

Drug Safety 9 (2): 93-103, 1993
0114-5916/93/0008-0093/\$05.50/0
© Adis International Limited. All rights reserved.
DRS1 188

Benzodiazepine Dependence Avoidance and Withdrawal

Sarah Marriott and Peter Tyrer

Department of Community Psychiatry, St Charles' Hospital, London, England

Contents

93	Summary
94	1. Structural and Functional Considerations in Benzodiazepine Dependence
94	2. Risk Factors for Benzodiazepine Dependence
95	2.1 Pharmacokinetic and Pharmacodynamic Considerations
97	2.2 Personality
98	3. Avoiding Dependence in Clinical Practice
99	4. The Withdrawal Syndrome
100	5. Management of Benzodiazepine Withdrawal
102	6. Conclusion

Summary

Benzodiazepine dependence is a frequent complication of regular prescriptions for 4 weeks or longer, occurring in almost one-third of patients. Although it is also manifested by tolerance to drug effects and occasional drug seeking behaviour, particularly in those prone to drug abuse, most dependence is characterised by a withdrawal syndrome on stopping treatment. The withdrawal syndrome includes symptoms of anxiety and those of perceptual disturbance such as depersonalisation, hypersensitivity of all major senses, dysphoria and (rarely) epileptic seizures and psychotic episodes. Risk factors for dependence include high dosage, use of more potent and short acting benzodiazepines, long duration of therapy and dependent premorbid personality characteristics. If none of these apply, benzodiazepines can be prescribed with safety.

Benzodiazepines were introduced to clinical psychiatry in the early 1960s. Their use increased steadily through the rest of the decade and well into the 1970s (Lader 1991). The peak of prescribing was in 1979 in the UK (Beaumont 1990), and in most other countries the peak occurred within 2 or 3 years of this date. Although the potential for dependence was recognised early this was considered an infrequent occurrence, and it was not until the early 1980s that the benzodiazepine abstinence

syndrome began to be appreciated to its full extent. It is a salutary lesson that in spite of early warnings prescribing patterns increased in the 1970s, and by 1986 prescriptions were being issued at 80% of the peak rate (Brandon 1990).

Although there are several case reports of pharmacological dependence with benzodiazepines from the time of their introduction until 1980, almost all of these were associated with consumption of high doses beyond the therapeutic range (Marks

1978), and dependence on normal prescribed dosage was alleged to be a minor problem. However, since the demonstration that unequivocal withdrawal symptoms can follow reduction of benzodiazepines after they have been taken in low dosage (Petursson & Lader 1981; Tyrer 1980; Tyrer et al. 1981; Winokur et al. 1980) the problems of 'low dose' dependence have been recognised to be significant in clinical practice. Media concern has highlighted this problem in many countries and has led to calls for legal action against both pharmaceutical companies and doctors for allegedly promoting and prescribing these drugs inappropriately. The profession is now left with 2 important problems that were not recognised before 1980; the need to avoid dependence in patients prescribed benzodiazepines and the introduction of programmes for withdrawing patients who have already developed dependence, often from an initial prescription given at the time when low-dose dependence was unrecognised.

The phenomenon of pharmacological dependence with benzodiazepines is now undisputed. Recent advances in our understanding of the mechanisms of action of the benzodiazepines, and of the γ -aminobutyric acid (GABA) receptor complex may suggest new approaches to avoidance and treatment of the abstinence syndrome. However, this understanding has not yet led to successful treatments for dependence.

1. Structural and Functional Considerations in Benzodiazepine Dependence

The benzodiazepines are a family of glycoproteins with a specific high affinity for the benzodiazepine receptor. They appear to act through potentiation of GABA, the major inhibitory neurotransmitter in the brain (Cowen & Nutt 1982). Elegant work on the benzodiazepine receptor has contributed not only to an understanding of allosteric modulation, but has also revealed a further novel feature of molecule receptor interaction through the discovery of inverse agonist and agonist properties of the ligand receptor interaction. The inverse

agonist induces a stimulus which is opposite to the agonist, while a partial agonist produces a weaker stimulus resulting in a sub-maximal response, even at 100% receptor occupancy.

Changes in function with long term administration may be related to subsensitivity to agonists and increased sensitivity to inverse agonists. This suggests a change in the efficacy of the inverse agonist after long term administration of the agonist. It is supported by the finding that in flurazepam-dependent mice, administration of an antagonist (an agent characteristically producing no response) is pro-convulsant (Nutt 1990). Such a mechanism may offer an important clue to furthering our understanding of the mechanisms of tolerance and withdrawal.

Tolerance, the phenomenon of reduced pharmacological effects with repeated use, is well demonstrated with the short term effects of benzodiazepines but substantive evidence of loss of anxiolytic efficacy with benzodiazepines is lacking (Nutt 1990). It may be that enhancement of GABA is attenuated through down regulation of benzodiazepine receptors but there is no clear evidence for change in receptor numbers or sensitivity after repeated use. It is possible that changes in function with long term administration are related to subsensitivity to agonists, and increased sensitivity to inverse agonists. This line of reasoning has led to the 'receptor shift hypothesis', which suggests a change in the relative efficacy of the inverse agonist after long term administration of the agonist (Little et al. 1987).

2. Risk Factors for Benzodiazepine Dependence

One of the problems in interpreting animal data is that only a minority of patients prescribed benzodiazepines long term develop dependence. It is extremely difficult to determine the exact incidence of dependence in patients receiving benzodiazepines, largely because the evidence used to identify dependence is mainly through the exhibition of a withdrawal syndrome. For many pharmacologists this is not a satisfactory definition as,