Sleep-Related Eating Disorder and Zolpidem: An Open Interventional Cohort Study

To the Editor: Sleep-related eating disorder (SRED) is a newly recognized parasomnia that describes a clinical condition of compulsive eating under an altered level of consciousness during sleep. The prevalence rate varies from 4% to 16.7% among different clinical psychiatric populations.[1,2] The exact etiology of SRED is unclear, but it is postulated that SRED might share features of both sleepwalking and eating disorders.[3] In addition, there have been accumulating reports of SRED related to the use of various psychotropic medications including triazolam, zolpidem, olanzapine, risperidone, and combinations of psychotropics.[4–8]

Among these drugs, recent attention has focused on zolpidem, a nonbenzodiazepine hypnotic. Our clinical epidemiologic study in psychiatric outpatients[2] showed that 1 out of 7 subjects regularly taking zolpidem could develop SRED in their lifetime. In addition, among a psychiatric population, most of the adult-onset sleepwalking cases were highly comorbid with SRED features.[9] Thus, there seems to be a robust association of zolpidem and SRED on the basis of both cross-sectional clinical series and epidemiologic evidence.

Warnings were issued in 2007 by both the Therapeutic Goods Administration of Australia[10] and US Food and Drug Administration[11] with regard to SRED as a potential side effect of zolpidem. Nonetheless, in order to confirm a definite association of zolpidem and SRED, resolution or reduction of SRED symptoms upon cessation of zolpidem treatment should be demonstrated. In particular, the episodic nature of the SRED attacks would argue the need for a longer-term follow-up period to document a clear resolution of the symptoms.

Method. Eight subjects who presented with SREDs while taking therapeutic dosages of zolpidem between 2006 and 2008 were prospectively followed up. They were invited for clinical interview and video-polysomnographic assessment at baseline. Clinical assessments included the Structured Clinical Interview for *DSM-IV* for establishment of psychiatric diagnosis and confirmation of

the diagnosis of SRED according to the diagnostic criteria of the *International Classification of Sleep Disorders,* Second Edition.[12] As zolpidem has been reported to be associated with SRED, modification of the drug regimen, including the options of discontinuing or decreasing the dosage of zolpidem, was suggested to patients as an open intervention. The subjects were reassessed by clinical interview after at least 6 months' duration of drug regimen modification, with additional collateral information from informants if available. This study was approved by the institutional ethics committee.

Results. Eight subjects (5 women, 62.5%), with a mean ± SD age of 49.9 ± 14.6 years, presented with a mean duration of recurrent sleep-related eating features of 2.4 ± 2.1 years (range, 0.5–6 years). Clinical characteristics of individual subjects are shown in Table 1. Frequency of SRED symptoms varied from only a few times per year (3/8) to weekly to monthly (2/8) and nearly nightly attacks (3/8). During SRED attacks, the subjects usually consumed carbohydrates such as rice, instant noodles, and biscuits after a period of sleep. The subjects' behaviors occurred exclusively under an altered level of consciousness at which they had no or little recollection upon awakening, but the behaviors were evident by leftover food, residuals on the mouth, or stained clothes. Half of the subjects reported complex cooking behaviors under impaired consciousness, with an incidence of burning of kitchen utensils. Other undesirable outcomes including consumption of frozen or raw food (4/8) and subjective weight gains (5/8) were reported. All subjects had no prior history of sleepwalking before the occurrence of SRED.

Seven subjects underwent 1-night video-polysomnography (vPSG). There was no automatism or sleep-related eating behavior during vPSG recording. Six subjects had comorbid obstructive sleep apnea syndrome (OSAS), for which 1 was already receiving continuous positive airway pressure (CPAP) treatment before onset of SRED. Of 5 remaining subjects, only the one with severe OSAS agreed to have CPAP treatment. None was diagnosed with restless legs syndrome or periodic limb movement disorder.

All subjects except 1 (primary insomnia) suffered from mood disorders. Three subjects reported binge-eating episodes during depressive periods, but the severity was not up to a threshold diagnosis of binge-eating disorder. Most subjects were receiving polypharmacy, particularly antidepressants and benzodiazepines. The mean duration of zolpidem usage at baseline was 3.6 ± 2.3 years (range, 1–8 years), much longer than that of SRED symptoms (2.4 ± 2.1 years; range, 0.5–6 years). Five of 8 subjects reported persistent prominent insomnia (> 3 times/wk) despite the regular usage of hypnotics.

