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Original article

Amnestic sleep-related eating disorder associated with zolpidem

Timothy I. Morgenthaler[a,b,*], Michael H. Silber[a,c]

[a]*Sleep Disorders Center, Mayo Clinic, 200 1st Street SW, Rochester, MN 55905, USA*
[b]*Division of Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, MN, USA*
[c]*Department of Neurology, Mayo Clinic, Rochester, MN, USA*

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Abstract

Objective: To describe the association of amnestic nocturnal eating behavior with use of zolpidem for insomnia.

Background: Sleep-related eating disorder is increasingly recognized in relationship to other diagnosable sleep disorders. Many of these disorders, like restless legs syndrome (RLS), give rise to complaints of insomnia. Zolpidem is the most commonly prescribed drug for insomnia complaints, and although it has sometimes been associated with side effects of transient amnesia and sleep walking, an association with sleep-related eating has not been previously emphasized.

Methods: Consecutive case series of five patients who were using zolpidem and evaluated with nocturnal eating behaviors.

Results: We evaluated five patients over 11 months with problematic amnestic nocturnal eating associated with zolpidem used for complaints of insomnia. All five patients had RLS, three had obstructive sleep apnea syndrome, two had sleep walking, and one had psychophysiologic insomnia. With discontinuation of zolpidem and effective treatment of their sleep disorders, nocturnal eating resolved.

Conclusions: Zolpidem, at least in patients with underlying sleep disorders that cause frequent arousals, may cause or augment sleep-related eating behavior. This report demonstrates the importance of arriving at a specific diagnosis for insomnia complaints, and alerts the sleep practitioner to this unusual side effect of zolpidem.

Keywords: Parasomnias/therapy/physiopathology/diagnosis; Eating disorders/complications/drug therapy; Sleep arousal disorders; Restless legs syndrome/drug therapy/diagnosis; Substance-related disorders/complications; Wakefulness/physiology; Hypnotics and sedatives/adverse effects; Amnesia/chemically induced

1. Introduction

Sleep-related eating syndromes comprise a spectrum of abnormal behaviors combining features of sleep and eating disorders (Table 1). Although first described four decades ago as 'night-eating syndrome' (NES) [1], more detailed observations have been published only in the last decade [2–4]. Sleep-related eating disorder (SRED) is characterized by partial arousals from sleep to ingest food, usually within the first 3 h after sleep onset [2]. Patients afflicted may describe an 'automatic' inclination to eat and a perceived inability to return to sleep without eating. Ingested substances can be ordinary, but often are highly caloric, and can be unusual. This behavior can lead to morning bloating, guilt, embarrassment, or to difficulty with perceived or actual weight control. Patients are totally or partially amnestic for up to half of eating episodes [4]. Amnestic eating and ingestion of unusual substances have drawn particular attention to these irregular behaviors, both in clinical and lay publications. In some series, the majority of patients are found to have restless legs syndrome (RLS), periodic limb movement disorder (PLMD), or obstructive sleep apnea syndrome (OSA) [2]. In one series, the majority of patients were taking psychotropic medications at the time of evaluation [4].

We report the onset or worsening of amnestic nocturnal eating behavior when zolpidem therapy was begun for insomnia, and the subsequent resolution of eating behavior with discontinuation of zolpidem and treatment of underlying intrinsic sleep disorders. These observations extend previous reports of amnestic complications and sleepwalking with zolpidem, describe an association of zolpidem with nocturnal eating, and emphasize the importance of accurate diagnoses in dealing with abnormal sleep behaviors.

2. Case reports

Five patients with sleep-related eating disorder (SRED) who were taking zolpidem presented to the Mayo Clinic

* Corresponding author. Tel.: +1-507-284-3464; fax: 1-507-266-7772.
E-mail address: morgenthaler.timothy@mayo.edu (T.I. Morgenthaler).

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Table 1
Disorders relating sleep and eating

Nocturnal eating syndrome (NES) [1,22–24,26,27]
Sleep related eating disorder (SRED) [2,4,11,13,28,29]
Kleine–Levin syndrome [30]
Dissociative disorder [12,31]
Bulimia nervosa with nocturnal eating [13,27,31]
Binge eating disorder [31,32]

Sleep Disorders Center over an 11 month period. Their clinical features are summarized in Table 2. None of our patients had a prior history of daytime eating disorders, but two patients had eaten in the middle of their sleep period prior to using zolpidem. Case 3 had nightly eating since age 15. He had regarded the behavior as normal, and had no amnesia to events prior to using zolpidem. With zolpidem, he experienced more eating episodes per night (two to three per night), greater caloric intake with associated weight gain, and amnesia to most episodes. Case 5 had total recall of nightly eating for 34 years prior to zolpidem. With zolpidem use, her nightly eating episodes increased to three times per night, and she was amnestic to two-thirds of these events. Details of illustrative cases follow.

