High-dose zolpidem dependence - Psychostimulant effects? A case report and literature review

Zolpidem, an imidazoline nonbenzodiazepine sedative drug, is used widely. Initial reports showed minimal abuse potential. However, multiple reports have appeared of dose escalation and abuse. Subjective effects of high-dose zolpidem are not known. In light of accumulating evidence of abuse potential, we hereby report a case of high-dose dependence and a review of relevant literature. A 33-year-old male presented with 5 years of daily use of 600–1700 mg of zolpidem tartrate. He reported subjective effects of euphoria, intense craving, and inability to stop use. Loss of receptor specificity, pharmacokinetic factors, and different receptor distributions can explain paradoxical stimulatory effects of high-dose zolpidem. Further studies are required to characterize subjective effects of high-dose zolpidem.

Keywords: Craving, dependence, high dose, zolpidem

It is in this light that we present a case of zolpidem dependence in a male with no prior substance use, psychiatric problems, or physical problems. This case is interesting in terms of rapid escalation of drug use for its pleasurable high instead of anxiolysis/sedation and high amount of craving.

CASE REPORT

Mr. Y, a 33-year-old married male, who is a businessman by occupation presented to the deaddiction outpatient services with a history of 5 years of zolpidem dependence and 4 years of nicotine dependence.

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The patient started consuming zolpidem 5 years prior for the sake of experimentation.

Initial consumption was 10 mg/day, which escalated within months to 700 mg/day with a maximum use of 1700 mg/day. When the patient presented to us, he was on 300 mg/day for 2 weeks along with tablet quetiapine 200 mg, which was started by a psychiatrist for last 1 week. The patient reported using tablet quetiapine only at night as prescribed and had significant sedation with it. Zolpidem use was associated with loss of control, salience, tolerance, and continued use despite harm. No withdrawal symptoms were reported apart from minor headaches.

The patient reports that consumption of zolpidem gives him a "high", euphoria and he is perceived by others as sociable and talkative. This was the major maintaining factor for continued substance use. The patient also reported a significant increase in hunger, especially at night with significant weight gain. He performed complex actions (e.g., driving) of which he had no recollection. The patient had remained abstinent for a month earlier. Relapses were due to high craving and minor domestic issues which prompted the patient to restart zolpidem consumption.

The patient procured zolpidem by scouting different pharmacies and ordering piecemeal requirements of his average dose from each.

The patient had no psychiatric or medical comorbidities except dyslipidemia. He has never used any other substances except nicotine. There was no family history of substance use disorder.

On examination, mild tremors of hands and conjunctiva injection were noted.

Body mass index = 32.97. At the time of admission, the Clinical Institute Withdrawal Assessment-Benzodiazepines score was 9.

**DISCUSSION**

We presented this case for the following reasons: (discussed further)

- There are no vulnerabilities and such a patient is not considered high risk for prescription drug abuse
- Subjective effects of such high doses are not reported earlier.

The patient is male, had no family history or prior history of substance use, and in fact developed nicotine dependence much after onset of zolpidem use. There were no psychiatric or physical comorbidities, and the patient had a stable working and interpersonal environment. Therefore, this was a case which is usually considered at low risk of substance abuse.

Another unique feature is that zolpidem was taken for “high” and not for anxiolysis or sedation. A recent study on subjective effects of zolpidem sheds light on this issue where 10 mg was rated to be unpleasant while 20 mg was rated as “likable” and giving a “high.” Similar to this case, activation instead of somnolence is reported when zolpidem is used at high doses such as 40 mg/day for blepharospasm. There can be multiple pharmacokinetic and pharmacodynamic explanations of these unexpected effects and side effects. A plausible pharmacokinetic explanation is that short half-life agents have higher abuse potential. It is possible that at higher doses, zolpidem loses its selectivity for α1 subtype of GABA-A receptors. There is also a possibility that there can be multiple subtypes of receptors with different brain localizations. Further, it has been noted that zolpidem does not decrease cerebral glucose metabolism as is noted with most sedatives and natural sleep.

Current understanding of zolpidem’s pharmacodynamics is selectivity for α1 GABA-A receptors. However, there are a number of effects and side effects which cannot be explained. These include its efficacy in movement disorders, coma, catatonia, and aphasia. Zolpidem also has some unique neuropsychiatric side effects which are unexpected for a sedative-hypnotic. These include sleepwalking with and without sleep-related eating disorder, compulsive behaviors, seizures, psychostimulant effects, and psychotic experiences.

**CONCLUSION**

Despite being available for more than two decades, there are multiple questions that remain unanswered regarding zolpidem. Its abuse liability has been well reported. There is a need to elucidate subjective effects at high doses. Health professionals should be aware of zolpidem’s abuse liability. Larger studies should be undertaken to examine the prevalence of zolpidem abuse.

**Financial support and sponsorship**
Nil.

**Conflicts of interest**
There are no conflicts of interest.

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