PEARLS

- Drug type, dosage, time of driving after drug intake, drug half-life, and patient characteristics all have a significant effect on the magnitude of next-day driving impairment.
- Impairment is more pronounced when time between drug intake and driving is shorter, with higher drug dosages, and with drugs with a longer half-life.
- More research is needed to determine effects of chronic drug use on driving and to explore gender, age, and disease differences associated with these effects.

SUMMARY

The World Health Organization has identified traffic accidents as one of the major causes of injury and death around the world. An important factor contributing to traffic accidents is inattention of the driver due to reduced alertness or increased sleepiness. It is therefore important to understand the effects of sedating drugs on driving and their impact on the risk for crashes. A standardized method to examine ability to drive is the on-the-road driving test. Results from 30 years of Dutch on-the-road driving research have demonstrated that some hypnotic drugs are safe whereas others impair driving performance, thereby influencing drug labeling. In addition, differences between drugs in degree of impairment also vary as a function of dosage, half-life, and time since drug ingestion, demonstrating the importance of treatment compliance with directions for use of the drug to ensure driving safety.

DISCLAIMER

Although the information presented in this chapter has been gathered and evaluated with great care, the authors will not accept any liability after use of the information by patients taking the medicines discussed. Patients should always consult their physician concerning whether or not it is safe to drive a car.

DISCLOSURE OF INTEREST

Joris Verster has received grants and research support from The Dutch Ministry of Infrastructure and the Environment, Janssen Research and Development, Takeda, and Red Bull and has acted as a consultant for Canadian Beverage Association, Centraal Bureau Drogisterijbedrijven, Coleman Frost, Deenox, Eisai, Purdue Pharma, Red Bull, Sanofi-Aventis, Sepracor, Takeda, Transcept, and Trimbos Institute.

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REVIEW QUESTIONS

1. What tests are considered useful in determining a drug's effect on driving ability?
   A. On-the-road driving test
   B. Driving simulator
   C. Cognitive and psychomotor tests
   D. All of the above
2. Which of the following factors is *not* clearly related to the driving impairment observed in individual patients treated with a benzodiazepine hypnotic?
   A. Drug dosage
   B. Half-life
   C. Blood drug concentration
   D. Time between drug intake and driving
3. Which of the following statements is *correct* regarding driving simulators as opposed to on-the-road driving tests?
   A. Standard Deviation of Lateral Position (SDLP) values are lower.
   B. Reported sleepiness scores are lower.
   C. Risk-taking behavior is increased.
   D. None of the above
4. Taken at bedtime, which of the following drugs has *not* been shown to impair on-the-road driving?
   A. Zopiclone
   B. Flurazepam
   C. Ramelteon
   D. Zolpidem
5. Other than SDLP, what measures are available from an on-the road-driving test?
   A. Standard deviation of speed
   B. Frequency of lapses
   C. Frequency of stopped driving episodes
   D. All of the above

ANSWERS

1. **D.** Although the standardized on-the-road driving test is regarded as the gold standard to determine drug effects on driving, this test focuses on highway driving. Other features of driving (e.g., city driving, emergency brakes, risk taking) are not assessed. Therefore results from different modalities and test methodologies are complementary and all should be considered when determining a patient's fitness for driving or the effects of a drug on driving.
2. **C.** It has been shown that driving performance is worse with higher dosages, with benzodiazepine hypnotics with a longer half-life, and when the time between drug intake and driving is shortened. Blood drug concentrations may correlate significantly with SDLP increment (i.e., driving impairment) at a group level, but there are large individual differences. In other words, there is a poor relationship between Standard Deviation of Lateral Position (SDLP) increment and blood drug concentration in individual drivers.
3. **C.** In driving simulators SDLP values and sleepiness scores are generally higher compared with on-the-road driving. Risk-taking behavior may be increased because the consequences of having a crash in terms of injury or death, which are apparent on the road, are absent in driving simulators. Some participants may regard the driving simulator as a game and conduct the test accordingly.
4. **D.** Zopiclone and flurazepam have a long half-life and hence cause impairment. Although ramelteon has a short half-life, it clearly impaired performance on the on-road-driving task. The mediator of impairment is not well understood. Zolpidem has a short half-life and does not impair driving in the morning after bedtime ingestion. However, it does impair driving if taken in the middle of the night.
5. **D.** All of the above measures can be obtained in on-the-road driving studies. Although standard deviation of speed and frequency of stopped driving episodes are not very sensitive to drug effects, frequency of lapses is a promising assay of drug performance that complements SDLP.