The mean follow-up duration was 22 ± 9.7 months (range, 8–33 months). Six subjects stopped taking zolpidem, but 2 subjects agreed only to decrease the dosage. Because of concomitant insomniac symptoms, 3 subjects were prescribed clonazepam to replace zolpidem. After zolpidem treatment was discontinued, all subjects reported disappearance of SRED symptoms, except for 1 subject who reported residual SRED symptoms with much lower frequency, from nightly to less than monthly attacks. No other automatism or sleepwalking episode was reported.

Our prospective cohort extended previous findings[2,4,5] of the association of therapeutic dosage of zolpidem with SRED and replicated the clinical features of high preference of carbohydrates or high-energy food during SRED attacks and amnesic features associated with complex automatism, including cooking behavior. Similarly, our SRED patients were prone to the complications of the disorder, including fire hazard and consumption of inedible food.

The immediate cessation and sustained disappearance of SRED in this case series provided further strengthening evidence of the key role of zolpidem in precipitating SRED. In fact, the wide range (from daily to a few times per year) and episodic nature of SRED behaviors argued for the necessity of long-term follow-up in order to demonstrate a clear resolution of the symptoms. On the other hand, the real-time correlation of onset between SRED and duration of zolpidem usage was not perfectly matched, as zolpidem usage preceded SRED symptoms by over a year. Moreover, although the subjects were taking zolpidem on a regular and daily basis, they suffered from only episodic attacks of SRED. Hence, there must be additional contributing factors. The current concept of sleepwalking and related disorders recognizes a series of predisposing, precipitating, and perpetuating factors that might deepen or fragment sleep and thereby contribute to the occurrence of sleepwalking episodes.[13] Proper recognition of these etiologic factors would be important in identifying high-risk individuals and hence improving the safety of the drug. In our study, SRED was highly comorbid with other sleep disorders including OSAS and insomnia.[4] Comorbid sleep disorders might serve as possible precipitating and facilitating factors for SRED. OSAS was suggested to increase the fragmentation of sleep and hence precipitate automatism attacks for vulnerable individuals.[14] Interestingly, only 2 out of 6 subjects with comorbid OSAS had undergone successful treatment for OSAS in our series, but all subjects still responded well to modification of their zolpidem regimen, with or without the concomitant use of clonazepam. Further studies are needed to clarify the interactive relationship between zolpidem, comorbid OSAS, and SRED.

The other conspicuous feature of the study sample is that our subjects suffered from chronic insomnia comorbid with depression, which resulted in prolonged usage of zolpidem. There has been a recent advance in the conceptual understanding of the close interactive and comorbid relationship between insomnia and depression.[15,16] Our cases further demonstrated that insomnia comorbid with depression could be very resistant to management and often resulted in polypharmacy, which further exacerbated the sleep problems in a vicious cycle. In this regard, there is a need for enhancement of integrated management of insomnia by both cognitive-behavioral therapy and newer types of pharmacologic intervention that will be specially geared toward the chronic nature of insomnia,[17] especially in patients with comorbid insomnia and depressive disorders. From a pragmatic perspective, clinicians should have heightened alertness to the occurrence of SRED, especially for those comorbid cases with late-onset sleepwalking and chronic usage of zolpidem.

Polypharmacy with concurrent medication usage was another risk factor in our series. The presence of concomitant sedative drugs (eg, tricylic antidepressants, antihistamines) might contribute to the development of SRED by further impairing the arousal level.[2] Eating disorders have been reported to be associated with SRED.[1] Our findings suggested that binge-eating behavior could be associated with the development of SRED after zolpidem usage. The uniqueness of zolpidem among other benzodiazepines and nonbenzodiazepine hypnotics with regard to precipitating SRED remains unknown.[2] Different benzodiazepine and nonbenzodiazepine hypnotics have shown various potentials for inducing amnesia and complex behavior.[18] Among different benzodiazepine and nonbenzodiazepine hypnotics, zolpidem has the highest affinity at the $GABA_A$ α_1 subunit. Apart from its amnesic effect, zolpidem was suggested to have a role in modulation of slow-wave sleep[19] and hyperphagic response in animals.[20] Further pharmacologic study is needed to delineate the specificity of zolpidem in inducing complex automatism with a predilection toward eating and appetite regulation.

