

Zolpidem may cause visual distortions and other psychotic symptoms

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Zolpidem, an imidazopyridine hypnotic, has been used as an alternative to benzodiazepines for treating short-term insomnia because it has a relatively favorable side effect profile and less potential for abuse.¹

However, several cases of zolpidem-related psychotic symptoms have been reported,² including a report of an association between zolpidem and hallucinations.¹ The case illustrated here describes distortion of visual perception that can occur after ingestion of more than the recommended dosage of zolpidem.

CASE: Terrified and paranoid with distorted vision

Ms. K, age 33, an English-speaking woman from Portugal with a history of schizoaffective disorder, is brought to the emergency department in a terrified state. She describes visual distortion and paranoia because she fears losing her vision. She complains of suicidal ideation, depressed mood, insomnia, auditory hallucinations, and distortion of visual perception. She reports seeing shadows, recurring movements of the ceiling bearing down on her, and molding or melting walls.

Ms. K reports that the visual distortions began when she started zolpidem, 10 mg/d, 2 months earlier, after her mother in Portugal gave it to her.

Ms. K describes feeling disoriented and disconnected from reality. She reports taking extra doses of zolpidem (40 mg)—recommended maximum dosage is 10 mg³—and clonazepam (1 mg) to address her insomnia.

On examination, Ms. K appears shaky and tremulous, and we note that her eyeballs roll upward. Vital signs are within normal limits,

Box

Take-away advice

- Taking more than the recommended dosage of zolpidem and the presence of a psychotic disorder or anorexia nervosa when taking zolpidem are risk factors for visual distortions
- Be aware of the additive influence of age and sex pharmacokinetics on the potential for visual distortions associated with zolpidem

and she is awake, alert, and oriented to person, place, and time.

We diagnose exacerbation of schizoaffective disorder.

Ms. K is admitted to the inpatient psychiatric unit for observation and treatment. Quetiapine, 100 mg at bedtime, and sertraline, 100 mg/d, are started and zolpidem is discontinued.

The morning after admission, Ms. K reports that her vision has improved and that she no longer sees shadows or colored spots. All visual distortions resolve within 1 day after discontinuing zolpidem.

Discussion

Ms. K had no history of ophthalmologic or neurologic disease or alcohol or substance use. Physical and neurologic examination and laboratory testing failed to reveal any abnormality that accounts for her clinical presentation. Also, she reported visual distortions in the absence of drowsiness,⁴ thereby ruling out hypnagogic hallucination.⁵

Visual hallucinations are uncommon in schizoaffective disorder, but have been

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Visual hallucinations are uncommon in schizoaffective disorder, but have been shown to occur with zolpidem use

shown to occur with zolpidem use.^{1,4} The clinical manifestations in Ms. K's case are consistent with those of 3 reports, in which patients reported visual symptoms shortly after an initial dose of zolpidem, 10 mg.^{1,6} In those cases, symptoms resolved soon after zolpidem was discontinued.

Ms. K's case is similar to other reports in regard to time of onset and manifestations of visual distortions. Iruela and colleagues documented that hallucinations could be reproduced with a lower challenge dose of zolpidem (5 or 2.5 mg), and that, with such a challenge, symptoms should be less severe.⁷

How zolpidem induces visual hallucinations remains unknown. Several studies have looked at variables that might predispose a patient taking zolpidem to visual perceptual distortions.¹

Sex might play an important role.^{1,7} After administering the same dosage of zolpidem, women age 20 to 40 had a blood concentration of the drug that was, on average, 45% higher than those measured in men.⁶ This difference in serum concentration is more remarkable in older women; the blood concentration of the drug in women age >60 was 63% higher than that of men.

Influence of hormones. Pharmacokinetics of zolpidem seem to be related to endocrine factors associated with cytochrome P450 (CYP) 3A4 metabolism. A low plasma concentration of free testosterone may contribute to lower CYP3A activity, with women achieving as much as a 50% higher plasma level of zolpidem, whereas exposure to testosterone activates biotransformation via CYP3A.⁸

Body weight is important when dosing zolpidem. Zolpidem-induced macropsia has been reported in women with anorexia.⁷

The protein-binding capacity of zolpidem is approximately 92%, mainly to albumin (66%) and α 1-acid glycoprotein (56.6%).⁴ In malnourished patients with anorexia nervosa, hypoalbuminemia is common and, therefore, unbound drug concentration is higher. This effect could account for, or contribute to, zolpidem toxicity.⁷

Ms. K did not have anorexia nervosa and was not underweight, and her liver function and kidney function were within normal limits. However, prescribing guidelines call for an initial dosage of 5 mg/d for women (10 mg/d for men)³; Ms. K ingested 8 times the recommended daily dosage.

The lesson for practitioners? When you encounter a patient who has a psychiatric disorder with psychotic features, explore causes unrelated to their primary disorder—such as taking a hypnotic or multiple psychoactive medications—as a possible source of the presenting symptoms (*Box, page 31*). In Ms. K's case, her unusual symptoms resolved after a change in pharmacotherapy, leading us to conclude that her visual distortions likely were secondary to zolpidem and *not* to her schizoaffective disorder—a confounding factor.

References

- Huang CL, Chang CJ, Hung CF, et al. Zolpidem-induced distortion in visual perception. *Ann Pharmacother.* 2003; 37(5):683-686.
- Ansseau M, Pitchot W, Hansenne M, et al. Psychotic reaction to zolpidem (letter). *Lancet.* 1992;339(8796):809.
- Ambien [package insert]. Bridgewater, NJ: sanofi-aventis U.S. LLC; 2013.
- van Puijenbroek EP, Egberts AC, Krom HJ. Visual hallucinations and amnesia associated with the use of zolpidem (letter). *Int J Clin Pharmacol Ther.* 1996;34(7):318.
- Morselli PL. Zolpidem side-effects (letter). *Lancet.* 1993; 342(8875):868-869.
- Salvà P, Costa J. Clinical pharmacokinetics and pharmacodynamics of zolpidem. Therapeutic implications. *Clin Pharmacokinet.* 1995;29(3):142-153.
- Iruela LM, Ibañez-Rojo V, Baca E. Zolpidem-induced macropsia in anorexic woman (letter). *Lancet.* 1993; 342(8868):443-444.
- Cubala WJ, Wiglusz M, Burkiewicz A, et al. Zolpidem pharmacokinetics and pharmacodynamics in metabolic interactions involving CYP3A: sex as a differentiating factor. *Eur J Clin Pharmacol.* 2010;66(9):955.