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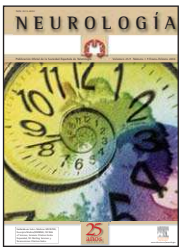

ORIGINAL ARTICLE

Zolpidem-induced sleep-related behavioural disorders

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KEYWORDS
Zolpidem;
Sleep-related food disorder;
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Sleep;
Side effect;
Obesity;
Hyperphagia;
Amnesia

Abstract
Objective: To present five patients with zolpidem-induced sleep-related behavioural disorders.
Methods: Evaluation using a questionnaire designed to study sleep behaviours and past medical history in all patients.
Results: The patients performed complex actions while sleep-walking (telephoning, house-cleaning, feeding the dog or waxing their legs). Inappropriate feeding behaviour with excessive food intake during the night were reported by all patients. All had weight gain, which in one patient led to extreme obesity. Two patients suffered injuries (knife cuts and burns) related to attempting to prepare food. One patient took a laxative.
Conclusion: Withdrawal of zolpidem resolved the behaviours in all cases, highlighting the importance of an adequate diagnosis of this side effect.

PALABRAS CLAVE
Zolpidem;
Síndrome de la cena durante el sueño;
Síndrome del comer nocturno;
Sonambulismo;
Sueño;
Efecto secundario;

Conductas complejas durante el sueño inducidas por zolpidem

Resumen
Objetivo: Presentar cinco pacientes con trastornos conductuales durante el sueño, sin conciencia posterior de los mismos, inducidos por zolpidem.
Métodos: Evaluación con un cuestionario diseñado para estudiar las características y las conductas realizadas durante el sueño por todos los pacientes.
Resultados: Las conductas realizadas por los pacientes fueron muy variadas (telefonear, limpieza y labores del hogar, alimentar al perro o depilarse), aunque en todos los pacientes se recogieron conductas alimentarias inapropiadas. Todos sufrieron una ganancia pon-

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Obesidad;
Hiperfagia;
Amnesia

deral importante, debido a su preferencia por alimentos hipercalóricos durante los episodios, que en una de las pacientes desembocó en una obesidad extrema. Dos de los pacientes sufrieron lesiones (cortes con cuchillo y quemaduras) en relación con el intento de elaboración de platos. Un paciente llegó a ingerir un laxante.
Conclusiones: La retirada de zolpidem resolvió de forma inmediata las conductas anormales durante el sueño en todos los casos. Esto subraya la importancia de diagnosticar adecuadamente este efecto secundario.

Introduction

Zolpidem (ZPD) is a sedative-hypnotic drug which is widely used in the short-term treatment of insomnia. It is considered a non-benzodiazepine agonist of benzodiazepine (BZD) receptors. BZD and BZD receptor agonists bind to the $GABA_A$ (Á-aminobutyric acid type A) receptor at a different binding site to that of GABA itself, which is the main inhibitory neurotransmitter in the central nervous system, and allosterically enhance the activity of the ligand-gated chloride channel. Its rapid action, short half-life, lower potential for abuse and dependence, and reduced side effects when compared to BZD and barbiturates justify its widespread use.

The development of complex behaviours during sleep are a little known side effect of ZPD. Two post-marketing studies, conducted in 1988 and 1995, reported an incidence of somnambulism of 1 in 96 patients (1%) and 7 in 192 patients (0.3%), respectively.[1,2] A recent review of the literature found 15 patients with complex behaviours during sleep induced by ZPD and 2 cases associated with other non-BZD receptor agonists, such as zaleplon and zopiclone.[3] This review did not include a series of 19 cases with sleep-related eating disorders associated with ZPD published as abstracts.[4,5] Three more cases have been reported since then,[6-8] which means that there are at least 37 known cases. Behaviours during sleep induced by non-BZD receptor agonists are diverse and include cleaning, shopping[9], sending emails[4,10] and driving vehicles.[4,10] Nevertheless, eating disorders are by far the behaviours most commonly associated with ZPD.[3,4,11]

The aim of this work is to describe the cases of 5 patients with complex behaviours during sleep associated with ZPD, observed between December 2006 and March 2009, at our Multidisciplinary Sleep Disorders Unit in the Hospital Clínico of Barcelona.

