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Zolpidem and Driving Impairment — Identifying Persons at Risk

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Zolpidem (Ambien, Sanofi) is the most widely used prescription drug for insomnia and one of the most commonly used drugs in the United States. Treatment of insomnia, which has important effects on patients' quality of life, may also have larger public health benefits. In its 2006 report, the Institute of Medicine (IOM) Committee on Sleep Medicine and Research concluded that sleep deprivation and sleep disorders represent an unaddressed public health problem that has substantial health consequences and leads to high health care costs.[1] The IOM noted that one of every five serious injuries from driving accidents can be attributed to driver sleepiness. Numerous sleep drugs are available for treating insomnia and are also used to reduce next-day somnolence. But it is widely recognized that these drugs themselves can sometimes contribute to next-day somnolence, depending on such factors as drug dose, dosage form, and individual patient characteristics.

The treatment of insomnia may focus on two distinct problems: falling asleep and remaining asleep; drugs that treat insomnia may be directed at one or both of these problems. For patients whose main problem is falling asleep, shorter-acting drugs can be effective without conferring a risk of sedation the following morning. When the problem is staying asleep during the night (sleep maintenance), longer-acting drugs — drugs with longer half-lives or controlled-release formulations — are generally used. Some patients can also take a very small dose of a sleep drug (e.g., zolpidem is available at a dose of 1.75 to 3.5 mg) or a very short-acting drug (e.g., zaleplon) if they wake up in the middle of the night and have difficulty falling back asleep.

Zolpidem was initially approved, in 1992, in an immediate-release formulation (Ambien) for insomnia characterized by difficulty in falling asleep. At the time of its approval, there was concern regarding morning impairment, even after a 7-to-8-hour period of sleep, particularly with regard to activities requiring full alertness, such as driving a motor vehicle. There was also some recognition that people's risk of impairment could vary, and the drug label advised that "the dose of Ambien should be individualized." Although the recommended adult dose was 10 mg, the recommended dose for the elderly (who had higher levels of the drug in their blood the next morning) and for patients with hepatic impairment (who metabolized the drug more slowly) was 5 mg. Individual differences became more apparent as new dosage forms of zolpidem were developed to address sleep maintenance and middle-of-the-night waking.

In 2005, a modified-release for-

mulation of zolpidem (Ambien CR, Sanofi) was approved for insomnia characterized by difficulty falling asleep, difficulty staying asleep, or both; it came in a 12.5-mg dose. In 2011, a sublingual, lower-dose tablet (Intermezzo, Purdue) was approved for difficulty falling back to sleep after a middle-of-the-night awakening. Intermezzo was labeled so as to provide doses of zolpidem that differed for men and women (3.5 mg for men and 1.75 mg for women), since new data revealed a difference between men and women in morning blood drug levels.

The review and approval of Intermezzo was particularly informative, because a study was conducted to assess the relationship between blood zolpidem levels and driving impairment. The study assessed patients 3 hours after taking the drug (the label instructs patients to take the product at least 4 hours before morning awakening) and revealed significant impairment in driving ability in patients whose blood concentration of zolpidem was above 50 ng per milliliter. Such impairment is thought to increase the risk of a motor vehicle accident.

Recognition of a threshold blood level that would lead to concern about driving allowed assessment of other dosage forms of zolpidem in order to determine what doses would pose a risk of morning driving impairment. In some patients — particularly women, who clear zolpidem more slowly than men — blood levels the morning after taking the recommended bedtime doses could be considerably higher than 50 ng per milliliter. Reanalysis of data from studies of immediate-release zolpidem products showed that 8 hours (i.e., a typical period of sleep) after taking 10 mg of an immediate-release zolpidem product, 15% of women and 3% of men still had blood zolpidem levels of 50 ng per milliliter or higher; when a modified-release higher-dose (12.5 mg) product was taken, the percentages were much higher — 33% of women and 25% of men. These findings, consistent with the sex difference observed with the sublingual low-dose product (Intermezzo), prompted the Food and Drug Administration (FDA) earlier this year to revise the dosing recommendations for the labels of zolpidem-containing products to lower doses, particularly for women.[2,3]

Manufacturers of zolpidem-containing products, such as Ambien, Ambien CR, Edluar, and Zolpimist, must now make dosage recommendations that differ for women and men, to decrease the likelihood that women will have blood levels of the drug after they wake up that will impair their driving ability. Accordingly, the recommended dose of zolpidem for women has been reduced from 10 mg to 5 mg for immediate-release products (Ambien, Edluar, and Zolpimist) and from 12.5 mg to 6.25 mg for modified-release products (e.g., Ambien CR). Although labeling will also suggest that the lower doses should be considered for men, the stronger recommendation for reduced dosage in women underscores the clear sex-associated differences in zolpidem pharmacokinetics observed in studies.

