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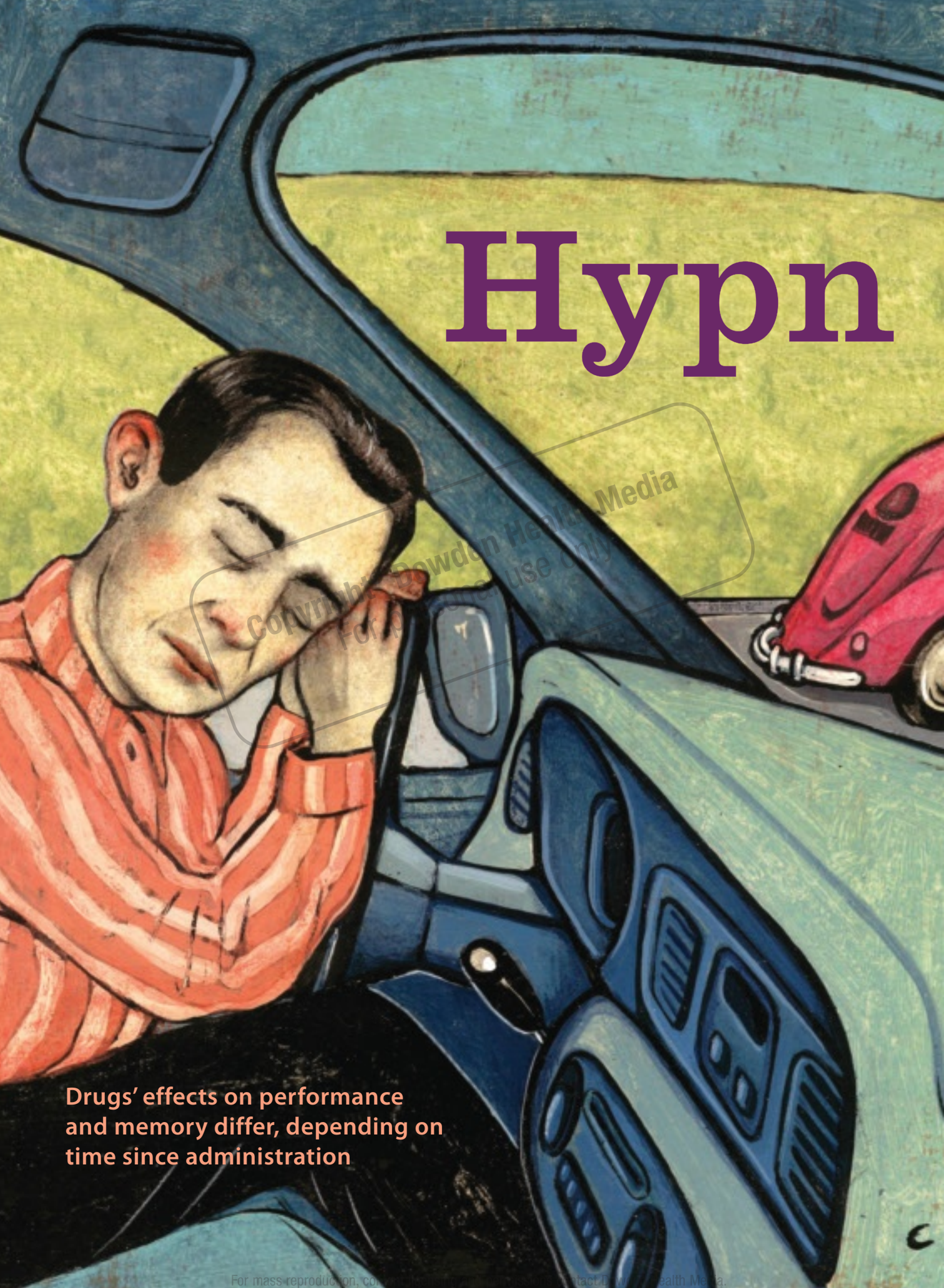

