

Alprazolam Dependence: A case report

Chaudhury S*, Meshram S**, Azim M**

Abstract

A 50 years old housewife presented with complaints of heaviness of head and insomnia of 3-4 years duration. History revealed that the symptoms persisted despite consuming 10 mg of alprazolam per day. Reduction of the dose of alprazolam caused severe withdrawal symptoms which abated on administration of the drug. She was managed with gradual withdrawal of alprazolam together with administration of antidepressants and supportive psychotherapy. Benzodiazepine dependence and withdrawal are briefly discussed

Key Words: *alprazolam; dependence; withdrawal.*

Introduction

Humans have been using sedative-hypnotic agents since time immemorial. The use of alcohol goes back 8000 years and its use in medicine continued till the beginning of the nineteenth century [1]. In continuation of the noble tradition of introduction by mistake, the first psychotropic drug to be so used was bromide. Potassium bromide was believed to lessen sexual urges and thereby relieve epilepsy which was thought to result as a consequence of masturbation. Bromides were introduced by Locock for the treatment of epilepsy, apparently with gratifying results! By the 1870s, bromides were being used very widely as sedatives and the dependence potential of this drug eventually became apparent[1]. Subsequently, chloral hydrate and paraldehyde were introduced, but both these were also associated with abuse and dependence [2]. Barbiturates appeared in the 1930s and were found to be very addicting[2]. The first benzodiazepine, was marketed in the early 1960s. Due to their effectiveness and safety profile the benzodiazepines were considered as a panacea, but unfortunately these were also associated with abuse,

dependence, and withdrawal symptoms.[1,2] Alprazolam was introduced in 1981 and by 1988 it was the number one selling benzodiazepine[2]. Initial studies of this drug indicated low rates of side effects. Subsequently several reports of adverse effects of alprazolam during both treatment (hostility, rebound insomnia, major depression, amnesia, aggressive and violent behavior, mania, hepatitis, hepatomegaly, jaundice, and altered liver function) and withdrawal (seizures, rebound anxiety, delirium, psychosis, mania, and paranoia) have appeared. Many cases involving generalized benzodiazepine withdrawal symptoms have also been reported [1-3].

Case Report

A 50 year old married, Hindu female, presented with complaints of heaviness of head and reduced sleep for past 3-4 years. History revealed that she was apparently asymptomatic 4 years back, when following a tooth extraction, she developed heaviness of head and insomnia for which she was prescribed alprazolam (0.5 mg) at bedtime. She obtained relief and continued the medication daily. Gradually she needed increasing amounts of the drug to get sleep. On presentation despite consuming 20 tablets of alprazolam (0.5 mg each) she gets about 3-4 hours of sleep and remains awake thereafter. However, her son became worried and refused to give her more than 20 tablets per day thereby restricting intake. If she does not take the tablets she gets no sleep at all. Together with this she has headache, feels jittery, restless and uncomfortable, talks irrelevantly and excessively to herself, seems confused, forgetful and

*Prof & Head, Dept of Psychiatry

**Internee, Dept of Psychiatry

Address for Correspondence:

Dr. Suprakash Chaudhury,
Prof & Head, Dept of Psychiatry,
Pravara Rural Hospital, Rural Medical College
Pravara Institute of Medical Sciences, Loni
Tal. Rahata, Dist. Ahmednagar, Maharashtra-413736