2.1. Case 1

A 54-year-old woman sought evaluation for 3 years of nocturnal eating. Two weeks prior to onset of nocturnal eating, she had abdominal surgery for Crohn's disease, stopped smoking, and had been started on zolpidem 10 mg each night for insomnia. She explained that an uncontrollable desire to eat began within 30 min of sleep onset. She was sometimes amnestic, but most frequently aware of eating episodes, in which she would retrieve ordinary food from her kitchen, and often take it to her bed to eat. She denied bedtime hunger, ate well during the day, and had a stable and normal weight. She was frustrated and embarrassed by her inability to stop this nightly behavior. She also complained that she often had difficulty remembering what she had read after taking zolpidem. Insomnia had been present for most of her adult life. She described typical symptoms of RLS, and had been told by bed partners about frequent leg jerks during sleep. She had used carbidopa/levodopa 25/100 mg at bedtime infrequently over the past year. Other medications included paroxetine 10 mg for depression, mesalamine for Crohn's disease, conjugated estrogens, cetirizine, and inhaled asthma medications.

On advice after evaluation, zolpidem was discontinued, and she was advised to take carbidopa/levodopa 25/100 mg at bedtime along with clonazepam 0.5 mg. On her return visit 45 days later, she explained that she no longer had amnestic or conscious eating episodes during her sleep period. She slept more soundly and awakened more refreshed than previously. Because she was still having some sleep onset insomnia, she was advised to increase her dose of clonazepam to 1 mg, and to take it 1 h prior to bedtime. She has done well on this regimen at 5 months follow up.

2.2. Case 4

A 67-year-old man developed insomnia, largely related to RLS, 2 years after the onset of Parkinson's disease. Soon after the prescription of 50 mg trazodone and 10–20 mg zolpidem before sleep, he developed episodes of sleep-related eating. Initially he had some recall of the events, but later developed amnesia with his wife noticing food left on the counter and dropped on the floor. The most severe episode involved him falling down 12 steps after eating with no recall of the event. During part of this time he was also receiving ropinerole and fluoxetine, but sleep walking commenced prior to the use of these medications. A sleep study about 1 year after onset of sleep-related eating was performed 4 days after discontinuing ropinerole and trazodone and 2 weeks after discontinuing zolpidem. This showed frequent periodic limb movements of wakefulness, 122 periodic limb movements per hour of sleep, 97% associated with arousals, and 18 obstructive hypopneas per hour. No sleep walking occurred. He was treated with 0.5 mg pramipexole twice daily and nasal CPAP. Zolpidem, trazodone, and fluoxetine were discontinued. After 2 months follow up, no further sleep walking or sleep-related eating had occurred, and his insomnia had completely resolved.

3. Discussion

Most patients with SRED appear to have underlying intrinsic sleep disorders. Schenck et al. [2] have noted association with somnambulism (70%), RLS/PLMD (13%), OSA (10%), and narcolepsy. The onset of this syndrome has been reported after withdrawal from alcohol, tobacco products, opiates, and cocaine, and also with triazolam use [5–7]. Of the prior reports of nocturnal wanderings associated with zolpidem [8,9], only one patient is described with amnestic nocturnal eating [10]. This is the first case series emphasizing the association of SRED with zolpidem.

This report illustrates several associations which deserve discussion, that of insomnia with nocturnal eating, of disorders of arousal with SRED, of zolpidem with nocturnal wanderings, and finally of zolpidem and SRED. Each of our patients had started zolpidem for sleep onset insomnia, and in each case, there was a new onset or an increase of amnestic nocturnal eating. In cases 1, 2, and 4, nocturnal eating began only after initiation of zolpidem, while in cases 3 and 5, pre-existing nocturnal eating continued but with increased frequency and amnesia to events. The association of insomnia and nocturnal eating syndrome onset was noted in seven of 120 patients (5.8%) prospectively evaluated for chronic insomnia [11]. None of these patients had amnesia for the events. The etiology of insomnia included RLS without PLMD in two patients. Winkelman [4] reported 23 patients with SRED, of whom 3/23 (13%) presented a