The FDA has also pointed out that the risk of impairment with modified-release formulations of zolpidem (Ambien CR and generics) is greater than the risk with immediate-release formulations.[2] Accordingly, the agency announced in May 2013 that patients who take modified-release formulations, either 6.25 mg or 12.5 mg, even if they then sleep for the required 8-hour period, should refrain, for the day subsequent to using the drug, from driving or engaging in any activity that requires full alertness.[3] This recommendation reflects not only the higher zolpidem content in the modified-release formulation but also the ability of the modified-release design to prolong the period of drug exposure.

Although the evaluation of driving impairment caused by prescription drugs is not new, quantitative analyses of the relationships among drug dose, blood levels, and driving impairment, as illustrated in the approval of Intermezzo and the associated review of zolpidem products, are likely to be of growing interest (and perhaps debate). It is clear that performance on a driving test cannot be directly and quantitatively translated to driving risk, but similar data about effects on performance have been used to set standards for blood alcohol levels, and the tests of performance have considerable face validity. Certainly, these data are far more informative than reports of motor vehicle accidents, in which the relation to drug dose, the time between zolpidem ingestion and the accident, and the use of ethanol or other drugs is generally uncertain. The FDA has asked the makers of insomnia drugs to submit all available data addressing the risk of residual impairment after prescribed use, and the agency is currently analyzing these data.

It could be asked why the FDA did not leave the recommended doses unchanged and continue to warn patients to watch for driving impairment. A variety of new data have shown that people affected by impairment after taking zolpidem frequently do not recognize their impaired state; patient self-perception is not an

adequate gauge for impairment. Among patients whose sleep needs are satisfied with the use of the lower doses, unnecessary risk can be avoided, and as the labels point out, patients whose symptoms do not respond to the lower doses can be given the higher doses. The sex-specific labeling revisions reflect an evidence-based approach to risk management and dose individualization.

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1. Colten HR, Altevogt BM, eds. Sleep disorders and sleep deprivation: an unmet public health problem. Washington, DC: National Academies Press, 2006.
2. FDA drug safety communication: risk of next-morning impairment after use of insomnia drugs; FDA requires lower recommended doses for certain drugs containing zolpidem (Ambien, Ambien CR, Edluar, and Zolpimist) (http://www.fda.gov/Drugs/DrugSafety/ucm334033.htm).
3. FDA drug safety communication: FDA approves new label changes and dosing for zolpidem products and a recommendation to avoid driving the day after using Ambien CR (http://www.fda.gov/Drugs/DrugSafety/ucm352085.htm).

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The Unanticipated Consequences of Postponing the Employer Mandate

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The Obama administration's decision to postpone implementation of the employer mandate is the latest in a series of delays and alterations of the Affordable Care Act (ACA). But postponing the mandate — which requires larger employers to offer lower-income workers health insurance coverage similar to that available in the new insurance exchanges, on equal and affordable financial terms — may create large ripple effects. The good news is that as compared with instituting the mandate as planned, postponing it should barely increase the number of uninsured Americans after ACA implementation. But it affects other provisions, particularly the individual subsidies for purchasing insurance, and creates distorted incentives that may leave the government paying significantly more than planned.

More than 90% of Americans who obtain private health insurance today receive it through employers, but the centerpiece of the ACA's effort to make coverage more attractive to the uninsured focuses on insurance exchanges for individuals purchasing coverage directly. However, because both consumers and employers can in principle finance or obtain private health insurance in either setting, ACA provisions had to be compatible with both coverage channels. Moreover, the legislation created tax-financed subsidies for buying insurance only through the exchanges while relying largely on regulations and mandates to deal with employment-based coverage. Inevitably, this grafting of a new institutional and subsidy structure onto an already-complex system raises problems of potentially incompatible and inequitable incentives.

Fortunately, postponing the mandate will probably not vastly increase the number of people who remain uninsured, because most large employers already provide health benefits. Most would therefore face little burden in complying, even though the proximate cause of postponement is apparently the challenge of drafting reporting requirements. The 95% of firms that offer coverage, however, don't offer it to every worker at low explicit premiums, often excluding part-time, new, temporary, and low-wage workers. About 10% of uninsured Americans (5.5 million people) live in households with a worker affected by the large-employer mandate (see table). The $10 billion in revenues expected from the mandate's penalty (5 million uninsured workers × $2,000) is a small fraction of the eventual cost of the exchange subsidies. (The Congressional Budget Office estimates that in 2023, with full implementation, the annual subsidy cost will be $153 billion.[1]) So although the mandate would have reduced the coverage gap and raised some revenue, the effects of delaying it will be modest.

Meanwhile, the ACA's individual mandate remains in place. To the extent that this mandate causes people to seek or retain coverage, workers may still prefer their qualified coverage to be furnished through work rather than exchanges — especially if they are uninsured or incompletely insured but have income high enough that the tax exemption for employment-based coverage is worth more than their ex-