unable to do household work. All these symptoms are relieved on taking alprazolam. Since a single medical shop refuses to sell large quantities of the drug, she visits a number of different shops to buy the drug over the counter. There is no past history of neurological or psychiatric disorders. She hails from an urban, lower middle class family. She is married for 30 years and has two children aged 28 and 25 years. No marital disharmony is reported. There is no family history of mental illness. Physical examination revealed no specific abnormality. Mental status examination showed a kempt, cooperative lady who was in touch with reality. Talk was relevant and coherent. She had intense craving for the drug but was concerned about withdrawal symptoms. Though willing to reduce or stop taking alprazolam she clearly stated that unless she was prescribed an effective alternative hypnotic medication she would be unable to stop taking alprazolam. She refused to surrender her stock of the drug. She was anxious and mildly depressed. There were no features of hallucinations, delusions or psychosis. Memory, orientation and insight were unimpaired. Sleep and appetite were reduced. Her total score on the Benzodiazepine Dependence Questionnaire [4] as well as scores on the general dependence subscale, pleasant effects subscale as well as the perceived need subscale were all above the 75th percentile score thereby indicting a very high probability of benzodiazepine dependence. The patient was treated with tapering doses of alprazolam and a sedating antidepressant (amitriptylline 25 mg HS x 30 days) with satisfactory response.

Discussion

Low and medium potency benzodiazepines were initially introduced for the treatment of insomnia and anxiety. Their therapeutic actions as anxiolytics, sedative hypnotics, anticonvulsants, and muscle relaxants (with their low toxicity) increased their utility, and they became one of the most prescribed classes of drugs. Novel therapeutic uses of benzodiazepines were discovered with the introduction of the high-potency benzodiazepines (e.g., alprazolam, clonazepam, and lorazepam). They are effective in treating panic disorder and panic attacks with or without agoraphobia. In addition, they are useful as add-on therapy for selective serotonin reuptake inhibitors in the treatment of obsessive-compulsive disorder and panic disorder. They are also recommended as adjunctive therapy in treating patients with acute mania or acute agitation. High-

potency benzodiazepines have replaced low and medium potency benzodiazepines due to their greater therapeutic effects and rapid onset of action. Differences in distribution, elimination, half-life, and rate of absorption are important considerations when choosing a high-potency benzodiazepine. Typically, a benzodiazepine with long distribution and elimination half-life is preferred. A maximum dose of 2 mg/day of any of the high-potency benzodiazepines when administered for more than 1 week is recommended. Although as a class, benzodiazepines act rapidly and are well tolerated, their use presents clinical issues such as tolerance, abuse, dependence, rebound anxiety, memory impairment, and withdrawal syndromes [3, 5].

Despite repeated recommendations to limit benzodiazepines to short-term use (2–3 weeks), doctors all over the world are still prescribing them for months or years. This over-prescribing has resulted in large populations of long-term users who are dependent on benzodiazepines. This therapeutic dose dependent group forms the largest population of benzodiazepine-dependent patients. A considerable proportion of these patients are elderly females consuming benzodiazepine hypnotics[6]. In India the problem is further compounded by the fact that benzodiazepines are easily available over the counter. A minority of patients who start on prescribed benzodiazepines escalate their dosage excessively. This small group comprises the high-dose dependence patients, who may consume upto 20 mg of alprazolam per day. [2, 7] In addition to therapeutic dose dependence and high dose dependence, recreational benzodiazepine abuse is also reported. Benzodiazepines commonly form part of a polysubstance abuse pattern. They are consumed by at least half of opiate, amphetamine, cocaine and other illegal drug users worldwide and also by alcoholics. Other users include patients with mental illness and co-morbid other substance abuse. Reasons given for taking benzodiazepines recreationally are that they enhance the 'high' obtained from illicit drugs, alleviate withdrawal effects, serve as 'downers' from the effects of stimulant drugs ('uppers') and also produce a 'kick' when taken alone in high doses or injected intravenously[7].

The pharmacological mechanisms underlying benzodiazepine dependence are complex and still unclear. Tolerance to benzodiazepine results from neuroadaptive processes involving both desensitization of inhibitory gamma-aminobutyric acid (GABA) receptors and sensitization of excitatory glutaminergic

receptors. Changes in GABA receptors may include conformational alterations towards a low affinity state for GABA and uncoupling of benzodiazepine receptors from their sites on certain GABA receptors, followed by internalization and long-term effects on intraneural gene transcription. Changes in the glutamergic system may include sensitization of N-methyl-D-aspartate (NMDA) receptors. Rapid withdrawal of benzodiazepine, once tolerance has developed, exposes the recipient to the consequences of all these drug-induced adaptations, namely, underactivity of inhibitory GABA functions and a surge in excitatory nervous activity, giving rise to the benzodiazepine withdrawal symptoms. The various receptor changes occurring during tolerance may be slow to reverse and may do so at different rates, possibly explaining the variable time of emergence and duration of individual withdrawal symptoms and sometimes protracted nature of benzodiazepine withdrawal [7].

