Drugs’ effects on performance and memory differ, depending on time since administration.
FDA action and clinical trials show need for precautions

Sleep driving blamed on the hypnotic zolpidem was used as a defense last year in Virginia in a criminal case involving impaired driving. The defendant’s attorney argued that the defendant should not be held criminally liable because he was “essentially unconscious” and the accident therefore was involuntary.

The “sleep driving” defense failed when testimony revealed the defendant had taken 5 times the recommended zolpidem dose before the accident. The judge found him guilty of a felony charge of driving under the influence of a sleep medication.

Sedative-hypnotics are increasingly being used to treat insomnia and as a result some patients try to drive while under the drugs’ sedating effects. Also, new FDA-ordered labeling for all 13 available prescription sleep aids warns of potential risks of “complex sleep-related behaviors,” including driving, phoning, and eating while asleep (Box 1, page 40).

Hypnotics can improve quality of life and well-being by addressing insomnia’s complications—hypertension, diabetes, coronary artery disease, depression, and anxiety—but they also have been associated with impaired motor coordination and somnambulism. To help you and your patients weigh sleep medications’ relative risks and benefits, we report on clinical studies
and court cases in the literature. Most of the data focus on zolpidem, by far the most prescribed hypnotic (Box 2, page 43).8,9

**Zolpidem incidents and cases**

In 2005, Americans filled 43 million prescriptions for sedative-hypnotics—26.5 million for zolpidem alone—compared with 29 million prescriptions in 2001.1 In addition to the new FDA-requested warnings about sleep-related behaviors, zolpidem’s labeling cautions patients about operating heavy machinery, driving, or engaging in hazardous occupations after taking the drug. The manufacturer tells patients:

- to ingest zolpidem only before going to bed
- that they may experience residual sedation the following day.

Not all patients heed the precautions or follow dosing recommendations, however.

**Impaired driving**. Besides the “sleep-driving” case in Virginia, a highly publicized zolpidem-related driving incident occurred May 4, 2006, when U.S. Representative Patrick Kennedy was involved in an accident after having taken zolpidem in combination with an antinausea medication. Another driving-related case has used zolpidem as a defense for impairment, but the court decided that the medication was not at fault because the defendant also had ingested alcohol.10

**Other litigation.** Although zolpidem-related impairment apparently has not been used successfully as a defense for a driving incident, class action suits alleging failure to disclose potentially harmful side effects have been filed against the manufacturer.

In Janet Makinen and others v. sanofi-aventis,11 at least 500 plaintiffs claim zolpidem is related to sleep-driving, sleep-eating, and other somnambulistic behaviors. Plaintiffs allege negligence, breach of implied warranties, fraud, unfair trade practices, express warranty violations, strict liability, and consumer fraud violations. Other suits claim dangerous sleep-related side effects with zolpidem use.12

**What clinical evidence shows**

**Driving impairment.** Clinical studies have shown conflicting results about driving impairment associated with zolpidem. The literature falls into 2 categories, based on treatment duration:

- Zolpidem affects performance and memory within the first 4 to 5 hours of administration (Table 1, page 44).
- Beyond 5 hours, no residual effects on performance have been identified (Table 2, page 46), and repeat nightly dosing has not caused impairment or tolerance.

Verster et al13 examined residual effects of benzodiazepines and the nonbenzodiazepines zolpidem, zopiclone (available in the United States as eszopiclone), and zaleplon on driving ability, as reported in studies of on-the-road driving, driving simulators, epidemiologic data, and closed-road driving. This review found that:

- All sedative hypnotic benzodiazepines had statistically significant residual effects 10 to 11 hours after ingestion, with longer periods of impairment corresponding to medications with longer half-lives.

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Zopiclone was associated with significant residual impairment for up to 10 hours after ingestion.

Zolpidem and zaleplon showed no significant impairment in driving 10 to 11 hours after ingestion. Impairment was found, however, when zolpidem was taken within 5 hours of driving.\textsuperscript{14,18}

**Acute effects (<5 hours)**

**Combined with alcohol.** Wilkinson\textsuperscript{14} conducted a randomized, 6-way crossover study in which subjects received 10- or 15-mg doses of zolpidem or placebo plus an alcoholic beverage (enough to obtain a blood alcohol concentration [BAC] of \textasciitilde0.08%) or placebo beverage. Tests given shortly after patients took the study medications showed that zolpidem caused statistically significant impairment both in combination with alcohol and alone during peak drug effect—identified as 45 minutes after ingestion. Alcohol did not potentiate the impairment associated with zolpidem.

