Report of Two Cases Where Sleep Related Eating Behavior Occurred With the Extended-Release Formulation but Not the Immediate-Release Formulation of a Sedative-Hypnotic Agent

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We report two cases in which amnestic sleep-related eating disorder (SRED) occurred with extended-release zolpidem but not with the immediate-release formulation. These cases illustrate how even relatively small differences such as formulation can affect the likelihood of experiencing such events.

Keywords: Sleep-related eating disorder, parasomnia, insomnia, hypnotic


Case Report

The U.S. Food and Drug Administration recently requested that manufacturers of sedative-hypnotics strengthen their product labeling to include stronger language concerning potential risks of parasomnias, such as nocturnal eating.1 While it is well established that such events can happen in individuals not taking sedative-hypnotic medications, there is a growing case report literature documenting that they can occur in association with sedative-hypnotic use.2–6 However, because of the absence of controlled studies and systematic data collection, little is known about the nature of these parasomnias occurring with sedative-hypnotic agents.

To our knowledge, there are no data addressing how much the risk of parasomnias might vary in an individual as a function of the sedative-hypnotic agent chosen, the dosage, or the formulation of the agent. Here we present two cases that may help address this issue. Both patients have complex histories, with restless legs syndrome and sleep apnea in addition to insomnia, but neither had any past history or family history of parasomnia or eating disorder; nor did they have parasomnias while taking zolpidem for a long period of time. However, both developed amnestic nocturnal eating behavior after the zolpidem was switched to extended-release (ER) zolpidem. These cases illustrate that, at least in some individuals, the likelihood of developing parasomnias may be affected by relatively small differences in pharmacotherapy.

CASE REPORT

Case 1 is that of a 75-year-old white female with restless legs syndrome, mild obstructive sleep apnea, and sleep maintenance insomnia. Her restless legs syndrome had been under good control with gabapentin for several years. For the past one year, she had been treated with auto-CPAP of 5 to 12 cm H₂O for obstructive sleep apnea with variable compliance. For three years she had been taking zolpidem 10 mg as needed for her insomnia without any event of parasomnia. Despite zolpidem, she complained of difficulty staying asleep occurring in association with increased stress in her life. She was switched from zolpidem 10 mg to 12.5 mg of ER zolpidem to address her sleep maintenance difficulty. As soon as she started taking the ER formulation, and with no other changes in her treatment regimen or CPAP use, she developed amnestic sleep-related eating behavior for four consecutive nights. After she stopped taking the ER zolpidem and resumed her usual zolpidem 10 mg therapy, her parasomnia resolved and has not recurred at 6 months follow-up.

Case 2 is that of a 70-year-old white female with restless legs syndrome, complex sleep apnea, and insomnia. Her restless legs syndrome had been under good control with pramipexole and gabapentin for several years. For the past one year, she had been treated with auto-CPAP of 5 to 12 cm H₂O for obstructive sleep apnea with variable compliance. For three years she had been taking zolpidem 10 mg as needed for her insomnia without any event of parasomnia. Despite zolpidem, she complained of difficulty staying asleep occurring in association with increased stress in her life. She was switched from zolpidem 10 mg to 12.5 mg of ER zolpidem to address her sleep maintenance difficulty. As soon as she started taking the ER formulation, and with no other changes in her treatment regimen or CPAP use, she developed amnestic sleep-related eating behavior for four consecutive nights. After she stopped taking the ER zolpidem and resumed her usual zolpidem 10 mg therapy, her parasomnia resolved and has not recurred at 6 months follow-up.

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plaints of inadequate hours of sleep at night with regular use of zolpidem, a decision was made to try ER zolpidem. Soon after she was started on the ER zolpidem of 12.5 mg and without other changes in her treatment regimen or CPAP use pattern, she developed amnestic sleep related eating behavior for several nights. After switching back to the immediate-release formulation of zolpidem, her nocturnal eating behavior resolved and she has remained free from recurrence of similar events at 12 months follow-up.

**DISCUSSION**

These two cases establish that some individuals may not experience parasomnias with a sedative-hypnotic agent but may develop such events when switched to another formulation of the same agent. However, we caution that it should not be taken that a specific link exists between ER zolpidem and parasomnia, which can only be made on the basis of controlled and/or systematic comparisons of this agent with placebo and other insomnia therapies.

Why in these individuals an ER formulation change would lead to the development of sleep related eating behavior is unclear. The only differences between the ER and immediate-release formulations are the total dosage (12.5 mg vs. 10 mg) and timing of release. It is possible that the absorption of the ER formulation is less staggered over the night in some individuals leading to a higher peak blood level which predisposes them to SRED. Another possibility is that the greater blood level achieved later in the night with the ER formulation may be more likely to align with a tendency toward partial arousals in predisposed individuals. The sleep apnea and restless legs syndrome in these patients or their concomitant medications could have also made it more likely that they had events with the ER formulation. Given that differences as small as formulation can affect the likelihood of sleep related eating disorder, it is reasonable for clinicians to expect that in some individuals, such events may only be observed with particular agents or at particular dosages. Future research will be needed to determine if it is possible to predict the pharmacologic profile that increases the risks for an individual patient.

**REFERENCES**

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