Clinical cases

All patients were evaluated through a questionnaire designed to assess their medical history and other clinical characteristics (table 1), complex behaviours during sleep (table 2) and sleep-related eating disorders (SRED) (table 3). SRED describes sleep-related eating behaviours of which the patient has little or no recollection afterwards.[5]

Case 1

This was a 39-year old woman who complained of abnormal behaviours during her sleep. At first, after waking up in the morning, she would find remains of food, such as yogurt and fruit, or empty water bottles in the kitchen. On up to 3 occasions she awoke to find depilatory wax stuck to her feet, once with a large burn on her leg, probably resulting from an attempt to wax, which she had no recollection of. Her husband confirmed the "strange" behaviour she had been displaying for "a few weeks", between 1 and 3 hours after going to sleep. In addition to these behaviours, she would also clean the house and fry eggs —she once burned herself with hot oil. She had also tried to leave the house to "go shopping or to the bank", and had no memory of it the next morning, so her family had to hide her keys. The onset of these behaviours coincided with the beginning of her treatment, 6 months earlier, for chronic insomnia associated with a major depressive episode,[12] consisting of 2 Zolpidem 10mg tablets before bedtime. When her psychiatrist gradually decreased the dose of ZPD, the frequency and severity of the episodes was reduced, and when the medication was completely suspended, they all eventually disappeared. The patient put on around 9kg during the time she was displaying these behaviours but her weight went back to normal once the problem was detected and solved. She also suffered from anorexia nervosa with bulimic tendencies when awake. During this same period she displayed sleep-related behavioural disorders. She has not displayed any of these behaviours for the past 3 years, and her anorexia/bulimia nervosa associated with the major depressive episode was also resolved around the same time.

Case 2

This 55-year old woman was displaying inappropriate behaviours during the night. She had a history of bronchial asthma, hypothyroidism, anxiety-depression syndrome with chronic insomnia which had been treated with 10mg of Zolpidem just before bedtime for the past 9 years, and bariatric surgery, which she had undergone 2 years before checking into our unit and had resulted in a weight loss of 43kg. Seven months before the first visit, she had decided to stop treatment with fluoxetine and alprazolam which she was taking for an affective disorder, although she did not stop taking ZPD. A few months before the visit, her mother

Table 1 Personal history and other clinical characteristics of the patients

Case	Age/ gender	Concurrent depressive disorder[12]	Awakening disorders	Treatment with other hypnotic-sedatives without SRED	Use of alcohol or other abuse substances (except tobacco)	History of RLS	History of OSAS	Other adverse effects of ZPD
1	39/ ♀	Major depressive disorder (single episode)	No	No	No	No	No	No
2	55 / ♀	Chronic major depressive disorder	No	No	No	No	No	Psychosis
3	53/ ♀	Chronic major depressive disorder	Yes (history of childhood night terrors)	Yes (clonazepam and alprazolam)	No	No	No	No
4	79 / ♀	Dysthymic disorder	No	Yes (lorazepam and trazodone)	No	No	No	No
5	27/ ♂	No	Yes (night terrors-disoriented awakening-somnambulism)	Yes (clonazepam, lormetazepam and diazepam)	Two liquors during weekends	No	No	No

OSAS: obstructive sleep apnoea syndrome during sleep; RLS: restless legs syndrome; SRED: sleep-related eating disorder.

Table 2 Clinical characteristics of complex behaviours during sleep associated with ZPD

Case	Dose (mg/night)	Third of the night in which behaviours appeared	Nº of episodes per night	Complex amnesic behaviours	Amnesia	Coincidence of behaviours with dreams	Verbal interaction during episodes
1	20	1st	1	Eating Drinking Clearing Waxing Leaving the house	Total	No	No
2	10	1st	1	Eating Dishwasher Washing machine Cleaning entrance	Total	No	Yes
3	10	1st	1	Eating Feeding the dog	Total	No	Yes
4	10	Unknown	Unknown	Eating	Total	No	Unknown
5	10	1st	Up to 4	Eating Cleaning Using the telephone Using computer	Partial	Variable	Yes

moved in with her and was alarmed by the abnormal behaviour her daughter was displaying during her first hour of sleep. The first time she found her, "she was on the terrace, crouching on all fours eating a watermelon without using her hands". On another occasion, she managed to prevent her from burning herself when she found her clumsily preparing an infusion in the microwave. During those episodes she would eat "anything within reach" (bread and milk, cold meats, sandwiches, salads). Her children later claimed that she had been displaying similar behaviour patterns for several years before her surgery, but they had not given it any importance. For them it was also "normal" for their mother to put on the dishwasher or washing machine or scrub the floor in the entrance to the building in the middle of the night. The patient was not aware of these behaviours although, before the bariatric surgery, she had noticed that every morning she would wake up with a "knotted stomach", would never eat breakfast and felt that her daily food intake did not justify her obesity ("she was always on a diet"). When ZPD was replaced by clonazepam 5mg/night, her abnormal sleep-related behaviours stopped.