Drugs' effects on performance and memory differ, depending on time since administration

Current PSYCHIATRY

otics and driving

FDA action and clinical trials show need for precautions

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"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.[1]

Sedative-hypnotics are increasingly being used to treat insomnia[2-4] 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[5-7]—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

Hypnotics and driving

Clinical Point

Zolpidem affects performance and memory within the first 4 to 5 hours of administration

Box 1

New labeling for hypnotics: Sleep-related behaviors

Labeling of all sedative-hypnotic drugs now carries FDA-ordered precautions about "sleep-driving and other complex behaviors" that may occur without the patient being fully awake. FDA cited reports of patients preparing and eating food, making phone calls, and having sex after taking a sedative-hypnotic, usually without memory of the event. A warning also was added about rare, potentially fatal anaphylactic reactions in patients taking first or later doses of sleep medications.

Steven Galson, MD, MPH, director of FDA's Center for Drug Evaluation and Research, said the labeling changes were needed to inform patients and prescribers about the risks of sleep aids that "are well-tolerated and effective for many people."

Source: Walsh S, Rawlings K. FDA requests label change for all sleep disorder drug products. Available at www.fda.gov/bbs/topics/NEWS/2007/NEW01587.html.

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.[4] In addition to the new the 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 al[13] 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.

continued on page 43

continued from page 40

• 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.[14-18]

Acute effects (<5 hours)

Combined with alcohol. Wilkinson[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 ~0.08%) 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[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[14] to be more impairing than the recommended maximum 10-mg dose.

A study from the University of Toronto[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.

Box 2

Zolpidem: Approved for 'short-term' insomnia

Zolpidem, a benzodiazepine receptor agonist, was the 7th most prescribed drug in the United States in 2005 (2006 data not available).[8] It is FDA-approved for short-term treatment of insomnia, although "short-term" is not defined. Package labeling states:

This nonbenzodiazepine hypnotic has been shown to decrease sleep latency and increase sleep duration for up to 35 days in controlled clinical trials. Patients should be evaluated for a primary psychiatric or medical illness if insomnia does not remit after 7 to 10 days of treatment.

An imidazopyridine that acts as an agonist of GABA A[1], zolpidem produces sedation while avoiding anticonvulsant, anxiolytic, and muscle relaxation effects. Available in 5- and 10-mg tablets, the drug is rapidly absorbed in the GI tract and excreted primarily through the kidneys. Its half-life is approximately 2.5 hours (approximately 3 hours in elderly patients). The most common side effects are daytime drowsiness, dizziness, and diarrhea; others include asthenia, hiccup, and diplopia.[9]

Middle-of-the-night dosing. Effects of zolpidem and zaleplon on driving ability, memory, and psychomotor performance were compared by Verster et al[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

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Clinical Point

A 15-mg dose of zolpidem may cause greater acute impairment than the recommended maximum 10-mg dose

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)

Author/design	Doses and timing	Driving skills assessments	Conclusions
Wilkinson, 1995[14] 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[15] 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-impairing effects of zolpidem were virtually indistinguishable from those of classic benzodiazepines, such as triazolam
Mattila et al, 1998[16] 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[17] 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[18] 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; zolpidem, 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

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[20] 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 Mintzner 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 zolpidem-related anterograde amnestic episodes, which also occur with some benzodiazepines (such as midazolam).

Similar to benzodiazepines? Rush et al's results[21] support Mintzer's assertion[17] 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 Couper[22] 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 al[24] 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 al[25] reported similar results when comparing zolpidem, zopiclone, lormetazepam (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)[26] 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)[27] 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.

continued

Clinical Point

Performance impairment seen with zolpidem may be indistinguishable from a benzodiazepine effect, except that the duration is shorter

Hypnotics and driving

Clinical Point

When prescribing hypnotics, adopt a risk management approach as you would with other medications that can have serious side effects

Table 2

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

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

* 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/d). 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 incidence or spontaneously reported adverse events.