Using a similar design, Mattila et al\textsuperscript{16} compared acute performance impairment associated with zolpidem, diazepam, oxazepam, and zopiclone. In this randomized, double-blinded, crossover study, all comparison medications impaired antecedent learning and memory, but zolpidem given at 15 mg had the greatest effect. Zolpidem impaired coordination, reactive functioning, and cognitive skills at 1 and 3.5 hours after administration, and simulated driving test performance remained impaired at 5 hours (approximately two half-lives of the medication). Of note is that the 15-mg zolpidem dose used in this study was shown by Wilkinson et al\textsuperscript{14} to be more impairing than the recommended maximum 10-mg dose.

A study from the University of Toronto\textsuperscript{19} that did not include zolpidem examined potential psychomotor performance deficits and sleepiness in a comparison of time-released melatonin, 6 mg; zaleplon, 10 mg; zopiclone, 7.5 mg; temazepam, 15 mg, and placebo. Tests were given to 9 men and 14 women, ages 21 to 53, just before drug administration and 7 hours later.

Zaleplon had the greatest effect on psychomotor performance, followed by temazepam and zopiclone. Aside from prolonged perceived sleepiness, melatonin and placebo did not interfere with performance testing.

**Middle-of-the-night dosing.** Effects of zolpidem and zaleplon on driving ability, memory, and psychomotor performance were compared by Verster et al\textsuperscript{18} in a randomized, controlled trial. The double-blind, 5-period crossover design measured the effects of middle-of-the-night use of zaleplon, 10 or 20 mg; zolpidem, 10 or 20 mg; or placebo on:

- driving ability 4 hours after administration
- memory and psychomotor performance 6 hours after administration.

As expected, subjects taking zolpidem showed impairment on all measures. The 10- and 20-mg doses significantly impaired driving 4 hours after ingestion, with the
### Clinical Point

Patients who scored poorly on driving tests alone 5.5 hours after taking 10-mg of zolpidem might have been more susceptible to the drug’s effects.

### Table 1

**Studies of zolpidem-associated driving skills impairment (<5 hours after dosing)**

<table>
<thead>
<tr>
<th>Author/design</th>
<th>Doses and timing</th>
<th>Driving skills assessments</th>
<th>Conclusions</th>
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</table>
| Wilkinson, 1995<sup>14</sup>  
Blinded;  
29 subjects | Zolpidem, 10 mg, 15 mg, and placebo in combination with an alcoholic drink (to reach a BAC of 0.08%) or placebo drink; testing 45 min, 130 min, and 230 min after administration | Visual backward masking test (approximates driving performance) and attention tests | Zolpidem produced significant impairment in combination with alcohol and when administered alone during peak effect assessment; alcohol did not potentiate zolpidem’s effects; additive effects of alcohol seen with 10-mg dose but not 15-mg dose of zolpidem |
| Rush et al, 1998<sup>15</sup>  
Double-blind, crossover;  
9 subjects | Zolpidem, 7.5, 15, and 22.5 mg; quazepam, 15, 30, and 45 mg; triazolam, 0.1875, 0.375, and 0.5625 mg; testing ½, 1, 1½, 2, 2½, 3, 4, 5, and 6 hours after administration | Subject- and observer-rated questionnaires; tests of recall and delayed recognition | Performance-imparing effects of zolpidem were virtually indistinguishable from those of classic benzodiazepines, such as triazolam |
| Mattila et al, 1998<sup>16</sup>  
Randomized, placebo-controlled, double-blind, crossover;  
12 subjects | Zolpidem, 15 mg; diazepam, 15 mg; oxazepam, 30 mg; zopiclone, 7.5 mg; alcohol testing before and 1, 3½, and 5 hours after administration | Simulated driving and other measures | Zolpidem impaired coordination, reaction, and cognition at 1 and 3½ hours; tracking remained impaired at 5 hours; all agents (especially zolpidem) impaired learning and memory |
| Mintzer et al, 1999<sup>17</sup>  
Double-blind, placebo-controlled;  
16 subjects | Zolpidem, 15 mg/70 kg (dosed by subject weight); testing ½, 1, 2, and 3 hours after administration | Memory tasks (recall, fragment completion, recognition) | Zolpidem interfered with explicit but not implicit memory after administration; zolpidem produced a specific deficit in acquisition of contextual information |
| Verster et al, 2004<sup>18</sup>  
2-step randomized, placebo-controlled, double-blind, crossover;  
30 subjects | Zolpidem, 10 mg and 20 mg; zaleplon, 10 mg and 20 mg; middle-of-the-night dosing; testing 4 hours after dosing | On-the-road driving and other tests of attention, learning, and thinking | Zolpidem, 10 mg and 20 mg, significantly impaired driving function; zaleplon, 20 mg, produced significant impairment on all psychomotor and memory tests; zaleplon, 10 mg and 20 mg, did not differ significantly from placebo |

