PSYCHOTROPIC DRUGS 3

Benzodiazepine withdrawal in general practice

DAVID R. HOPKINS, MB, MRCP, KULWANT B. S. SETHI, MA, MRCGP, JOHN C. MUCKLOW, MD, MRCP

SUMMARY. A study of benzodiazepine prescribing in a single-handed general practice was carried out over a period of three months. It seemed that the existing pattern of prescribing was indiscriminate and ineffective, and that repeat prescriptions were poorly controlled. A programme of controlled withdrawal was instituted for patients whose consumption of benzodiazepines was felt to be no longer appropriate. Of 103 patients identified who had been taking benzodiazepines for longer than three months, 78 were entered into the programme. On completion, 45 patients (58 per cent) had discontinued benzodiazepines completely, and a further 13 (17 per cent) were taking less than half their original dose. Four patients had failed to reduce consumption at all and two were lost to follow-up. At follow-up between three and five months later, 49 patients (63 per cent) had discontinued benzodiazepines completely and only two had restarted treatment. The median time taken to complete the programme was 3.2 weeks, with 95 per cent of patients completing within six weeks. Withdrawal was generally well tolerated, with a temporary increase in insomnia as the main symptom. Two patients experienced severe symptoms, but both had stopped treatment abruptly.

Introduction

LONG-TERM prescribing of benzodiazepines accounts for a considerable work-load in general practice, and many patients are involved. Balter and colleagues (1974) showed that 8.6 per cent of adults surveyed in the UK had, at some time during the previous year, taken anxiolytics for at least one month continuously, and in 1974 diazepam accounted for 4.3 per cent of all NHS prescriptions (Skegg *et al.*, 1977).

Benzodiazepines can produce psychological and, if given over a prolonged period, physical dependence (Marks, 1978). Their hypnotic effects can decrease or disappear over periods as short as two weeks (Kales *et al.*, 1974). There is little convincing evidence that benzodiazepines are efficacious in the treatment of anxiety after four months' continuous treatment (Committee on the Review of Medicines, 1980), and some patients will then develop a psychological dependence on continual treatment.

For these reasons we felt it was desirable to carry out an audit of benzodiazepine prescribing in general practice, and to try to withdraw treatment. It has already been shown feasible to discontinue or substitute barbiturates in general practice (Wells, 1973), and we felt that a similar exercise could be applied to benzodiazepines.

Aims

1. To prevent or cure psychological dependence in patients taking benzodiazepines over prolonged periods by withdrawal of treatment from those for whom the original indications for treatment had become inappropriate.
2. To reduce the amount of repeat prescribing.
3. To reduce prescribing costs.
4. To develop a more critical and rational use of benzodiazepines.
5. To study the effects of withdrawal on sleep and mood.

Methods

The study was carried out in a single-handed urban practice of approximately 2,800 patients. Those included had all been taking benzodiazepines for at least three months and were identified when they requested a repeat prescription, at consultation or from receptionists. Those with acute physical illness or a history of psychosis were excluded, as were patients under hospital supervision for psychiatric illness.

David R. Hopkins, General Practitioner Trainee, Stoke-on-Trent; Kulwant B. S. Sethi, General Practitioner, Stoke-on-Trent; John C. Mucklow, Consultant Physician, Department of Clinical Pharmacology, City General Hospital, Stoke-on-Trent.

© *Journal of the Royal College of General Practitioners*, 1982, **32**, 758-762.

Table 1. Regimen for withdrawing benzodiazepine tranquillizers.

	Baseline	Stage 1	Stage 2	Stage 3	Stage 4
Nitrazepam	10 mg	7.5 mg	5 mg	2.5 mg	—
	5 mg	2.5 mg	—	—	—
Diazepam	5 mg t.d.s.	5 mg b.d.	5 mg daily	2 mg daily	—
	5 mg b.d.	5 mg daily	2 mg daily	—	—
	5 mg daily	4 mg daily	2 mg daily	—	—
	2 mg t.d.s.	2 mg b.d.	2 mg daily	—	—
Chlordiazepoxide	10 mg t.d.s.	10 mg b.d.	10 mg daily	5 mg daily	—
	10 mg b.d.	10 mg daily	5 mg daily	—	—
	10 mg daily	5 mg daily	—	—	—
Lorazepam	2.5 mg b.d.	2.5 mg daily	1 mg daily	—	—
	2.5 mg daily	1 mg daily	—	—	—
	1 mg daily	0.5 mg daily	—	—	—
Flurazepam	30 mg	15 mg	—	—	—
Temazepam	20 mg	10 mg	—	—	—

At the first interview (conducted by D.R.H. or K.B.S.S. using a questionnaire) enquiry was made about treatment, the reasons for starting it and continuing it, and sleep pattern. When and who (general practitioner or consultant) started treatment were determined from the records or, if these were not available, from patients' recollection.