Other Adverse Events: Dose-relatedness of adverse events was assessed using data from this same clinical trial involving 3 fixed oral dosage ranges (5±2.5, 10±2.5, or 15±2.5 mg/d) compared with placebo. The following treatment-emergent events showed a statistically significant trend: asthenia, dry mouth, nausea, somnolence, tremor.

In an 8-week, randomized, double-blind study in patients with schizophrenia, schizophreniform disorder, or schizoaffective disorder comparing fixed doses of 10, 20, and 40 mg/d, statistically significant differences were seen between doses for the following: baseline to endpoint weight gain, 10 vs 40 mg/d; incidence of treatment-emergent prolactin elevations >24.2 ng/mL (female) or >18.77 ng/mL (male), 10 vs 40 mg/d and 20 vs 40 mg/d; fatigue, 10 vs 40 mg/d and 20 vs 40 mg/d; and dizziness, 20 vs 40 mg/d.

Vital Sign Changes—Oral olanzapine was associated with orthostatic hypotension and tachycardia in clinical trials. Intramuscular olanzapine for injection was associated with bradycardia, hypotension, and tachycardia in clinical trials (*see* PRECAUTIONS).

Weight Gain—In placebo-controlled 6-week schizophrenia studies, weight gain was reported in 5.6% of oral olanzapine patients (average 2.8-kg gain) compared to 0.8% of placebo patients (average 0.4-kg loss); 29% of olanzapine patients gained >7% of their baseline weight, compared to 3% of placebo patients. During continuation therapy (238 median days of exposure), 56% of patients met the criterion for having gained >7% of their baseline weight. Average gain during long-term therapy was 5.4 kg.

Laboratory Changes—Olanzapine is associated with asymptomatic increases in SGPT, SGOT, and GGT and with increases in serum prolactin and CPK (*see* PRECAUTIONS). Asymptomatic elevation of eosinophils was reported in 0.3% of olanzapine patients in premarketing trials. There was no indication of a risk of clinically significant neutropenia associated with olanzapine in the premarketing database.

In clinical trials among olanzapine-treated patients with baseline random triglyceride levels of <150 mg/dL (N=659), 0.5% experienced triglyceride levels of ≥500 mg/dL anytime during the trials. In these same trials, olanzapine-treated patients (N=1185) had a mean triglyceride increase of 20 mg/dL from a mean baseline of 175 mg/dL. In placebo-controlled trials, olanzapine-treated patients with baseline random cholesterol levels of <200 mg/dL (N=1034) experienced cholesterol levels of ≥240 mg/dL anytime during the trials more often than placebo-treated patients (N=602; 3.6% vs 2.2% respectively). In these same trials, olanzapine-treated patients (N=2528) had a mean increase of 0.4 mg/dL in cholesterol from a mean baseline of 203 mg/dL, which was significantly different compared to placebo-treated patients (N=1415) with a mean decrease of 4.6 mg/dL from a mean baseline of 203 mg/dL.

ECG Changes—Analyses of pooled placebo-controlled trials revealed no statistically significant olanzapine/placebo differences in incidence of potentially important changes in ECG parameters, including QT, QTc, and PR intervals. Olanzapine was associated with a mean increase in heart rate of 2.4 BPM compared to no change among placebo patients.