BAC: Blood alcohol concentration

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20-mg dose—twice the recommended maximum dose—producing greater impairment. The 20-mg dose—but not the 10-mg dose—also significantly impaired memory and psychomotor function. Zaleplon did not impair driving ability, memory, or psychomotor testing.

Partinen et al<sup>20</sup> used the recommended zolpidem dose in a similar study of after-midnight use by women with insomnia. The double-blind, randomized, controlled trial evaluated performance with a driving simulator and neuropsychological testing 5.5 hours after medication dosing. Patients taking zolpidem, 10 mg, showed no significant impairment when compared with those taking placebo. Some patients scored poorly on the driving tests alone, and the authors concluded that this group was more susceptible to zolpidem’s effect.
**Memory.** In a double-blind, placebo-controlled trial by Mintzer et al,17 zolpidem dosed by patient weight at 15 mg/70 kg:

- significantly impaired explicit memory (requires conscious recollection for recall)
- did not affect implicit memory (lack of conscious awareness in the act of recollection).

Explicit memory for material presented before drug administration and previously acquired knowledge was not affected. Zolpidem spared explicit and implicit memory for material presented before administration, but subjects had difficulty acquiring contextual information after the dose was given.

These findings support complaints of zolpidam-related anterograde amnestic episodes, which also occur with some benzodiazepines (such as midazolam).

**Similar to benzodiazepines?** Rush et al’s results21 support Mintzer’s assertion17 that zolpidem shares many side effects with benzodiazepines. Performance impairment associated with zolpidem—as rated by subjects and observers—is virtually indistinguishable from a benzodiazepine effect, except that the duration is shorter with zolpidem (5 hours), compared with up to 10 hours for benzodiazepines.

Logan and Couper22 reviewed police reports and toxicology profiles of individuals suspected of driving while impaired. Zolpidem was found in 29 subjects, 5 of whom showed no other substances. In those 5, zolpidem blood levels ranged from 0.08 to 1.40 mg/L and did not appear to correlate with the degree of impairment.

**Residual effects (>5 hours)**

**Older patients.** In a randomized, placebo-controlled trial by Fairweather et al,23 zolpidem improved sleep latency in 24 subjects ages 63 to 80. No evidence of impairment in reactive time, memory, or word recognition was found 8.5 hours after nighttime dosing, and tolerance was not seen after 1 week of repeated dosing.

**Driving impairment.** Bocca et al24 compared degree of driving impairment by zolpidem, zopiclone, flunitrazepam (not approved in the United States), and placebo. The 16 subjects received each medication at 11 PM, with a 2-week washout between medications. One group of 8 was tested at 9 AM and the other 8 subjects at 11 AM. Those taking zolpidem showed no residual performance impairment, as measured by simulated driving, a test drive, and saccadic eye movements.

Staner et al25 reported similar results when comparing zolpidem, zopiclone, lor-metazepam (not approved in the United States), and placebo. Using a driving simulator and electroencephalography (EEG), they evaluated 23 subjects diagnosed with insomnia at 9 and 11 hours post-dose. Zolpidem did not significantly impair driving ability and did not differ from placebo on EEG analysis (resting or driving). The study showed driving impairment with zopiclone and lormetazepam, along with characteristic benzodiazepine EEG changes. This study further supports evidence of limited impairment on driving after appropriate use of zolpidem.