Mood was assessed using a series of visual analogue scales rating subjective feelings (Bond and Lader, 1974). The dangers of dependence on long-term treatment and the benefits of withdrawal were then explained. Patients satisfying selection criteria were invited to participate, and all those doing so gave their informed consent.

Because benzodiazepines can be potentiated by alcohol and other cerebral depressants, patients were asked about their alcohol intake. No excessive drinkers (more than six pints of beer or 12 measures of spirits per week) were identified.

Patients were instructed to reduce the dosage and frequency of medication according to a predetermined regimen (Table 1) in order to minimize withdrawal symptoms such as poor appetite, nausea, vomiting, trembling, faintness, insomnia and lack of energy (Covi *et al.*, 1973). In patients taking medication more than once daily, withdrawal was planned to take four weeks in the first instance. Where medication was taken less frequently or only in response to emotional upset, treatment was stopped abruptly. A check was made on the rate of consumption of tablets by reference to the number of repeat prescriptions obtained recently, and in most cases this accorded with patients' estimates.

Interviews were repeated weekly whenever possible during withdrawal, either at the surgery or at home. A special surgery was arranged for the first few weeks of the study to cope with the additional work. The questions about sleep pattern and mood were repeated at each visit, and any symptoms associated with withdrawal were recorded. We recognized that further supplies of tablets might be obtained from hoarded stocks or from relatives and friends, but that this was impossible to prevent. Interviews were continued until either complete withdrawal for one week had been accomplished or the patient was removed from the study. Indications for removal were intercurrent mental or physical illness, major life events and inability or unwillingness to continue withdrawal.

Patients complaining of increased anxiety or insomnia were encouraged to continue withdrawal, but it proved necessary in some cases to maintain a constant dosage until symptoms were relieved, after which the withdrawal regimen continued. Patients removed from the study continued treatment with the lowest effective dosage. In many cases patients did not adhere closely to the regimen, although this was still used as a guideline. An extra tablet to cope with a stressful situation or the precipitate withdrawal of treatment were amongst the variations noted.

It was recognized that patients might restart treatment after complete withdrawal and all patients were therefore interviewed again (by K.B.S.S.) between three and five months after the end of the study. Patients were questioned about their consumption of benzodiazepines, if any, since the end of the study, and were asked whether they had obtained further supplies from relatives or hoarded stocks. The presence or absence of withdrawal symptoms was again noted, and patients were asked whether their sleep was better or worse than before the study.

Differences between groups of patients were assessed for statistical significance using the chi-square test with Yates's correction where appropriate.

Results

One hundred and three patients (3.7 per cent of the practice) were identified who had been receiving benzodiazepines for longer than three months. Of all patients over 30 years old, 3.7 per cent of men and 8.2 per cent of women were receiving treatment.

Twenty-five patients were excluded for various reasons (Table 2). Of the 78 patients entered into the study, 56 were women. Ages ranged from 30 to 86 years (mean 60.0). Table 3 shows the preparations prescribed for these patients. The dose and frequency varied widely, and 18 patients took the medication as required rather than regularly. The duration of treatment prior to the study is shown in Table 4. Almost two thirds of patients had taken benzodiazepines for more than three years. Treatment had been started by a general practitioner in 79 per cent of cases; the reasons for starting are shown in Table 5. In many instances the reason was no longer operative, but 46 patients (59 per cent) had required continued treatment because of recurrent anxiety, and 32 (41 per cent) because of recurrent insomnia. Many

Table 2. Reasons for exclusion.

Unwilling to reduce dosage	6
Severe anxiety	7
Senile dementia	2
Severe psychiatric illness	3*
Severe physical illness	3
Not contacted after two visits	2
Under hospital supervision	1
Recent bereavement	1
Total	25

*One each of schizophrenia, manic depressive psychosis and endogenous depression.

Table 3. Benzodiazepines prescribed.

