Brit. J. Psychiat. (1980), **137**, 576–577

Comments

DEPENDENCE ON BENZODIAZEPINES

Each day about 40 billion doses of benzodiazepine drugs are consumed throughout the world. This figure is staggering by any standards, and at present one of the benzodiazepines, diazepam, is top of the prescription drug league. No drug can achieve this level of popularity without a good press, and considering that the benzodiazepines have been in general use for over twenty years they have come through remarkably well. They are much better than the barbiturates that preceded them, they are remarkably safe even in colossal overdosage and they are highly effective drugs which reduce anxiety preferentially with a minimum of higher cortical disturbance. The recent discovery of benzodiazepine receptors (Möhler and Okada, 1977) and the evidence that benzodiazepines facilitate GABA-ergic synapses (Haefely, 1978) confirms their selectivity at the biochemical level.

But clouds are now appearing on the horizon. Although anxiety is commonplace, many patients do seem to be on benzodiazepines for an unconscionably long time and the idea that patients might become dependent on them has been lurking in the background. Short term treatment is recommended (Committee on the Review of Medicines, 1980) and the doctor may intend his initial prescription to be only one, but patients have the habit of coming back and asking for more. The reasons for this are still open to argument and it is quite possible that as pathological anxiety and insomnia are often chronic it should not be surprising that patients continue to need further prescriptions. However, when the demand for a drug is led by patients, dependence needs to be considered. It has been known for many years that benzodiazepines can produce classical pharmacological dependence. It was first noticed by Hollister and his colleagues in one of the early studies with chlordiazepoxide, when patients who were suddenly withdrawn from high dosage developed psychic and physical withdrawal symptoms, including fits (Hollister *et al*, 1961). Since then there has been a trickle of published case reports of similar problems with benzodiazepines, usually in high dosage, including the development of tolerance as well as severe symptoms following withdrawal. Taken against the backcloth of benzodiazepine consumption in the population these reports impress more by their rarity than by their content, and Marks (1978) has calculated that the risk of true pharmacological dependence with benzodiazepines is only one case per five million patient months.

A more important clinical question is whether benzodiazepines can produce dependence in therapeutic doses. This is more difficult to assess than might at first appear. Anxiety and its associated symptoms run a fluctuating course and an increase in dosage may merely indicate a temporary increase in symptoms rather than true tolerance. Withdrawal syndromes are not diagnostically specific and extreme anxiety is one of their important components, so apparent symptoms of withdrawal after stopping a benzodiazepine may be the recrudescence of pre-existing anxiety formerly relieved by the drug. There have been few studies of the clinical features following withdrawal from benzodiazepines in therapeutic dosage. Covi and his colleagues (1973) showed, using a placebo substitution technique, that patients who had taken chlordiazepoxide in therapeutic dosage regularly for 20 weeks experienced 'minor symptoms of abstinence' such as trembling, poor appetite and faintness after withdrawal. As such symptoms were not marked in similar patients after only 10 weeks of treatment this was presumptive evidence for a withdrawal syndrome occurring after prolonged therapy. There have been two single case studies since published which describe the main characteristics of the withdrawal syndrome (Pevnick *et al*, 1978; Winokur *et al*, 1980). In these cases the patients had been taking diazepam in doses of 15–45 mg daily for twenty months and six years respectively. The withdrawal syndrome after cessation of drug treatment included symptoms of anxiety, dysphoria, muscle twitching, insomnia, dizziness, palpitations, hypersensitivity to noise and touch, and shaking. Lader (1980) has reported similar symptoms in patients dependent on somewhat higher dosage; these also include depersonalization and perceptual changes such as feelings of motion and awareness of shimmering lights. Despite the extensive range of these symptoms they are not indicative of a with-

https://doi.org/10.1192/bjp.137.6.576 Published online by Cambridge University Press

drawal syndrome, and indeed, rather similar symptoms have been reported during acute therapy with a new benzodiazepine, triazolam, in Holland. This created such concern that the drug was subsequently withdrawn, although whether the symptoms were caused by the drug is controversial (Lasagna, 1980). What makes it likely that these symptoms are genuinely those of withdrawal is that they are immediately relieved by retaking the benzodiazepine and that they last for only a few days if the patient takes no further benzodiazepine.

