

Case report

Tolerance to zolpidem-induced hallucinations: case report

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INTRODUCTION

Zolpidem is a substance with a hypnotic selective effect. It acts in type-1 benzodiazepine agents of the GABA-A complex and does not have active metabolites. The first publications reporting its use date back to 1985. It was launched in France¹ in 1988 and approved by the Food and Drug Administration (FDA)² in 1992. Zolpidem is the most prescribed hypnotic drug in the world and is shown to be well tolerated.^{3,4} Its use is not free from occasional severe adverse effects, such as induction to hallucinations. We will firstly report on a case of zolpidem-induced hallucination that, to our knowledge, is the first described in the literature to show tolerance to such an adverse effect.

CASE REPORT

A 22-year-old female patient presented a clinical picture compliant to nervous anorexia 6 years ago recovering uneventfully without treatment. Three years ago she looked for psychotherapy treatment due to social phobic and depressive symptoms, and improved after some time. Since then, she has noticed that her mood is oscillating and confirms that she is a very impulsive person. She looked for psychiatric help due to “strong depression and anguish.” She was administered fluoxetine, valproate, clonazepam and she is currently in use of venlafaxine. The patient’s history includes three suicide attempts and one episode of self-aggression.

About a year ago, she felt distressed, depressed, had insomnia and was not able to go to the university due to constant fluctuation in her clinical status. She described many short-term anxious and depressive symptoms and said she was extremely inconstant as to her self-esteem and relationships. When she came to us under such conditions she was diagnosed with borderline personality disorder. She was managed with an increased dose of carbamazepine, and continued with the antidepressant she had been taking for 6 months (venlafaxine 75 mg/day). After 3 weeks with carbamazepine 600 mg/day and plasma level of 5.63 mcg/ml she had an improvement of depressive and anxious symptoms, but mood oscillation and complaints of insomnia persisted. The

carbamazepine dose titration was 800 mg/day. Venlafaxine was maintained and trazodone 50 mg was included. She did not have a good response to trazodone and continued with insomnia. The drug was discontinued and levomepromazine 25 mg replaced it, no satisfactory result was found as well. For a period of about 1 month she used both trozadone and levomepromazine. The hypnotic medication was then replaced by zolpidem 10 mg before sleep. When she started to take zolpidem she was using venlafaxine 75 mg/day and carbamazepine 800 mg/day.

She reported that after having some very good night sleeps she had a very “weird” experience. About 20 minutes after taking the drug, she was brushing her teeth preparing to sleep when she realized the sound of voices and the presence of indistinct figures around her, while her teeth, a teddy bear and a picture became alive and talked to her. She described such an experience as a remarkable and vivid sensation, as if she was part of a film, interacting with people and listening to a beautiful song. The event took about 15 minutes, she was taken to bed by her sister and felt asleep. In the following morning, she talked to her sister about the strange event and recorded the “feelings” as if they were real. She was not impressed with that and continued to take the drug in doses of 5 and 10 mg at night. She had the same alteration of sensory perception with both doses, and highlighted the presence of indistinct figures, voices and objects that became alive. The treatment was continued and the patient observed that such manifestations, which initially had a weekly frequency, started to become rare, until they disappeared at all, in a period of about 2 months since they appeared for the first time. After 6 months, she is now free of any phenomenon of sensory perception alteration, probably having developed tolerance to the drug.

DISCUSSION

Visual and auditory hallucinatory episodes lasted about 20 minutes, and disappeared after she felt asleep, there was not daytime conscience fluctuation. There was no history of hallucinations prior to the use of zolpidem.

The fact that she had borderline personality disorder could justify the arousal of transient psychotic phenomena. Some conditions, however, makes us think of a pharmacologic induction: firstly, the psychotic phenomena of borderline personality disorder usually occurs at different moments, not only before going to sleep; second, they arise specially after stressful situations or that are adverse to the individual, which was not the case; and, eventually, hallucinations only occurred after the patient took zolpidem.