Preparation	Daily dosage range (mg)	Number
Diazepam	2–15	37
Nitrazepam	5–10	26
Chlordiazepoxide	10–30	8
Lorazepam	1–5	3
Flurazepam	30	1
Temazepam	20	1
Diazepam and nitrazepam	—	2
Total		78

patients were receiving other prescribed drugs, analgesics and antihypertensive agents most commonly.

Forty-six patients (59 per cent) were able to stop taking benzodiazepines completely. Another 26 (33 per cent) succeeded in reducing their intake and in 13 of these the final dosage was less than half the original. Two patients were lost to follow-up after the first interview but have requested no further repeat prescriptions. Only four patients proved unable to achieve any dose reduction.

At follow-up between three and five months later, 49 patients (63 per cent) had stopped treatment completely, and 15 (19 per cent) had reduced their intake. Four patients (5 per cent) had not changed their intake and a further eight (10 per cent) were lost to follow-up. Of these, two had left the practice and the remaining six failed to attend follow-up interviews. Only two patients had started treatment after complete withdrawal.

The time taken to reach the final dosage is shown in the Figure. Ninety-five per cent of patients had either withdrawn completely or reached their final dosage within six weeks. The median time taken was 3.2 weeks.

When patients who were successful in complete withdrawal were compared with those remaining on treatment at the end of the study, it was found that the likelihood of withdrawal was related to duration of previous treatment (Table 6), successful withdrawal becoming less likely as duration increased ($\chi^2 = 7.27$ with two degrees of freedom, $p < 0.05$). There was no relationship between successful withdrawal and either age, sex, who had started treatment (consultant or general practitioner) or the reason for continuing treatment.

The effect of withdrawal on sleep pattern was determined by the main indication for treatment. Patients tended not to complain of disturbed sleep when treatment was taken as an anxiolytic, but insomnia was noticed more readily when it was hypnotics that were being withdrawn. Subjective estimation of duration and quality of sleep is notoriously unreliable, but in general patients noted either difficulty falling asleep or frequent waking. Early waking was rare. In most cases sleep disturbance was transient, lasting up to two weeks. Patients usually persisted with withdrawal after encouragement, but 13 patients were unable to tolerate this disturbance and withdrawal was terminated. In these patients dosage was either increased to the original level or kept at the reduced level, depending on the severity of the disturbance. Withdrawal appeared to have little effect on waking, and indeed several patients noted increased alertness and a sense of well-being on waking once treatment had been withdrawn.

Many patients reported agitation or tension during withdrawal which usually settled within one or two weeks and which often settled with reassurance; another 13 patients were unable to tolerate these symptoms and withdrawal was terminated.

The results of the visual analogue scales were analysed by allocating a score from 0 to 100 for each rating according to its position on the 10 cm line, a score of 100 corresponding to maximum mental sedation, physical sedation or tranquillization. Fewer than half of all patients had a fully completed analogue scale at each interview. Many had difficulty in comprehending what

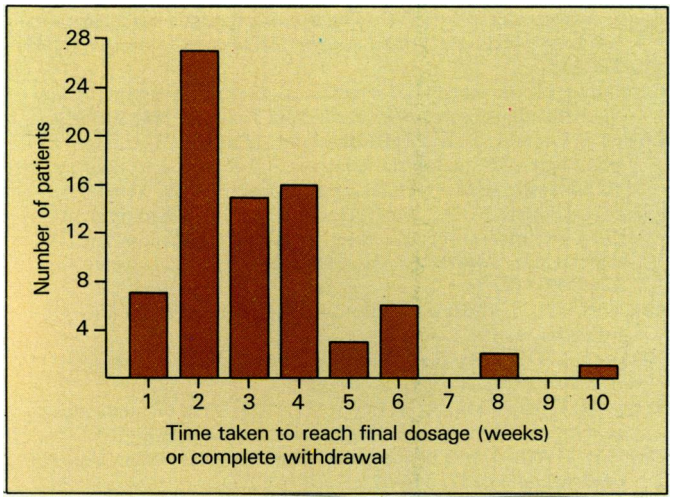
Table 4. Duration of treatment prior to study.