In this regard, the current study was limited by the lack of further investigation of the sleep microarchitecture, such as cyclic alternating patterns rate, which might indicate the NREM sleep instability that is commonly found in some sleep disorders including sleepwalking.[13] In addition, further study is needed to delineate the real-time correlation of some of the factors well known to precipitate sleepwalking and other disorders, such as daytime stress, life events, and sleep deprivation,[13] to SRED attacks in order to understand this complex but potentially dangerous sleep condition.

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Table 1. Individual Clinical Characteristics and Follow-Up Response[a]

Patient	Sex/ Age (y)	Psychiatric Diagnosis	Physical and Sleep Disorders	SRED Duration at Diagnosis (y)	Duration of Zolpidem Usage at Diagnosis (y)	Baseline SRED Frequency	Baseline Psychotropics	Drug Regimen Modification	Duration of Drug Regimen Modification (mo)	SRED Features at Follow-Up?	Follow-Up Psychotropics
1	F/61	Depression	OSAS	1	1.7	Monthly	Paroxetine CR 25 mg Zolpidem 10 mg	Zolpidem discontinued Changed to clonazepam	25	No	Paroxetine 30 mg Clonazepam 1 mg
2	M/64	Primary insomnia	Ischemic heart disease, hypertension, diabetes mellitus, hyperlipidemia, OSAS	5	8.3	Few times per year	Zolpidem 10 mg prn Chlorphenamine 4 mg prn	Zolpidem discontinued Changed to clonazepam	7	No	Clonazepam 1 mg
3	M/63	Depression	Diabetes mellitus, OSAS	0.5	5.9	Nightly	Dosulepin 75 mg Zolpidem 10 mg	Zolpidem discontinued Changed to clonazepam	6	No	Dosulepin 75 mg Clonazepam 0.5 mg
4	F/54	Depression	Hypertension	0.5	3.1	Monthly	Paroxetine CR 25 mg Diazepam 10 mg Zolpidem 10 mg	Zolpidem discontinued	25	No	Duloxetine 90 mg Quetiapine 50 mg
5	F/56	Depression	Narcolepsy	6	5.25	Nightly	Paroxetine 20 mg Gabapentin 900 mg Lorazepam 0.5 mg Modafinil 300 mg Zolpidem 10 mg	Zolpidem discontinued	6	No	Paroxetine 20 mg Gabapentin 900 mg Lorazepam 0.5 mg Modafinil 300 mg
6	F/44	Bipolar disorder	None	1	2	Few times per year	Escitalopram 10 mg Lithium CR 600 mg Lorazepam 1 mg Flupenthixol/ melitracen 1 mg Zolpidem 10 mg	Zolpidem discontinued	34	No	Escitalopram 10 mg Lithium CR 400 mg Lorazepam 1 mg Flupenthixol/ melitracen, 1 tablet
7	F/29	Depression	History of Graves disease OSAS	2	2.25	Nightly	Escitalopram 10 mg Chlordiazepoxide 5 mg Zolpidem 10 mg	Zolpidem dosage decreased	8	< Monthly	Trazodone 150 mg Amisulpride 150 mg Zolpidem 5–10 mg prn
8	M/28	Depression	Epilepsy OSAS	3	3.5	Few times per year	Paroxetine CR 50 mg, sodium valproate CR 1000 mg Zolpidem 10 mg	Zolpidem dosage decreased	15	No	Paroxetine 60 mg Sodium valproate CR 1000 mg Lorazepam 1 mg Zolpidem 5 mg

[a]Medication doses expressed as daily doses.
Abbreviations: CR = controlled release, F = female, M = male, OSAS = obstructive sleep apnea syndrome, SRED = sleep-related eating disorder.

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Yun K. Wing, FRCPsych, FHKAM (Psych)
ykwing@cuhk.edu.hk
Siu P. Lam, MRCPsych, FHKAM (Psych)
Shirley X. Li, BSc
Jihui Zhang, MD
Mandy W. M. Yu, MPH, RPSGT

Author affiliations: Sleep Assessment Unit, Department of Psychiatry, Faculty of Medicine, The Chinese University of Hong Kong, Shatin, Hong Kong SAR.

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