REVIEW ARTICLE

Benzodiazepines — a challenge to rational prescribing

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HUMAN response to most things in life has a strong similarity to the swing of a pendulum. Great enthusiasm for the new drug, car, washing-machine is followed by an excess of caution about its faults or dangers. Eventually a proper balance between cost and benefit is achieved but often after much time has elapsed. The benzodiazepines are currently receiving much adverse comment on the radio and in the press, both lay and medical. As general practitioners are the greatest prescribers of these drugs, how are we to respond to these comments? Are we now in a position to define the place of benzodiazepines in the medical armamentarium?

Mankind has always sought relief from the stresses and strains of life: opium, gin, tobacco and religion have been used by the masses. The benzodiazepines were introduced for this purpose nearly 30 years ago and, at a time when accidental and deliberate poisoning from barbiturate overdose was at an all-time peak, were greatly welcomed since in contrast to the other drugs used for stress and insomnia it is almost impossible to kill yourself with them. For this reason alone they deserve to have eclipsed barbiturates, meprobamate and chloral. Self-poisoning from these drugs has almost disappeared though, of course, those determined on self-destruction will find other means.

The benzodiazepines have attained phenomenal popularity. Several thousand have been synthesized and 33 marketed. Other alternatives to the barbiturates (thalidomide, glutethimide and Mandrax), which arrived during the last 30 years, have been associated with much greater problems than those with the benzodiazepines.

The prescribing of all tranquillizers increased by 70 per cent between 1965 and 1970. Almost all of this was due to the advent of chlordiazepoxide and diazepam which more than replaced the decline in barbiturate prescribing. Parish[1] showed that, in 1969, more than 16 per cent of women and 8 per cent of men were prescribed a non-barbiturate hypnotic or sedative. In 1978 another study[2] estimated that 20 per cent of women and 10 per cent of men had taken a tranquillizer in that year and that 600,000 people, 2 per cent of the population, took a tranquillizer every day or night. A MORI poll in 1983 suggested that 23 per cent of adults had taken a benzodiazepine at some time and that 35 per cent of those had taken one regularly for more than four months.

The trend in this prescribing is now down. In 1977, when prescribing of diazepam reached a peak, 4 per cent of all prescriptions were for this drug.[3] It is believed that there has been a 20 per cent reduction in the prescription of tranquillizers in the UK since 1979. During the first six months of 1983, there were 15 per cent fewer prescriptions of tranquillizers and sedatives compared with the same period in 1982.[4] The trend seems to be occurring in other countries and Hollister[5] estimated that consumption of hypnotics had declined by 30 per cent in the USA over the past several years.

There has been, in most countries, a trend towards shorter usage of benzodiazepines, though in this respect the UK does not compare well with some other countries.[6] In Sweden 77 per cent of users in one year had taken a shorter course than one month and only 6 per cent a longer course than one year. In Britain 27 per cent had been on the drug more or less continually for a year or more. A recent study[7] in California, traditionally regarded as the home of 'pill-swallowers' showed that, of a random sample of 3,161 people, 11 per cent had used a tranquillizer in the past year and only 1.5 per cent took a regular dosage. These regular takers tended to be older women with severe anxiety and multiple health problems. Surprisingly, most of the takers took the drug on an occasional basis, never for more than one or two days at a time.

All benzodiazepines have the same pharmacological effects — anxiolytic, anticonvulsant and muscle relaxant. They differ in their mode and rate of hepatic elimination and this gives rise to two relevant differences. Firstly it affects their duration of effect and this is the main factor upon which choice is made. Some, including ketazolam, medazepam and prazepam, are metabolized to active

metabolites whose duration of effect is longer than that of the parent drug. It is this group that seem to be the most likely to have their elimination lengthened in elderly people. Secondly some, including triazolam and midazolam, are oxidized and this group may have their clearance inhibited by alcohol, cimetidine and the oral contraceptives. Other drug interactions include the possibility of increased blood levels of phenytoin and delayed absorption of chlorazepate at an alkaline pH, that is, administered with antacids. All in all, benzodiazepines are safe with other drugs and work similarly. This is probably due to the fact that they have a common site of action — the benzodiazepine receptors in the brain.[8] The discovery of these receptors is remarkable in that it is an example of finding specific receptors in the brain for a compound that does not seem to occur in nature and they have now been found to be fairly widely distributed throughout the nervous system. This has led to the fascinating hypothesis that there must be a similar endogenously occurring substance which affects 'anxiety levels' in people. That and the relationship between these receptors and those for gamma-aminobutyric acid (GABA) — the benzodiazepines indirectly potentiate synaptic actions of this inhibitory neurotransmitter — suggest an exciting field of research into our understanding of neurosis and psychosis.

In each of the precursors to the benzodiazepines, bromides, barbiturates and meprobamate, there has been a pattern in some patients of escalation of dosage, drug-seeking behaviour and withdrawal syndrome. Withdrawal symptoms were first reported with diazepam as long ago as 1961[9] and now there is increasing anxiety about drug dependence. How great a problem is this? Marks[10] in 1978 found only 151 certain cases worldwide in the multiple drug and alcohol abuse group and perhaps another less certain 250 cases. On the other hand, a recent letter[11] in the *British Medical Journal* has described the problem as a matter 'of grave national and international concern' and concluded that benzodiazepines no longer have a therapeutic role. The answer to the question is difficult to establish. There is now unequivocal evidence[12–15] of the existence of a withdrawal syndrome. It is almost certainly under-recognized and under-reported. Tyler[16] has pointed out that part of the problem is that symptoms of withdrawal may be confused with the original symptoms for which the drug was first prescribed, leading the physician to restart treatment. More than half of all long-term users can stop the drug abruptly without any problems occurring.[13] Most patients on long-term therapy remain on a steady dose and even those who increase the dose decrease it when the anxiety-provoking situation has been resolved.[17] There is very little evidence of long-term damage occurring to takers and, as has been pointed out, alternative drugs are invariably more dangerous. Furthermore, some chronically anxious patients have done well on a steady small dose for many years, but whether because of the drug or in spite of it is unknown.