Case 3

A 53 year-old woman, who had been suffering from chronic insomnia for about 5 years, in the context of a major depressive disorder,[12] and was being chronically treated with venlafaxine 150mg/day. She had started taking 10mg Zolpidem "shortly before" going to bed. "Some time after" initiating the treatment, the family dog began begging for food and suffering frequent diarrhoea and vomiting, so the family decided to consult with a vet. One night, one of the daughters, in whose room the dog slept, followed it and saw her mother giving the dog chocolate and ham, one piece for herself and one for the dog. The patient did not remember anything and when she was reproached for her behaviour —observed by her own daughter– she denied it. The solution was to close the door of the room where the dog slept, and the patient continued taking ZPD. She would eat everything that was in the fridge (stew leftovers, raw sardines with bones, cold meats, chocolate, biscuits...). The patient was diagnosed with sleep-related eating disorder (SRED) associated with Zolpidem around a year and half after she started taking it. After this, she suspended the treatment for 2 weeks, during which she did not suffer any episodes. She then decided to start taking it again, a decision approved by her psychiatrist, because it was "the only thing that improved her sleep". The nocturnal behaviour soon reappeared.

Case 4

This 79-year old patient was being treated for chronic insomnia associated with dysthymic disorder[12] with one 10mg Zolpidem tablet before bedtime. Three years after the start of the treatment she began to suspect that "someone was eating during the night, after she had gone to bed", because she would find hazelnut shells, almond skins or biscuit crumbs in the morning. Her first reaction was to scold her grandchildren who denied everything. After suffering a fall during the night next to the front door while she was handling glass bottles, the family decided to consult a specialist. Zolpidem was replaced by 10mg trazodone. The behaviours disappeared and have not recurred after 2 years of monitoring.

Case 5

This was a 27-year old male with a history of chronic insomnia, who was being treated with 10mg ZPD before

Table 3 Clinical characteristics of sleep-related eating disorders associated with ZPD

Cases	Mainly hypercaloric foods	Liquids	Toxics	Consumes foods from the usual diet	Morning anorexia or abdominal distension	Weight gain	Prepares meals	Lesions while elaborating meals
1	Yes (yogurt, fried eggs)	Yes (water)	No	Yes (fruit)	No	9kg in 2 years	Yes (frying eggs)	Yes (oil burns)
2	Yes (bread and milk, cold meats, sandwiches)	Yes (milk, water)	No	Yes (watermelon, salads)	Yes ("knotted stomach")	Bariatric surgery	Yes (infusion in microwave, sandwiches)	No
3	Yes (sardines with bones, chocolate, biscuits, cold meats)	No	No	No	Yes	4kg in one year and a half	Yes (sandwiches)	No
4	Yes (nuts, biscuits)	No	No	No	No	4kg in 2 years	No	No
5	Yes (yogurt, popcorn, sunflower seeds, chocolate)	No	Yes (laxative)	No	Yes	4kg in 2 months	Yes (heating soup, microwave, cutting ham)	Yes (cuts with knife)

bedtime, and who presented awakening disorders such as sleepwalking, with onset during childhood. Prior to treatment with Zolpidem, the patient was suffering 2 episodes of parasomnias per month, but 3 days after initiating treatment these episodes began to occur at least once a day. His most frequent sleep-related behaviours were eating disorders, but he would also tidy up the house, telephone friends or the bank, or fiddle around with the computer until he turned it on. On one occasion, he ingested bread with powdered magnesium laxative, which he confused with mayonnaise. As he ate it, he thought that the mayonnaise was strange because it did not stick to the bread. He managed to make popcorn in the microwave, cook soups on the stove and cut ham. This last activity resulted, on various occasions, in cuts on his fingers. He did not usually remember the episodes afterwards but did have some "awareness" of them if he saw any traces or if someone reminded him. He took Zolpidem for 2 months, and its suspension reduced the abnormal behaviours during his sleep back to the original pattern.

Discussion

We present 5 patients with complex, amnesic, sleep-related behaviours induced by Zolpidem. The association of these behaviours with the use of the drug is established by the fact that treatment interruption led to an immediate end of the behaviours in all 5 patients. In addition, one patient began to display sleep-related behaviours when she recommenced treatment with the drug. The time sequence between the initiation of treatment and the onset of symptoms is consistent, although it is difficult to establish the exact interval of time between both events because these disorders are amnesic and therefore they were only witnessed on some occasions and thus collected retrospectively.