**Informed consent**

In the informed consent process, failing to warn a patient about medication side effects can lead to legal claims against both manufacturers and prescribers. With any medication, patients have the right to know about a drug’s risks, benefits, and alternate therapies—including no therapy.

**Two standards** are associated with informed consent and negligence:

- The “reasonable practitioner” standard outlined in Natanson v. Kline (1960)28 mandates that the prescribing physician has revealed all that an “average, reasonable practitioner” would disclose in similar circumstances.
- The “reasonable patient” standard set in Canterbury v. Spence (1972)29 mandates that the prescribing physician has informed the patient about the proposed treatment, its side effects, and alternatives to the proposed treatment that a reasonable patient would consider material to the decision of whether or not to undergo treatment.

**Clinical Point**

**Performance impairment seen with zolpidem may be indistinguishable from a benzodiazepine effect, except that the duration is shorter.**
Studies of zolpidem-associated driving skills impairment (>5 hours after dosing)

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<tr>
<td>Fairweather et al, 1992 23 (Randomized, placebo-controlled; 24 older volunteers taking no other medications)</td>
<td>Zolpidem, 5 mg or 10 mg, or placebo taken before bedtime; testing 8.5 hours after administration</td>
<td>Numerous, including reactive time, memory, word recognition</td>
<td>Zolpidem consistently helped with sleep latency, with no residual performance deficits; no tolerance seen with repeated dosing</td>
</tr>
<tr>
<td>Bocca et al, 1999 24 (Double-blind, crossover; 16 volunteers)</td>
<td>Zolpidem, 10 mg; zopiclone, 7.5 mg; flunitrazepam,* 1 mg; and placebo given at 11 PM, with testing at 9 AM</td>
<td>Driving simulation and real time test drive; eye movements measured after driving tests</td>
<td>No residual effects with zolpidem; zopiclone impaired driving ability and increased saccadic latency; flunitrazepam impaired early morning driving and saccadic eye movements longer than zopiclone</td>
</tr>
<tr>
<td>Partinen et al, 2003 20 (Randomized, placebo-controlled, double-blind, 3-period crossover; 18 women with insomnia)</td>
<td>Zolpidem, 10 mg; temazepam, 20 mg; dosing at 2 AM, testing 5.5 hours after dosing</td>
<td>Driving simulation; delayed word recall and memory testing (FePsy test)</td>
<td>No statistically significant effects on driving ability with either drug; no significant differences in FePsy results compared with baseline or placebo</td>
</tr>
<tr>
<td>Staner et al, 2005 25 (Randomized, placebo-controlled, double-blind, four-way crossover; 23 subjects with DSM-IV-TR diagnosis of insomnia)</td>
<td>Zolpidem, 10 mg; zopiclone, 7.5 mg; lormetazepam,* 1 mg; 7 days of dosing; tests given 9 to 11 hours post-dosing</td>
<td>Driving simulation; EEG at rest and while driving</td>
<td>Zolpidem showed no impairment of driving ability and no EEG changes compared with placebo; driving impairment and EEG alterations were found with zopiclone and lormetazepam</td>
</tr>
</tbody>
</table>

* Hypnotics not approved in the United States but available elsewhere.

Failure to warn. Plaintiffs may allege a failure to warn if a drug manufacturer withheld information, thus not adequately warning the dispensing provider. In *Reyes v. Wyeth Laboratories*, for example, the U.S. Fifth Circuit Court of Appeals ruled that the polio vaccine’s manufacturer failed to warn the parents of a child who contracted polio from the vaccine about the 1-in-a-million chance of this adverse effect.28

The vaccine was licensed as a prescription drug but administered through county health departments. In 1970, a nurse in a Texas Department of Health clinic administered the vaccine to 8-month-old Anita Reyes without telling the girl’s parents of warnings in the package circular. Holding Wyeth Laboratories to a reasonableness standard, the court found that the company knew or should have known how the vaccine would be distributed.

The package insert was not shown to have given inadequate warning, and the vaccine was not shown to be defective (it was a trivalent live-virus Sabin oral polio vaccine, as intended).