Other Adverse Events Observed During Clinical Trials—The following treatment-emergent events were reported with oral olanzapine at multiple doses ≥1 mg/d in clinical trials (8661 patients, 4165 patient-years of exposure). This list may not include events previously listed elsewhere in labeling, those events for which a drug cause was remote, those terms which were so general as to be uninformative, and those events reported only once or twice which did not have a substantial probability of being acutely life-threatening. *Frequent* events occurred in ≥1/100 patients; *infrequent* events occurred in 1/100 to 1/1000 patients; *rare* events occurred in <1/1000 patients. ***Body as a Whole***—*Frequent:* dental pain, flu syndrome; *Infrequent:* abdomen enlarged, chills, face edema, intentional injury, malaise, moniliasis, neck pain, neck rigidity, pelvic pain, photosensitivity reaction, suicide attempt; *Rare:* chills and fever, hangover effect, sudden death. ***Cardiovascular***—*Frequent:* hypotension; *Infrequent:* atrial fibrillation, bradycardia, cerebrovascular accident, congestive heart failure, heart arrest, hemorrhage, migraine, pallor, palpitation, vasodilatation, ventricular extrasystoles; *Rare:* arteritis, heart failure, pulmonary embolus. ***Digestive***—*Frequent:* flatulence, increased salivation, thirst; *Infrequent:* dysphagia, esophagitis, fecal impaction, fecal incontinence, gastritis, gastroenteritis, gingivitis, hepatitis, melena, mouth ulceration, nausea and vomiting, oral moniliasis, periodontal abscess, rectal hemorrhage, stomatitis, tongue edema, tooth caries; *Rare:* aphthous stomatitis, enteritis, eructation, esophageal ulcer, glossitis, ileus, intestinal obstruction, liver fatty deposit, tongue discoloration. ***Endocrine***—*Infrequent:* diabetes mellitus; *Rare:* diabetic acidosis, goiter. ***Hemic and Lymphatic***—*Infrequent:* anemia, cyanosis, leukocytosis, leukopenia, lymphadenopathy, thrombocytopenia; *Rare:* normocytic anemia, thrombocythemia. ***Metabolic and Nutritional***—*Infrequent:* acidosis, alkaline phosphatase increased, bilirubinemia, dehydration, hypercholesteremia, hyperglycemia, hyperlipemia, hyperuricemia, hypoglycemia, hypokalemia, hyponatremia, lower extremity edema, upper extremity edema; *Rare:* gout, hyperkalemia, hypernatremia, hypoproteinemia, ketosis, water intoxication. ***Musculoskeletal***—*Frequent:* joint stiffness, twitching; *Infrequent:* arthritis, arthrosis, leg cramps, myasthenia; *Rare:* bone pain, bursitis, myopathy, osteoporosis, rheumatoid arthritis. ***Nervous System***—*Frequent:* abnormal dreams, amnesia, delusions, emotional lability, euphoria, manic reaction, paresthesia, schizophrenic reaction; *Infrequent:* akinesia, alcohol misuse, antisocial reaction, ataxia, CNS stimulation, cogwheel rigidity, delirium, dementia, depersonalization, dysarthria, facial paralysis, hypesthesia, hypokinesia, hypotonia, incoordination, libido decreased, libido increased, obsessive compulsive symptoms, phobias, somatization, stimulant misuse, stupor, stuttering, tardive dyskinesia, vertigo, withdrawal syndrome; *Rare:* circumoral paresthesia, coma, encephalopathy, neuralgia, neuropathy, nystagmus, paralysis, subarachnoid hemorrhage, tobacco misuse. ***Respiratory***—*Frequent:* dyspnea; *Infrequent:* apnea, asthma, epistaxis, hemoptysis, hyperventilation, hypoxia, laryngitis, voice alteration; *Rare:* atelectasis, hiccup, hypoventilation, lung edema, stridor. ***Skin and Appendages***—*Frequent:* sweating; *Infrequent:* alopecia, contact dermatitis, dry skin, eczema, maculopapular rash, pruritus, seborrhea, skin discoloration, skin ulcer, urticaria, vesiculobullous rash; *Rare:* hirsutism, pustular rash. ***Special Senses***—*Frequent:* conjunctivitis; *Infrequent:* abnormality of accommodation, blepharitis, cataract, deafness, diplopia, dry eyes, ear pain, eye hemorrhage, eye inflammation, eye pain, ocular muscle abnormality, taste perversion, tinnitus; *Rare:* corneal lesion, glaucoma, keratoconjunctivitis, macular hypopigmentation, miosis, mydriasis, pigment deposits lens. ***Urogenital***—*Frequent:* vaginitis*; *Infrequent:* abnormal ejaculation,* amenorrhea,* breast pain, cystitis, decreased menstruation,* dysuria, female lactation,* glycosuria, gynecomastia, hematuria, impotence,* increased menstruation,* menorrhagia,* metrorrhagia,* polyuria, premenstrual syndrome,* pyuria, urinary frequency, urinary retention, urinary urgency, urination impaired, uterine fibroids enlarged,* vaginal hemorrhage*; *Rare:* albuminuria, breast enlargement, mastitis, oliguria. (*Adjusted for gender.)