Onset of withdrawal symptoms typically occur within two days of ceasing short-acting benzodiazepines (e.g. alprazolam), and between two and ten days (rarely three weeks) after stopping long-acting benzodiazepines (e.g. diazepam) [8]. Benzodiazepines with a short half-life produce more severe withdrawal symptoms than benzodiazepines with a long half-life. Withdrawal is often protracted and may extend over a number of weeks or months. The benzodiazepine withdrawal syndrome comprises both physical and psychological symptoms. Physical signs of benzodiazepine withdrawal include elevated systolic and diastolic blood pressures, tachycardia, and sweating. Tingling, numbness, altered sensation, dizziness, light headedness, headache, formication (skin 'crawling'), nausea and vomiting, stomach cramps, tremors, muscle twitches, fasciculation, muscle pain, stiffness, tinnitus, and sensory hypersensitivity (light, sound, taste, smell). Psychological symptoms of benzodiazepine withdrawal include anxiety, panic, palpitations, agitation, insomnia, nightmares, restlessness, fatigue, mood swings, anger, excitability, and depression. Perceptual distortions, depersonalization, derealisation, hallucinations (visual, auditory), poor memory and poor concentration may also be observed. On rapid or abrupt withdrawal from high doses of benzodiazepines psychotic symptoms, confusion, delirium, and convulsions may occur. Rarely death, following alprazolam withdrawal seizures has been reported [9].

Management of benzodiazepine dependence involves gradual tapering of dose, treatment of withdrawal symptoms as they emerge and psychological support. The recommended rate of tapering for patients on therapeutic doses of benzodiazepine is withdrawal in steps of about one-eighth to one-tenth of the daily dose every 1–2 weeks. On the other hand high dose abusers are recommended a fairly rapid withdrawal of benzodiazepine, with diazepam substitution and tapering over 2–3 weeks [8].

References

1. Lader M. History of Benzodiazepine Dependence. *Journal of Substance Abuse Treatment*, 1991; 8: 53-59.
2. Dickinson, B., Rush, P.A., Radcliffe, A.B. Alprazolam Use and Dependence - A Retrospective Analysis of 30 Cases of Withdrawal. In *Addiction Medicine [Special Issue]*. *West J Med* 1990; 152:604-608.
3. Moylan S, Giorlando F, Nordfjærn T, Berk M. The role of alprazolam for the treatment of panic disorder in Australia. *Aust N Z J Psychiatry*. 2012;46(3):212-24.
4. Baillie A. Manual for the Benzodiazepine Dependence Questionnaire (BDEPQ). National Drug and Alcohol Research Center, University of New South Wales, 1996.
5. Chouinard G. Issues in the clinical use of benzodiazepines: potency, withdrawal, and rebound. *J Clin Psychiatry*. 2004;65 Suppl 5:7-12.
6. Heather N, Bowie A, Ashton H, et al. Randomised controlled trial of two brief interventions against long-term benzodiazepine use: outcome of intervention. *Addict Res Theory* 2004; 12:141–154.
7. Ashton, H. The diagnosis and management of benzodiazepine dependence. *Current Opinion in Psychiatry* 2005, 18:249–255.
8. Saunders, J. & Yang, J. *Clinical Protocols for Detoxification in Hospitals and Detoxification Facilities*. Brisbane; Alcohol and Drug Services, Royal Brisbane Hospital and The Prince Charles Hospital Health Service Districts. 2002.
9. Haque W, Watson DJ, Bryant SG. Death following suspected alprazolam withdrawal seizures: a case report. *Tex Med*. 1990;86(1):44-7.