

Clinical Case Report

Dependence syndrome and intoxication delirium associated with zolpidem

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ABSTRACT

The use of zolpidem by general practitioners and specialists alike has increased. Earlier, it was considered safe by physicians, i.e. devoid of dependence potential and the risk of serious adverse events. We report 5 patients seen over a 36-month period at the Post Graduate Institute of Medical Education and Research, which highlight the need for caution in the use of this drug.

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INTRODUCTION

Zolpidem, an imidazopyridine hypnotic, acting at the GABA-benzodiazepine complex, has become a popular alternative to benzodiazepines for sleep induction, due to its efficacy and better side-effect profile. We report 5 inpatients, seen over a 36-month period, at the Post Graduate Institute of Medical Education and Research, Chandigarh, a tertiary care hospital in northern India.

THE CASES

Case 1

A 57-year-old man with alcohol dependence was prescribed zolpidem (10 mg) for insomnia he experienced while abstaining from alcohol. He started taking 2 tablets of zolpidem at night on a regular basis. Over the next 4 months, he increased the dose to 8–10 tablets every night because of an inadequate effect at lower doses and by the eighth month, he was consuming 16–20 tablets/day (160–200 mg/day). He started taking zolpidem for daytime naps, which he believed would increase his efficiency. He experienced craving and withdrawal in the form of apprehension, restlessness, irritability and insomnia. He was diagnosed as having zolpidem dependence [Mental and behavioural disorders due to the use of sedatives or hypnotics (zolpidem) (F13.24)] and was successfully detoxified with clonazepam (8 mg/day). He was counselled regarding prevention of a relapse, but relapsed within 3 months.

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Case 2

A 45-year-old man with rapid-cycling bipolar disorder, diabetes mellitus, non-organic insomnia, drug-induced parkinsonism and nicotine dependence syndrome was prescribed zolpidem 10 mg for insomnia. Within a few weeks, he was taking 20–30 mg of zolpidem at night, as he found 10 mg ineffective. Later, he discovered that daytime use of 2–3 tablets of zolpidem alleviated ‘episodes’ of anxiety that he experienced during the day (detailed assessment did not establish the presence of syndromal anxiety disorder). Over the next few weeks, he experienced restlessness, palpitations, anxiety (not amounting to panic) and decreased sleep if he did not take zolpidem, and he gradually increased his dose to 12–15 tablets per day to relieve these symptoms. He also reported subjective craving for zolpidem. He was diagnosed to have dependence on zolpidem [Mental and behavioural disorders due to the use of sedatives or hypnotics (zolpidem) (F13.24)] and was successfully detoxified with clonazepam (8 mg/day) and counselled regarding prevention of a relapse. He remained abstinent over a follow up of about 6 months.

Case 3

A 65-year-old man with unstable angina and moderate depression, admitted to a coronary care unit, was prescribed mirtazepine 15 mg/day and alprazolam 0.5 mg/day for depression and anxiety and ecosprin 150 mg/day, enalapril 5 mg/day, atorvastatin 20 mg/day and pantoprazole 40 mg/day for coronary artery disease. He underwent coronary angioplasty and received 10 mg of zolpidem that night, as he was unable to sleep. About half an hour after taking zolpidem, he was observed to be agitated, talking irrelevantly and unable to recognize his relatives. These symptoms lasted for about an hour, following which the patient fell asleep. Zolpidem was discontinued and the symptoms did not recur. History, examination and investigations ruled out the possibility of a seizure and transient ischaemic attack/stroke, electrolyte imbalance, hypoglycaemia and blood gas abnormalities. All biochemical parameters were within normal limits. The patient was diagnosed to have delirium induced by zolpidem [Mental and behavioural disorders due to the use of sedatives or hypnotics (zolpidem), acute intoxication with delirium (F13.03)].