The following treatment-emergent events were reported with intramuscular olanzapine for injection at one or more doses ≥2.5 mg/injection in clinical trials (722 patients). This list may not include events previously listed elsewhere in labeling, those events for which a drug cause was remote, those terms which were so general as to be uninformative, and those events reported only once or twice which did not have a substantial probability of being acutely life-threatening. ***Body as a Whole***—*Frequent:* injection site pain; *Infrequent:* abdominal pain, fever. ***Cardiovascular***—*Infrequent:* AV block, heart block, syncope. ***Digestive***—*Infrequent:* diarrhea, nausea. ***Hemic and Lymphatic***—*Infrequent:* anemia. ***Metabolic and Nutritional***—*Infrequent:* creatine phosphokinase increased, dehydration, hyperkalemia. ***Musculoskeletal***—*Infrequent:* twitching. ***Nervous System***—*Infrequent:* abnormal gait, akathisia, articulation impairment, confusion, emotional lability. ***Skin and Appendages***—*Infrequent:* sweating.

Postintroduction Reports—Reported since market introduction and temporally (not necessarily causally) related to olanzapine therapy: allergic reaction (eg, anaphylactoid reaction, angioedema, pruritus or urticaria), diabetic coma, jaundice, neutropenia, pancreatitis, priapism, rhabdomyolysis, and venous thromboembolic events (including pulmonary embolism and deep venous thrombosis). Random cholesterol levels of ≥240 mg/dL and random triglyceride levels of ≥1000 mg/dL have been reported.

DRUG ABUSE AND DEPENDENCE: Olanzapine is not a controlled substance.

Literature revised November 30, 2006

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prescribing the drug. In *Humeston v. Merck & Co.*,[30] 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.[31]

As with the polio vaccine and Vioxx litigations, courts are being asked to decide if patients were adequately informed about sleep-driving and other risks associated with the use of sedative-hypnotics.

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 as you would with other medications that can have serious side effects. An approach to benzodiazepine prescribing proposed by Bursztajn et al[31] 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, such as:

- Do not drive or operate heavy equipment for at least 5 to 6 hours after administration.
- Have a safety plan in place for transportation during those hours.

- Do not use this medication with alcohol or other sedative/hypnotics.
- Contact the prescriber about any suspected adverse effects.

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Related Resources

- MedlinePlus information on sleep disorders. National Institutes of Health and National Library of Medicine. www.nlm.nih.gov/medlineplus/sleepdisorders.html.
- Zolpidem (systemic). Mayoclinic.com: Tools for healthier lives. www.mayoclinic.com/health/drug-information/DR202707.

Drug Brand Names

Diazepam • Valium
Eszopiclone • Lunesta
Midazolam • Versed
Oxazepam • Serax
Quazepam • Doral
Rofecoxib • Vioxx
Temazepam • Restoril
Triazolam • Halcion
Zaleplon • Sonata
Zolpidem • Ambien, Ambien CR
Zopiclone • Imovane (in Europe)

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.

Bottom Line

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.