What are withdrawal symptoms? They cover a spectrum similar to that produced by alcohol withdrawal. Mild symptoms include anxiety, apprehension, insomnia, giddiness, headache, loss of appetite, intolerance to noise and bright lights and muscle pain. More severe symptoms include nausea and vomiting, vertigo, cramps, sweating, palpitation, panic, hallucination, delusion and occasionally paranoid psychoses. One death has been reported.[18]

Can we predict who is at risk? There is an increase with duration of usage, and four to six months of continuous use seems to be the threshold above which it occurs. After a year perhaps 20 per cent of takers will have some symptoms upon withdrawal. Tyler[19] has suggested that the best predictor of susceptibility to drug dependence is a passive or dependent personality. As there is a higher incidence of these traits among persons with anxiety and insomnia we may actually be treating a group of people who are particularly at risk to withdrawal problems. True addiction is rare and is probably limited to 'addiction prone' individuals who ingest very large quantities.[20] There is some evidence that, paradoxically, those benzodiazepines with a short half-life are more likely to be associated with dependence than those with a long half-life, though this may just be due to the fact that withdrawal symptoms come on more quickly.

Can we handle withdrawal to avoid symptoms? Unfortunately, however smooth and gently withdrawal takes place symptoms may develop but with the longer acting drugs this may not occur for several days. It might be helpful to substitute a long-acting drug such as diazepam, chlordiazepoxide, flurazepam, chlorazepate or nitrazepam if withdrawal is to be attempted. Withdrawal should take place in very small increments over at least eight weeks and the dosage increased slightly for two or three weeks if symptoms occur before reduction is restarted. The addition of propranolol, 10–40 mg every six hours has been shown[21,22] to help alleviate somatic symptoms and sedative tricyclic antidepressants may be helpful if depression is a prominent feature but the phenothiazines may make matters worse.

The benzodiazepines are an important, useful and remarkably safe group of drugs if properly prescribed but there is now good reason to be much more circumspect in their use.

They have an undoubted use in the short-term treatment of anxiety but they are not the first line of management. Listening and explanation will suffice in many cases and recourse to other non-drug forms of help, counselling, relaxation, hypnosis and psychotherapy, will help in others. This may be due to their placebo effect, and good evidence to the contrary does not exist, but these forms of help are surely safer than long-term benzodiazepine medication. Unfortunately, they are not available or suitable for all patients. A careful explanation of the disadvantages of drug tolerance and the risk of drug dependence should precede the prescription, but this is not always easy to do when faced with an anxious patient. Intermittent taking of the drug is better than continuous

taking for the majority of patients whose symptoms can be controlled this way, and in any case regular prescribing for more than a few weeks should only be carried out under exceptional circumstances. Short-acting drugs, such as temazepam, triazolam and lormetazepam, are first choice for the treatment of insomnia because they produce less hangover. Patients should be told that there is no place for continuous long-term medication. Tolerance develops so quickly that it deprives them of useful help in the times of need.

Explanation to patients that they almost certainly sleep more than they think and that insomnia does little harm while worry about insomnia does much harm, together with simple advice about using hot drinks, reading or the radio is often sufficient.

For patients who are already on continuous medication reduction of dose or withdrawal should be considered. Patients who are obtaining repeat prescriptions should be recalled for interview. Careful and sympathetic explanation of the potential problem is necessary and other methods of support may be recruited. Intermittent dosage of either anxiolytic or hypnotic may be a useful first step in reduction. Some studies[23,24] have shown evidence of the effectiveness of other trained people in helping patients, and Skinner's study[24] showed that one year later two-thirds of patients had stopped taking anxiolytics and two-thirds reported an elimination of anxiety symptoms.

We need more such studies. In the meanwhile we have to learn to use the drug more carefully.

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Infant and perinatal mortality rates

Examination of the infant and perinatal mortality rates for 1982 by social class reveals that the traditional 'social class gradient' — the steady increase in rates between classes I and V — was not in evidence in any birthweight group for perinatal deaths and in infant deaths was only evident for those between 3,000 and 3,999g. For several birthweight categories it was not even true that lowest and highest rates were in classes I and V respectively. Indeed, as an example, for perinatal deaths to babies born weighing less than 1,500g, the social class I rate was 700.0 per 1,000 total births while the class V rate was 485.2.

Source: Office of Population Censuses and Surveys. Infant and perinatal mortality 1982: birthweight. *OPCS Monitor* 1984; DH3 84/7.

Computer systems for GPs

The Department of Health and Social Security has announced that it will be evaluating 20 different computer systems for doctors' surgeries. The Parliamentary Secretary for Health said: 'The new study, to be completed within a year, will not recommend a 'best buy', nor endorse any particular system but will give objective information for GPs about currently available microcomputer systems. It will look at the technical performance of the system and how the GP's staff use it. The report will give descriptions of hardware, software, an assessment of performance and accuracy and clarity of reference documentation. The study team will visit a practice using each system and questionnaires will be sent to other practices.'

Source: Department of Health and Social Security. Press Release 84/299.