	Months				
Months	3–12	13–36	37–60	61–120	>120
Patients	8	22	21	17	10
Percentage ($n=78$)	*10*	*28*	*27*	*22*	*13*

Table 5. Reasons for starting treatment

	Patients	Percentage ($n=78$)
Anxiety	33	*42*
Insomnia	17	*22*
Bereavement*	20	*26*
Hospital admission	7	*9*
Unknown	1	*1*
Total	78	*100*

*Leading to anxiety (14) or to insomnia (6).



Time taken to reach final dosage or complete withdrawal (n=76).

was required, and any recordings from these subjects would have been meaningless.

No statistically significant difference was found between ratings of symptoms before and after the study, and no difference was found in the ratings between those who were successful in withdrawal and those who continued treatment after the study. Further statistical analysis of results was thought to be inappropriate because of the lack of a control group and the small numbers studied.

It was difficult to distinguish between true withdrawal effects and those attributable to anxiety or psychological dependence. Most symptoms (Table 7) were subjective, their severity was difficult to quantify, and there were far fewer recorded at follow-up. In most cases symptoms were transient and mild, and both the patients who experienced severe reactions had discontinued treatment abruptly.

Discussion

The idea for this study arose when the practice took on a trainee (D.R.H.) for the first time. It was noted that prescribing of benzodiazepines appeared excessive, and patients were often able to obtain repeat prescriptions without a consultation. Most patients were anxious to stop treatment after the risks of going on had been explained, and were co-operative and ready to admit lapses in withdrawal.

We now realize that the indications for initiation of treatment were, in some instances, inappropriate. This criticism applied particularly to bereavement, and the use of psychotropic drugs to suppress a natural grief reaction must be questioned. Patients admitted to hospital may require hypnotics and/or anxiolytics, but several of our patients had been given further supplies following discharge.

Table 6. Results of withdrawal according to duration of treatment.

	Duration (months)				
	3–12	13–36	37–60	61–120	>120
Complete withdrawal ($n=46$)	5	17	13	7	4
Partial or no withdrawal ($n=30$)	2	5	7	10	6

Table 7. Symptoms associated with withdrawal.

	After withdrawal ($n=76$)		At follow-up ($n=68$)	
	Patients	Percentage	Patients	Percentage
Insomnia	41	*54*	4	*6*
Trembling	28	*37*	4	*6*
Lack of energy	28	*37*	2	*3*
Poor appetite	25	*32*	0	—
Nausea	20	*26*	0	—
Weakness	18	*24*	2	*3*
Faintness	15	*20*	0	—
Numbness	8	*11*	0	—
Vomiting	3	*4*	0	—
Palpitations	2	*3*	1	*1*

We were encouraged that 57 per cent of patients were able to discontinue treatment completely, and this rose to 63 per cent at follow-up several months later. These results suggest that withdrawal is feasible in the majority of patients on long-term treatment. The importance of this study has been highlighted by the recommendation of the Committee on the Review of Medicines (1980) that benzodiazepine therapy be limited to short-term use.

Although our regimen had allowed four weeks for withdrawal of medication, most patients required less time than this. We preferred to err on the side of caution rather than to risk withdrawal reactions. The fact that the only two severe reactions occurred when treatment was stopped abruptly suggests that advice to withdraw treatment slowly is sound (Tyrer, 1980). It was found more difficult to withdraw treatment in patients who had been taking it for many years. Our results suggest that this difficulty is not due solely to advancing age, as there was no relation between age and success in withdrawal.

The effect of withdrawal on sleep pattern confirms that patients may suffer a period of rebound insomnia (Kales *et al.*, 1974), lasting one or two weeks and being followed by reversion to a normal sleep pattern. Further comments on sleep pattern would be inappropriate, since the measurements of quality and duration of sleep were subjective. Our attempts to assess changes in mood pattern failed to reach any firm conclusions. The small

number of patients studied and the lack of a control group made detailed statistical analysis of ratings invalid. Symptoms associated with withdrawal were as difficult to assess as changes in sleep or mood pattern. They may be due to either true physical dependence, psychological dependence or unmasking of a continuing anxiety state by withdrawal. These may be impossible to distinguish, although the occurrence of headache, dysphoria or other symptoms unrelated to the original anxiety state might suggest physical dependence (*Lancet,* 1979). The two patients who withdrew treatment abruptly both experienced such symptoms. Others experienced milder symptoms which were probably due to anxiety or psychological dependence.