Table 2
Cases of SRED using zolpidem[a]

Clinical features	Cases				
	1	2	3	4	5
Gender	F	M	M	M	F
Age at presentation/onset of nocturnal eating	54/51	56/41	66/15	67/65	64/30
Presenting sleep complaints	Nocturnal eating	EDS, SOI	Nocturnal eating	SOI, nocturnal eating	SOI
Age at start of zolpidem use	51	41	64	65	56
Zolpidem dose (mg)	10	15–30	5–10	10–20	10
Prior eating behavior	Normal	Normal	No daytime eating disorder, one mid-sleep meal since age 15	Normal	No daytime eating disorder, one mid-sleep meal since age 30
Change in frequency of nocturnal eating with zolpidem	Commenced after zolpidem, one to two times nightly	Commenced after zolpidem, one time nightly	Increased to four to six times nightly	Commenced after zolpidem, one time nightly	Increased from once nightly to three times nightly
Recall of eating events with zolpidem	Sometimes amnestic from onset	Complete amnesia from onset	Full recall prior to zolpidem, increase in % amnestic eating	Initially some recall, later amnestic	Full recall prior to zolpidem, amnesia for 2/3 of events with zolpidem
Other problems since use of zolpidem	No recall of bedtime reading	None	None	Fell on stairs while sleep walking	Fell on stairs while sleep walking, no recall of bedtime reading
Prior sleep walking?	None	None	None	None	Fell out of bed once while sleeping in college years
Other medications at presentation	Infrequent carbidopa/levodopa, paroxetine	Alprazolam, bupropion	Amitriptyline, gabapentin	Trazodone, fluoxetine, ropinerole	Pramipexole
Sleep disorders	RLS	RLS, OSA (RDI 76/h)	RLS, OSA (RDI 30/h)	RLS, OSA (RDI 18/h) sleep walking	RLS, psychophysiologic insomnia, sleep walking
Treatment	Discontinue zolpidem, use carbidopa/levodopa 25/100 mg and clonazepam 1.0 mg q hs	Discontinue zolpidem, use CPAP, clonazepam 1.0 mg q hs	Discontinue zolpidem, use CPAP, clonazepam 0.5 mg q hs	Discontinue zolpidem and trazodone, use pramipexole 1.25 mg (0.5 mg am, 0.75 mg q hs)	Discontinue zolpidem, increase pramipexole, add temazepam 15 mg q hs
Follow up	5 months, No nocturnal eating, insomnia and RLS improved	46 days No nocturnal eating, hypersomnia improved insomnia persisted	40 days No nocturnal eating, hypersomnia improved	2 months No nocturnal eating, no sleep walking, no RLS, no insomnia	32 days No nocturnal eating, RLS, and insomnia have resolved

[a] Abbreviations: EDS = excessive daytime sleepiness; SOI = sleep onset insomnia; RLS = restless legs syndrome; OSA = obstructive sleep apnea; RDI = respiratory disturbance index; CPAP = continuous positive airway pressure.

complaint of insomnia. Although RLS was not emphasized in his series, six (26%) had PLMD and four (17%) had OSA.

SRED has also been associated with somnambulism [4,12]. Winkelman [4] noted that 11/23 (48%) patients had multiple abrupt awakenings from slow-wave sleep consistent with a diagnosis of somnambulism. Schenk et al. [2] reported that 84% of their patients with SRED had somnambulism. Two of our patients exhibited nocturnal wanderings without eating, but only after zolpidem. We did not observe ambulation during polysomnography, but both patients had multiple arousals from slow-wave sleep. All of our patients had RLS, one had PLMD, and three had OSA, suggesting that disturbed nocturnal sleep may predispose to SRED in general. PLMD, RLS, OSA, and withdrawal from nicotine, alcohol, opiates, and cocaine all produce fragmentation of sleep and are associated with SRED [5]. Because these disorders are also known to worsen somnambulism, many have proposed that SRED is a disorder of arousal. Although Winkelman et al. [4,13] have proposed that SRED might be characterized as either a disorder of arousal or a primary eating disorder, many of their patients had concurrent daytime eating disorders. None of our patients had a primary daytime eating disorder.