In the Psychotropic Prescribing Guide from the Physicians Desk Reference (PDR),⁵ which gathers information approved by the FDA, the possibility of zolpidem-induced hallucinations is described, though not shown to be frequent (between 1/100 and 1/1,000 cases). In the Psychotropic Drug Directory,⁶ however, we do not find any report of zolpidem-associated hallucinations.

Three national surveys investigated the use of zolpidem. In Switzerland, there were five cases out of 1,972 patients;³ in Germany, there were five cases out of 16,944 patients;² and in Brazil, no hallucinatory episode was found in 8,698 patients.⁷

Up to the present, there are 24 cases of zolpidem-induced hallucinations,^{1,4,8-20} of these, 20 are women and four men, ages varying from 4¹³ to 94 years.²⁰ Except for a 13-year-old girl,¹⁷ who had hallucinations after taking the drug at 5 mg/day, all the other individuals were taking doses between 10 and 60 mg/d. Fourteen of them were also taking antidepressants, specially ISRS.

The reason for the zolpidem-induced hallucinatory event is unknown, once there is no support for the hypotheses raised about its occurrence. It has been suggested that it was due to toxic plasma levels in susceptible patients, either because the plasma level in women can be 40 to 63% higher than in men,^{4,9,12,16} or by the competition for the protein bond in concomitant use with drugs that have high affinity with proteins, such as some antidepressants.^{1,11,16} The phenomenon, however, has been described in male patients^{13,15,19} taking low doses and in monotherapy^{8-10,13} as well as it was described in normal volunteers.²¹

The rapid absorption of zolpidem may decrease the surveillance level, facilitating the occurrence of hypnagogic distortions. This is not consistent for the case we reported here, once the

patient did not act as if she was sedated or sleepy, remaining oriented as to time and place. She described hallucinations in detail and remembered them when she was awake.

As to possible drug interactions in the case reported, venlafaxine is not a powerful inhibitor of cytochrome P450 isoenzymes 3A4, nor it has a high affinity rate with bond proteins;^{6,16} carbamazepine is a powerful inducer of isoenzymes 3A4 and other hepatic oxidative mechanisms;⁶ and zolpidem is metabolized by the cytochrome P450 isoenzymes 3A4.^{16,22,23} Thus, neither venlafaxine nor carbamazepine can significantly decrease the zolpidem metabolism, which would justify the arousal of toxic levels. Pharmacokinetic studies and clinical observations^{15,19,22-24} about drug interactions did not offer consistent evidence to the onset of zolpidem-related hallucinations. Therefore, drug interaction must not be considered the cause for the hallucinatory events.

We would rather consider a pharmacodynamic hypothesis in the case reported. The justification would be hypersensitivity of receptors of susceptible people, including interactions between the GABAergic neurotransmission and the serotonergic; however, there is not enough evidence to confirm such hypothesis. This would also justify tolerance to the hallucinatory phenomenon, resulting from mechanisms of neuroadaptation at the receptors level.

In order to minimize the chances of zolpidem-induced hallucinations and considering that women using antidepressants are a risk group known for presenting such phenomenon, we would recommend the careful use of the drug with an initial dosage lower than 10 mg before sleep, as well as patients should be advised as to the possibility of hallucinations.

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ABSTRACT

Background: Zolpidem is reported to be a safe and effective hypnotic agent. In the literature, there are some case reports of hallucinations after zolpidem administration. We report one more case in which zolpidem lead to hallucinations in young adult female.

Discussion: *This case, to our knowledge, is the first to suggest the possibility of tolerance to the rare but important hallucination side effect caused by this medicine. We discuss pharmacokinetic and pharmacodynamic hypotheses about this phenomenon.*

Conclusion: *Attention to zolpidem-induced hallucinations and tolerance to the drug is required, as well as a more comprehensive understanding of such phenomenon.*

Keywords: *Zolpidem, tolerance, hallucinations.*

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