We feel that a programme of withdrawal similar to this is practicable for any general practitioner to undertake. The time spent will be repaid in the long term by reduction in the work-load of repeat prescriptions. For most patients 10 to 15 minutes would be needed for an initial interview to explain that long-term treatment is risky and ineffective, to achieve the patient's co-operation and to suggest a programme of withdrawal. Subsequent interviews should be at weekly intervals and need last no longer than 5 to 10 minutes to enquire about withdrawal symptoms, to give encouragement and to suggest a new dosage for the following week. Most patients should need no more than six weeks to reach their final dosage. The severity of withdrawal symptoms varies considerably and Tyrer and colleagues (1981) have suggested that this variation may relate to the variable rate at which benzodiazepines and their active metabolites are eliminated. They found propranolol superior to placebo in the alleviation of symptoms during the withdrawal.

Conclusion

Our patients have benefited in several ways from the study. The dangers and cost of unnecessary and ineffective treatment have been eliminated, and other, more effective treatment can be explored (for example simple psychotherapy or relaxation therapy for anxiety states). The study teaches patients that long-term therapy cannot cure long-standing social or emotional problems. The problems we have outlined need never arise if a time limit is placed on the duration of therapy. We continue to use benzodiazepines for acute episodes of insomnia or anxiety as before, but it is explained that no further supplies will be given. We feel that this study is a good example of medical audit, the impetus coming from ourselves. As a result, the prescribing habits of the practice have altered, and improved standards of patient care have resulted.

References

Balter, M. B., Levine, J. & Manheimer, D. I. (1974). Cross-national study of the extent of anti-anxiety/sedative drug use. *New England Journal of Medicine,* **290**, 769-774.

Bond, A. & Lader, M. (1974). The use of analogue scales in rating subjective feelings. *British Journal of Medical Psychology,* **47**, 211-218.

Committee on the Review of Medicines (1980). Systematic review of the benzodiazepines. *British Medical Journal,* **280**, 910-912.

Covi, L., Lipman, R. S., Pattison, J. H. *et al.* (1973). Length of treatment with anxiolytic sedatives and response to their sudden withdrawal. *Acta Psychiatrica Scandinavica,* **49**, 51-64.

Kales, A., Bixler, E. O., Tan, T-L. *et al.* (1974). Chronic hypnotic-drug use: ineffectiveness, drug-withdrawal insomnia and dependence. *Journal of the American Medical Association,* **227**, 513-517.

Lancet (1979). Withdrawal symptoms with benzodiazepines. Editorial. **1**, 196.

Marks, J. (1978). *The Benzodiazepines; Use, Overuse, Misuse, Abuse.* Lancaster: M.T.P. Press.

Skegg, D. C. G., Doll, R. & Perry, J. (1977). Use of medicines in general practice. *British Medical Journal,* **1**, 1561-1563.

Tyrer, P. (1980). Dependence on benzodiazepines. *British Journal of Psychiatry,* **137**, 576-577.

Tyrer, P., Rutherford, D. & Huggett, T. (1981). Benzodiazepine withdrawal symptoms and propranolol. *Lancet,* **1**, 520-522.

Wells, F. O. (1973). Prescribing barbiturates: drug substitution in general practice. *Journal of the Royal College of General Practitioners,* **23**, 164-167.

Acknowledgements

We are grateful to Dr Douglas Garvie for his helpful criticism, and to Mrs Maureen Lowe, who typed the manuscript.

Address for reprints

Dr D. R. Hopkins, 50 Victoria Road, Worthing BN11 1XE.

Heart failure in outpatients

Using a randomized double-blind crossover protocol, we compared the effects of oral digoxin and placebo on the clinical courses of 25 outpatients without atrial fibrillation. According to a clinicoradiographic scoring system, the severity of heart failure was reduced by digoxin in 14 patients. The other 11 patients had no detectable improvement from digoxin. Patients who responded to digoxin had more chronic and more severe heart failure, greater left ventricular dilation and ejection-fraction depression and a third heart sound. Multivariate analysis showed that the third heart sound was the strongest correlate of the response to digoxin ($p<0.001$). These data suggest that long-term digoxin therapy is clinically beneficial in patients with heart failure unaccompanied by atrial fibrillation, whose failure persists despite diuretic treatment and who have a third heart sound.

Source: Lee, D. C-S., Johnson, R. A. & Bingham, J. B. (1982). Heart failure in outpatients. A randomized trial of digoxin versus placebo. *New England Journal of Medicine,* **306**, 699-705.