All our patients presented SRED (sleep-related eating disorders), which appears to be the most common complex behaviour associated with ZPD.[5] SRED consists of episodes which commence with partial awakening, usually during the first third of the night, and culminate with the consumption of food, often hypercaloric or unusual. Patients experience partial or complete amnesia of the events and present an "automatic" inclination to eat and an inability to return to bed without having done so.[13] Schenck et al described (as an abstract) the cases of 19 patients with SRED associated to ZPD. Of these, 84% were women, 84% suffered recent or concurrent major depression, 89.5% were taking concomitant antidepressants and all of them had received other sedative-hypnotic or psychotropic drugs before or after ZPD without developing SRED.[4] Only one patient presented symptoms consistent with restless legs syndrome and another had a history of anorexia/bulimia nervosa. The series concluded that women under treatment for major depression are more likely to develop Zolpidem-associated SRED. Of our patients, 4 were female and all were suffering a depressive disorder[12] when they started displaying the Zolpidem-associated behaviours. This higher female prevalence has also been reported in other series.[9,11]

Attempts to explain SRED have included hypothesis on sleep fragmentation which could induce partial arousals in

phases of deep sleep without rapid eye movement (NREM), and, in some patients, lead to SRED. This fragmentation would occur for various reasons: sleepwalking, restless legs syndrome/periodic limb movement disorder, obstructive sleep apnoea syndrome, narcolepsy, having given up smoking, consumption of opiates, cocaine, triazolam and midazolam.[14-17] Zolpidem increases the proportion of NREM sleep stages in total sleep time[18] and thus, the probability of inducing partial arousals during these phases. The stages of NREM sleep are proportionally more frequent in the first part of the night, which is possibly why 4 of our patients would suffer episodes during the first third of the night. However, ZPD does not cause fragmentation of sleep architecture,[19] so its association with SRED would not be explained by this effect. In fact, in 42.1% (8/19) of the patients in the ZPD-related SRED series of Schenck (obstructive sleep apnoea syndromes, n=3; narcolepsy, n=2; restless legs syndrome, REM sleep behaviour disorder, sleepwalking, n=1) and in 1 of our series (sleepwalking, n=1), SRED was associated with other disorders which might fragment sleep.[4]

Other factors which may contribute to the genesis of SRED are the induction of hyperphagic responses and transient anterograde amnesia. It is known that most BZDs induce hyperphagic responses in mammals. However, ZPD has always been considered neutral with respect to the regulation of appetite.[20,21] The combination of causes that contribute to sleep fragmentation with induced hyperphagic response could be a plausible hypothesis to explain this disorder. However, it is unclear why ZPD, as a non-benzodiazepine agonist of the BZD receptor, generates this type of behavioural disorders during sleep more often than BZDs themselves. Transient amnesia is another known side effect of ZPD, although it is not very prevalent (1%),[22] possibly due to the inhibition of the consolidation of memory from short to long term.[23-26] Some authors have considered ZPD-related behaviours as somnambulism, while others regard them as compulsive activities with anterograde amnesia, different from somnambulism.[9] The presence of fluent speech and the ability to perform relatively normal activities, albeit repetitive ones at inappropriate times, would distinguish these activities from somnambulism. The subsequent amnesia may be total or partial, and could be justified by being a known side effect of ZPD.[9]

Finally, it has been speculated that an eating disorder, with poor impulse control, could become amnesic with ZPD, thereby explaining the SRED. We must mention the transformation of a nocturnal eating syndrome into an amnesic one as a result of the use of ZPD,[11] and the increase of somnambulism and amnesic binge eating episodes during sleep[27,28] that could affect up to one third of patients with bulimia nervosa.[29] Nocturnal eating syndrome is characterized by rapid food binges before sleep or immediately after waking up but, unlike SRED, the patient is completely conscious during these episodes.[12] It is believed that this is an eating disorder similar to anorexia/bulimia nervosa.[30] In our series, none of the patients had a history of nocturnal eating syndrome and one patient had presented bulimic behaviours at the same time as the SRED associated with ZPD. In the series of Schenck, 1 of the 19 patients presented nocturnal eating syndrome and another had a history of anorexia/bulimia nervosa.[4]

It is important to consider the serious consequences which this disorder can have. All the patients in our series had suffered difficulty in controlling their weight to such an extent that one of the patients had even undergone bariatric surgery. The most surprising fact about this case is that the patient had been taking ZPD and been on diet for years and did not believe that her food intake justified her obesity. This leads us to consider whether ZPD may have had a decisive influence on her morbid obesity. Handling and ingesting toxic products is another potential risk for these patients. One patient in our series took a laxative which he mistook for mayonnaise. Activities which pose a threat to physical integrity should also be mentioned. In the series of Schenck, 4 patients with SRED would cook, 3 of them even managing to light small fires, and another 2 went out to buy food and returned home.[4] In our series, 2 patients suffered injuries, one from hot oil burns and the other from knife cuts while preparing a dish. The former also burned herself on one occasion when she tried to remove hairs from her legs with hot wax. Finally, there are also other interesting indirect consequences resulting from activities such as using the telephone or the computer.[6] One of our patients even managed to call the bank to give instructions.

The link between complex sleep-related behaviours and Zolpidem is possible and biologically plausible. Therefore, upon the onset of these behaviours, which have been proven to pose a threat to the health or physical integrity of the patients, it is important to rule out that the patient is being treated with this drug.

Conflict of interest

The authors declare no conflict of interest.

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