It is difficult to extrapolate from these data to clinical practice. A large proportion of psychiatric and general practice patients take benzodiazepines regularly and chronically (Tyrer, 1978). How many of these are dependent on their drugs and how many are taking them for longstanding anxiety? In a recently completed study of patients who had taken lorazepam or diazepam regularly in therapeutic dosage for four months or more and who then stopped medication abruptly 27 per cent of those who completed the study had an unequivocal withdrawal syndrome in that they had typical symptoms of abstinence of short duration which then resolved (Tyrer *et al*, 1980). This figure is almost certainly an underestimate as it does not include those who returned to taking benzodiazepines to relieve their symptoms. Half of the patients received the beta-adrenergic receptor blocking drug propranolol during the study, which relieved some of these symptoms, and probably reduced the incidence of withdrawal reactions.

If it is granted that a fair proportion of chronic benzodiazepine takers are to some extent dependent on their drug, what should doctors now do? If patients are dependent but otherwise well is it right to deprive them of their drugs? I find it best to discuss openly with patients the possibility of dependence in language that does not arouse alarm, in particular stressing that it is much less serious than opiate and barbiturate dependence. If they then wish to stop their medication it is best done gradually, in some cases over many months. If patients choose not to stop then prescription may continue but only on the basis that it is temporary and that I will be nagging at them to stop again before long. It is often helpful to ask patients to adopt a flexible dosage regimen so that the drugs are only taken in response to symptoms up to an agreed maximum. This usually leads to a reduction in consumption and a greater willingness to try withdrawal.

Some patients, and it may be as high as 30 per cent in psychiatric practice, are unable to stop benzodiazepines because of increasing anxiety symptoms which last long beyond the withdrawal phase. Once this is demonstrated it is reasonable to represcribe the benzodiazepine, and in so doing I reassure myself that the alternatives of handicapping anxiety or recourse to alcohol or similar drugs are a great deal worse. Even in such cases I again consider withdrawal at a later date and introduce new anti-anxiety therapy as necessary.

References

COMMITTEE ON THE REVIEW OF MEDICINES (1980) Systematic review of the benzodiazepines. *British Medical Journal*, *i*, 910–2.

COVI, L., LIPMAN, R. S., PATTISON, J. H., DEROGATIS, L. R. & UHLENLUTH, E. H. (1973) Length of treatment with anxiolytic sedatives and response to their sudden withdrawal. *Acta Psychiatrica Scandinavica*, **49**, 51–64.

HAEFELY, W. E. (1978) Central actions of benzodiazepines: general introduction. *British Journal of Psychiatry*, **133**, 231–8.

HOLLISTER, L. E., MOTZENBECKER, F. P. & DEGAN, R. O. (1961) Withdrawal reaction from chlordiazepoxide ('Librium'). *Psychopharmacologia (Berlin)*, **2**, 63–8.

LADER, M. Benzodiazepine dependence. In *Use and Misuse of Psychotropic Drugs*, (eds. Robin Murray *et al*). London: Gaskell Books, The Royal College of Psychiatrists, (in press).

LASAGNA, L. (1980) The Halcion story: trial by media. *Lancet*, *i*, 815–6.

MARKS, J. (1978) *The Benzodiazepines; Use, Overuse, Misuse, Abuse*. MTP Press: Lancaster.

MÖHLER, H. & OKADA, T. (1977) Benzodiazepine receptors demonstrated in the central nervous system. *Science*, **108**, 849–51.

PEVNICK, J. S., JASINSKI, D. R. & HAERTZEN, C. A. (1978) Abrupt withdrawal from therapeutically administered diazepam. *Archives of General Psychiatry*, **35**, 995–8.

TYRER, P. (1978) Drug treatment of psychiatric patients in general practice. *British Medical Journal*, *ii*, 1008–10.

—— HUGGETT, A. & RUTHERFORD, D. (1980) Benzodiazepine dependence and propranolol. Paper presented at 1st World Congress of Clinical Pharmacology and Therapeutics, London.

WINOKUR, A., RICKELS, K., GREENBLATT, D. J., SNYDER, P. J. & SCHATZ, N. J. (1980) Withdrawal reaction from long term, low dosage, administration of diazepam. *Archives of General Psychiatry*, **37**, 101–5.

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https://doi.org/10.1192/bjp.137.6.576 Published online by Cambridge University Press