Vioxx cases. Similarly, some plaintiffs have been awarded millions of dollars (as in *Ernst v. Merck & Co., Inc.*29) in rulings that Merck & Co. failed to disclose the risk of cardiotoxicity with the arthritis drug rofecoxib (Vioxx) and thus failed to provide physicians with information needed when

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highest dose of oral olanzapine (15±2.5 mg). In controlled clinical trials of intramuscular olanzapine for injection, there were no statistically significant differences from placebo in occurrence of any treatment-emergent extrapyramidal symptoms, assessed by either rating scales or spontaneously reported adverse events.

Other Adverse Events: Close-toxicities of adverse events was assessed using data from this same clinical trial involving treatment of 15±2.5 mg (N=220) or 7.5±2.5 mg (N=230) olanzapine. The following treatment-emergent events showed a statistically significant trend: dyskinesia, dysarthria, and tremor. In an 8-week, randomized, double-blind study in patients with schizophrenia, chlorpromazine, or other antipsychotic disorder, treatment-emergent adverse events of doses of 10, 20, and 40 mg; statistically significant differences were seen between doses for the following: baseline to endpoint weight gain, 10, 40; incidence of treatment-emergent protasis. (N=79, 1/1000; patients) revealed no dose-related patterns of events for adverse events. (N=79, 1/1000; patients) revealed no dose-related patterns of events for adverse events.

Gastrointestinal: -Ovarian or proximate hypotension and constipation were associated with rapid onset, nausea, vomiting, and constipation, respectively. However, given the medical and mental health risks of untreated insomnia, the benefits of a medication such as zolpidem will likely outweigh its risks.

Clinical recommendations
Zolpidem—like many other medications—carries a substantial risk of side effects, even when used appropriately. However, given the medical and mental health risks of untreated insomnia, the benefits of a medication such as zolpidem will likely outweigh its risks.

Numerous studies have shown that zolpidem is effective for improving sleep latency and that there are mild, if any, residual side effects beyond what would normally be a restful night’s sleep. Impairments are evident, however, during the hours following the drug’s administration, with some effects lasting >5 hours depending on the dose.

Risk management
When prescribing nonbenzodiazepine hypnotics such as zolpidem, you may want to adopt a risk management approach with other medications that can have serious side effects. An approach to benzodiazepine prescribing proposed by Bursztajn et al24 advocates:

- using the informed-consent process to build an alliance with patients
- not prescribing the medication in isolation of other beneficial therapies
- being aware of and always documenting your decision-making process

When you make patients aware of all risks, benefits, alternate therapies, and possible outcomes with no treatment, you have informed them effectively. Patients are then left to decide whether or not to agree to the treatment. You also are responsible for monitoring the patient, addressing the patient’s questions, and relaying important safety information.

When prescribing zolpidem, discuss safety information with the patient as follows:
- Do not drive or operate heavy equipment for at least 5 to 6 hours after treatment
- Have a safety plan in place for transportation during those hours

Continued from page 46

prescribing the drug. In Humeston v. Merck & Co.,33 a Texas court in 2005 held that Vioxx’s warning labels were adequate. In a retrial, however, the New Jersey Superior Court awarded the plaintiff $47.5 million.34

As with the polo vaccine and Vioxx litigation, courts are being asked to decide if patients were adequately informed about sleep-driving and other risks associated with the use of sedative-hypnotics.
• Do not use this medication with alcohol or other sedative/hypnotics.
• Contact the prescriber about any suspected adverse effects.

References

Related Resources

Drug Brand Names

- Dizepam - Valium
- Eszopiclone - Lunesta
- Midazolam - Versed
- Oxazepam - Serax
- Quazepam - Doral
- Rofecoxib - Vioxx
- Temazepam - Restoril
- Triazolam - Halcion
- Zaleplon - Sonata
- Zolpidem - Ambien, Ambien CR
- Zopiclone - Imovane

Zolpidem appears not to impair driving when used as prescribed, although rare cases of ‘sleep-driving’ have been reported with sedative-hypnotics. Negative outcomes can occur with misuse or in combination with alcohol or other substances. With all hypnotics, prescribe recommended dosages, and provide appropriate informed consent.

Disclosure
The authors report no financial relationships with any company whose products are mentioned in this article or with manufacturers of competing products.

Acknowledgments

The authors acknowledge the assistance and guidance of Linda T. Moore, JD, in preparing this manuscript.