Sleep Drug Labels to Address Adverse Reactions

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Warnings about the risks of complex sleep-related behaviors such as driving while asleep and about serious allergic reactions that have recently been associated with sleep drugs, are being added to their labels, at the request of the Food and Drug Administration.

The FDA announced that the manufacturers of the 13 approved sedative hypnotics, which include older drugs such as Dalmane and newer drugs such as Ambien and Lunesta, had been asked to describe cases of anaphylaxis and angioedema, and cases of complex sleep-related behaviors in their labels. In addition, the drugmakers have begun sending out "Dear Health Care Provider" letters describing these adverse events and the label changes.

The need for these changes are based on postmarketing reports of these events, "which we believe are serious and about which practitioners and patients need to know," Dr. Russell Katz, director of the FDA's division of neurology products, said during an FDA teleconference.

After receiving postmarketing reports of angioedema and anaphylaxis in people on the most recently approved hypnotic, ramelteon (Rozerem), the FDA reviewed the entire class for this effect and found similar cases. The review of complex sleep-related behaviors—which include driving, making phone calls, preparing and eating food, and having sex, all while asleep—began after such cases were publicized about 1 year ago. Although such cases can be difficult to interpret, "we believe the entire class is capable of producing those events as well," Dr. Katz said. Physicians should advise patients that the complex sleep behaviors are more likely to occur when people take higher than normal doses, and when they take these drugs with other drugs that can affect the ner-

vous system or with alcohol, he added.

Dr. Katz described both types of events as "relatively rare," based on the information available. He added that no deaths have been reported in association with any of the events reported to the FDA.

After the teleconference, an FDA spokesperson said that the agency had received a "couple of dozen" reports of complex sleep behaviors but emphasized that these events are likely to be underreported, and that the decision to strengthen labeling was not based on numbers but on the serious nature of these adverse effects. There were more cases of allergic reactions, but no specific numbers were provided.

Manufacturers also have been asked to develop "Patient Medication Guides" to directly inform patients about the risks and about what they can do to minimize their risks of experiencing these events. Medication guides are leaflets that are required for certain drugs with particular risks, which are distributed with each new prescription or refill. These will not be available soon, however, since the companies have until May to submit their versions of the guides, which will then need to be reviewed by the agency.

But the events also are being added to the "information for patients" section of the drug labels, which physicians can use to counsel patients. "Patients should be aware that there are behaviors that they can engage in that can decrease the risk of these events occurring, namely, to refrain from alcohol [and] other drugs that depress the nervous system and to make sure they take the right dose," Dr. Katz emphasized.

The FDA also has requested that the manufacturers conduct clinical trials to determine whether the complex sleep behaviors are more common with some of the drugs and not others. Dr. Katz said that none of the companies had approached the agency yet with plans for such studies and acknowledged that getting them to do studies would be more difficult than making the labeling changes.

The label change affects drugs including Zolpidem, marketed as Ambien/Ambien CR by Sanofi-Aventis; butabarbital, marketed as Butisol Sodium by Medpointe Pharmaceuticals HLC; flurazepam, marketed as Dalmane by Valeant Pharmaceuticals; quazepam, marketed as Doral by Questcor Pharmaceuticals; triazolam, marketed as Halcion by Pharmacia & Upjohn Inc.; eszopiclone, marketed as Lunesta by Sepracor Inc.; estazolam, marketed as Prosom by Abbott; temazepam, marketed as Restoril by Tyco Healthcare Group; ramelteon, marketed as Rozerem by Takeda Pharmaceutical Inc.; secobarbital, marketed as Seconal by Ranbaxy Pharmaceuticals Inc.; and zaleplon, marketed as Sonata by King Pharmaceuticals Inc. ■

Health care professionals can report serious adverse reactions to these and other drugs to the FDA's Medwatch program online at www.fda.gov/medwatch, by calling 800-332-1088, or by faxing 800-332-0178.

ADHD Patient Drug Guides to Be Revised

The Food and Drug Administration has sent letters to all manufacturers of medications approved for treating attention-deficit hyperactivity disorder, instructing them to develop patient medication guides within 30 days to address possible cardiovascular risks and adverse psychiatric symptoms associated with their use.

The ruling builds on regulatory action the FDA took last May when it directed manufacturers to revise product labeling for physicians to reflect concerns about adverse cardiovascular and psychiatric events. The concerns came from an FDA review of reports of sudden unexplained death in patients taking usual doses of ADHD products, said Dr. Tom Laughren, director of the division of psychiatry products at the FDA Center for Drug Evaluation and Research, during a teleconference.

Concern about adverse psychiatric events, principally psychotic symptoms, comes from another FDA review, including spontaneous reports and pooled analyses of placebo-controlled trials.

"The causal link is stronger for this event than it is for cardiovascular events," Dr. Laughren said, noting that adverse psychiatric events occur in about 1 of every 1,000 patients treated.

The ruling applies to 15 products: Adderall tablets, Adderall XR extended-release capsules, Concerta extended-release tablets, Daytrana transdermal system, Desoxyn tablets, Dexedrine Spansule capsules and tablets, Focalin tablets, Focalin XR extended-release capsules, Metadate CD extended-release capsules, Methylin oral solution, Methylin chewable tablets, Ritalin tablets, Ritalin SR sustained-release tablets, Ritalin LA extended-release capsules, and Strattera capsules.

Draft medication guides for these products can be found at www.fda.gov/cder/drug/infopage/ADHD/default.htm.

—Doug Brunk