Case 4

A 65-year-old widow, who presented with late-onset psychosis, was being treated with risperidone for the past 4 weeks. She had no history of fever, head injury, seizures, loss of consciousness or substance abuse. She developed symptoms of irrelevant talking, disorientation to time and place, fleeting ill-formed, short-lasting auditory and visual hallucinations an hour after taking zolpidem 10 mg at bedtime for insomnia. The symptoms lasted for 2–3 hours. All biochemical investigations, electroencephalogram and CT scan were within normal limits. She was diagnosed to have delirium induced by zolpidem [Mental and behavioural disorders due to the use of sedatives or hypnotics (zolpidem), acute intoxication with delirium (F13.03)]. No rechallenge was attempted.

Case 5

A 65-year-old man with bipolar affective disorder (index episode:

severe depressive episode without psychotic symptoms), with hypothyroidism and slightly deranged renal parameters (urea 52 mg/dl, serum creatinine 1.2 mg/dl), was observed to be talking irrelevantly, having visual and tactile hallucinations, restlessness, agitation, violent behaviour and disorientation, a few hours after taking zolpidem 10 mg. Other biochemical investigations and CT scan were within normal limits. Zolpidem was stopped, haloperidol 0.75 mg/day was started and the symptoms subsided after 3 days. The diagnosis given was delirium induced by zolpidem [Mental and behavioural disorders due to the use of sedatives or hypnotics (zolpidem), acute intoxication with delirium (F13.03)]. Subsequently, zolpidem was not prescribed for the patient.

DISCUSSION

Several recent publications have highlighted that the abuse potential of zolpidem was underestimated. A systematic review based on a Medline literature search identified 36 cases of zolpidem dependence.¹ Both sexes and all age groups were involved to a similar extent. In extreme cases, dose increases reached a factor of 30–120 above the recommended doses. The majority of patients had a history of former drug or alcohol abuse and/or other psychiatric conditions. The authors suggest that the relative incidence of reported dependence is lower than that of benzodiazepines used for the treatment of disturbed sleep. Two of our cases also had a history of prior alcohol abuse and/or other psychiatric conditions, but the dose increase was less extreme (a factor of 12–20 above the recommended doses) than that reported in the literature.

A few cases of delirium related to zolpidem use have been reported in the literature.^{2–6} Zolpidem has also been reported to have side-effects related to the central nervous system, such as headache (19%), depression (2%), memory deficit (1.8%) and abnormal dreams (1%). The three cases of delirium in our series occurred in elderly, physically/mentally ill patients, who were on multiple medications and higher (10 mg) than recommended

doses (5 mg) of zolpidem for the elderly.⁶ Also, it has been shown that women have zolpidem serum concentrations levels that are 45% higher than those in men at the same dose and in elderly women, this difference is exaggerated; this age group of women is known to have a 63% higher serum concentration than men in the same age group.⁷ Several studies have suggested that higher doses of zolpidem predispose patients to adverse reactions, particularly delirium and psychosis.^{5,8,9} High serum levels of zolpidem and drug–drug or drug–disease interactions could thus have caused the deliriums.

These cases highlight the need for caution in the use of zolpidem in patients with prior history of substance misuse because of the heightened abuse potential and, because of the risk of delirium, in the elderly, medically ill patients on other medications. Moreover, there is merit in strictly adhering to the recommended dose of 5 mg in the elderly.

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Erratum

In the article ‘Screening for HIV infection by health professionals in India’ by M. Kurien, K. Thomas, R. C. Ahuja, A. Patel, Shyla P. R., N. Wig, M. Mangalani, Sathyanathan, A. Kasthuri, B. Vyas, A. Brojen, T. D. Sudarsanam, A. Chaturvedi, O. C. Abraham, P. Tharyan, K. G. Selvaraj, J. Mathew (IndiaCLEN HIV Screening Study Group) that was published in *The National Medical Journal of India* (Natl Med J India 2007;**20**:59–66), the name of Dr Akoijam Brogen has been mis-spelt as A. Brojen. The correct spellings are A. Brogen

We regret the error.