Zolpidem has been previously reported in association with nocturnal wanderings [8–10]. In two of these patients a childhood history of sleep walking preceded the episodes associated with zolpidem use [8,9]. Additional cases of nocturnal confusion or agitation have been reported with zolpidem use, but these did not have characteristics of nocturnal eating or of wandering [14]. Only one report of zolpidem induced somnambulism included episodes of new onset and amnestic night eating behavior [10]. The authors describe a 46-year-old military helicopter pilot with a prior history of previously treated depression and a normal polysomnogram who was prescribed 10 mg of zolpidem for situational insomnia. On the fourth night of therapy, he was noted to arise, wander to the kitchen, prepare, and consume a meal with total amnesia of the events the following morning. After repeated episodes, zolpidem was discontinued and the nocturnal episodes of eating stopped. No mention is made of RLS.

In our patients, zolpidem therapy was followed by onset of amnesia to nocturnal eating behaviors. Two patients also reported difficulties recalling details of their reading, and two patients fell on stairs after taking zolpidem. Zolpidem has been reported to cause transient amnesia in two patients an hour after drug ingestion [15], in association with visual hallucinations [16], and when administered to volunteers who concurrently took imipramine [17]. Transient amnesia was reported with low prevalence in a large number of patients being treated long term with zolpidem for insomnia [18]. In a comparative study of the sedative, amnestic, and performance disruptive effects of selective and non-selective hypnotics, zolpidem was shown to produce amnestic effects in a dose dependent fashion [19]. Amnestic SRED has been reported in patients taking triazolam and midazolam, both other short acting benzodiazepine receptor agonists [5–7]. The association of SRED with these three short acting benzodiazepine receptor agonists may be specific to the drugs or may be related to the frequency with which these agents are being prescribed for insomnia. It is of interest that most benzodiazepines have been shown to induce hyperphagic responses in mammalian species, but zolpidem is reported to be neutral with regard to appetite regulation [20,21]. Given the association of zolpidem with SRED, the effect of zolpidem on appetite in humans may merit reassessment.

Deciding on an etiology for SRED, whether a disorder of arousal, an eating disorder, or even a metabolic or circadian abnormality, is difficult with what is currently known. SRED and NES are differentiated in some (but not all) reports by the presence or absence of amnesia while eating [22–24]. In one study, patients with NES, defined by the triad of insomnia, excessive eating after the evening meal, and morning anorexia were studied with actigraphy and neuroendocrine assays [23]. NES patients had more awakenings and an attenuated rise in melatonin and leptin levels compared with controls. NES patients consumed over 50% of their energy intake during the night. Polysomnographic study was not performed, and the issue of amnesia to eating was not specifically addressed. NES was reported by survey results in 27% of 111 bariatric surgery patients versus 1.5% of 2097 control subjects [24], prompting the authors to speculate that NES is an eating disorder. Unfortunately, there was little detail reported about other sleep symptoms and there were no polysomnographic data available. Speculatively, SRED could represent a specialized form of somnambulism in patients who might otherwise be classified as having NES. Perhaps the concurrence of a sleep disorder that increases arousals, such as OSA, RLS, and PLMD increases the likelihood of arousal during slow-wave sleep leading to sleep eating in a susceptible patient. Similarly, the addition of zolpidem to a patient with NES might enhance amnesia to an otherwise established nocturnal eating behavior. However, three of our patients (cases 1–3) never exhibited nocturnal eating prior to zolpidem therapy, and none had a previous diagnosis of an eating disorder.

We would suggest that SRED is a disorder of arousal, more likely to occur in patients with certain risk factors such as either intrinsic eating or metabolic disorders. Zolpidem may promote nocturnal eating and represent an additional risk factor. The mechanism for this is unclear, but perhaps related to some selective hyperphagic response. Zolpidem might also increase amnesia to nocturnal wanderings. Concurrent situations that increase fragmentation of sleep such as RLS, PLMD, OSA, or drug withdrawal increase the likelihood of nocturnal eating episodes.

We treated our patients by discontinuing zolpidem, managing underlying sleep disorders, and adding clonazepam to three patients. Sleep eating resolved in all patients. It is uncertain whether discontinuing zolpidem alone would

have been effective, but we speculate that other sleep disorders also need to be treated aggressively. The management of related conditions probably explains Schenck et al's [25] success with codeine and levodopa therapy.

Nocturnal eating is not uncommon in the population at large (4.6% of randomly selected college students) and may be more common in patients complaining of insomnia [13]. The sleep specialist must specifically ask patients regarding nocturnal eating behaviors, and should be aware that zolpidem may contribute to amnestic nocturnal eating behaviors.

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