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# Comparative Assessment of Efficacy and Withdrawal Symptoms After 6 and 12 Weeks' Treatment with Diazepam or Buspirone

SIOBHAN M. MURPHY, ROBERT OWEN and PETER TYRER

Fifty-one out-patients presenting with generalised anxiety disorder were included in a double-blind trial, and treated with either buspirone (a new non-benzodiazepine antianxiety drug) or diazepam over 6 or 12 weeks, after which they were abruptly withdrawn and continued on placebo to 14 weeks. Ratings of anxiety and other symptoms were administered fortnightly and additional withdrawal symptoms noted. Forty patients completed the study; 8 of the 11 drop-outs were taking buspirone. Both drugs reduced anxiety, diazepam more rapidly, but with greater withdrawal symptoms, particularly after 6 weeks. Regular treatment with diazepam for 6 weeks leads to a significant risk of pharmacological dependence that is not present with buspirone.

There is now abundant evidence that benzodiazepines are prone to lead to pharmacological dependence and that care should be taken in their prescription for anxiety and insomnia. Dependency is shown mainly in the form of withdrawal symptoms, which include increased anxiety, panic and autonomic symptoms, perceptual distortion, depersonalisation, hypersensitivity to all sensory stimuli, dysphoria and depression, and, more rarely, paranoid symptoms, hallucinations, and epileptic seizures (Rifkin *et al*, 1976; Pevnick *et al*, 1978; Winokur *et al*, 1980; Petursson & Lader, 1981; Tyrer *et al*, 1981, 1983; Busto *et al*, 1986). Because the risk of pharmacological dependence with tranquillisers is great, any new antianxiety compounds must be assumed to carry the risk of dependence until proved otherwise. Buspirone is a new compound with good evidence of efficacy in treating anxiety (Feighner *et al*, 1982; Rickels *et al*, 1982; Schuckit, 1984; Rickels *et al*, 1988), which has recently been introduced into the UK. Structurally it bears no obvious resemblance to other anxiolytics, and is unlike benzodiazepines in that it neither inhibits nor stimulates 3H-benzodiazepine binding *in vitro* receptor systems, does not facilitate gamma aminobutyric acid (GABA) transmission, yet has effects on both serotonergic (5HT) and dopamine receptors. It is a 5HT-1A agonist (Peroutka, 1985), and it is possible that this action is related to its effects on anxiety (Vandermaelen *et al*, 1986).

If buspirone is to be an effective alternative to the benzodiazepines, it needs to have both proven efficacy and little or no risk of dependence. In a 14-week trial, active drug was taken for at least six weeks in order to test for evidence of efficacy, followed by withdrawal under double-blind conditions. Diazepam was used as a comparison drug, to test whether dependence was a problem with benzodiazepines after short-term treatment, and to compare pre-treatment with withdrawal data. There is considerable overlap between benzodiazepine withdrawal symptoms and those of normal anxiety (Rodrigo & Williams, 1986), and any improvement in the definition of these withdrawal symptoms would be helpful.

## Method

### Patients

Out-patients seen at general practice psychiatric clinics in Nottingham between 1981 and 1984 were included in the study if they (a) satisfied DSM-III criteria for generalised anxiety disorder (American Psychiatric Association, 1980), (b) had taken no psychotropic drugs in the previous three weeks, and (c) gave informed consent.

### Design

A parallel group design was used, in which patients were randomly assigned to a flexible dose regime of one to four capsules a day of buspirone (5 mg) or diazepam (5 mg) using a double-blind procedure. Half the patients took active drug for six weeks and then switched abruptly to placebo capsules of identical appearance for the remaining eight weeks of the study, while the other half received active medication for 12 weeks before switching to placebo for two weeks. Capsules were returned at each assessment and the dosage taken calculated. Patients who dropped out of the study were monitored by the Pharmacy Department at Mapperley Hospital, Nottingham, and constrained randomised allocation was used towards the end of the study to ensure

TABLE I
*Main demographic data*

| *Groups* | *No.* | *Females* | *Males* | *Mean age: years* | *Age range: years* | *Mean duration of symptoms: months* | *Duration of symptoms log x + 1 x = no. weeks* | *Previous benzo-diazepine treatment* | *Previous psychiatric contact* |
|---|---|---|---|---|---|---|---|---|---|
| Diazepam, late withdrawal | 10 | 8 | 2 | 37.5 | 17–61 | 222 | 3.67 | 50% | 40% |
| Diazepam, early withdrawal | 10 | 5 | 5 | 37.6 | 21–55 | 87 | 3.46 | 50% | 40% |
| Buspirone, late withdrawal | 10 | 7 | 3 | 34.7 | 25–54 | 139 | 3.76 | 80% | 50% |
| Buspirone, early withdrawal | 10 | 7 | 3 | 33.3 | 20–51 | 91 | 3.43 | 50% | 30% |
| Drop-outs | 11 | 8 | 3 | 35.6 | 19–60 | 64 | 3.65 | 55% | 36% |

equal numbers in each of the four groups: diazepam, early withdrawal (DEW); diazepam, late withdrawal (DLW); buspirone, early withdrawal (BEW); and buspirone, late withdrawal (BLW).

### Assessments

Psychiatric symptoms were rated on entry to the study and at two-week intervals for the 14 weeks using the Comprehensive Psychopathological Rating Scale (CPRS) (Åsberg *et al*, 1978), together with an anxiety subscale, the Brief Scale for Anxiety (BSA) (Tyrer *et al*, 1984), derived from the CPRS. Additional questions were asked to cover more unusual symptoms, such as perceptual distortion and sensory hypersensitivity, which can be common in withdrawal from benzodiazepines (Petursson & Lader, 1981; Tyrer *et al*, 1981). All three authors acted as assessors.

## Results

Fifty-one patients entered the study, but 11 dropped out. Using the constrained randomised procedure, the remaining 40 patients included ten in each of the four treatment groups. Demographic data for each group are shown in Table I.

The BLW group had a higher initial CPRS score than the other three groups, but the distribution of BSA scores was similar. The apparent difference between the mean duration of symptoms in the DLW group reflects an excessively long duration of symptoms for two patients only.

### Drop-outs

Of the eleven drop-outs, three were taking diazepam and eight took buspirone. All the diazepam drop-outs took place in the first two weeks of treatment. Four of the drop-outs on buspirone left the study during the first four weeks. One patient dropped out of the BEW group three weeks after the change to placebo, and the remaining three were all in the BLW group, with patients dropping out of active treatment after 4, 6 and 12 weeks. The reasons for drop-out included headaches, nausea, and lack of efficacy (diazepam), and depersonalisation, nausea, and chest pain with admission to a general hospital (buspirone). There were no apparent demographic differences between the patients who dropped out and those who completed treatment. Analysis of individual symptoms showed no consistent differences. The patients who dropped out on buspirone did not show an excess of dysphoric symptoms, although three of them developed suicidal thoughts in the second week, which had not been present at baseline. In those completing the study, this symptom occurred in six patients, half of whom were taking diazepam.

### Dosage

The mean dosage taken at each phase of the study showed no significant differences between the groups at any stage. Dosage varied between 1.5 and 2.3 capsules daily (7.5–11.5 mg of diazepam or buspirone).

### Analysis of data

To reduce the exclusion bias that might result from analysis of only those patients with complete information, the initial analysis of variance (ANOVA) was applied to the CPRS and BSA scores of the 44 patients with the most complete data. Of the seven patients excluded, five (three allocated to diazepam and two to buspirone) were lost after the initial assessment, and two (both allocated to buspirone) after the second visit. Of the 44 patients included, 40 provided complete data. The remaining four had data missing

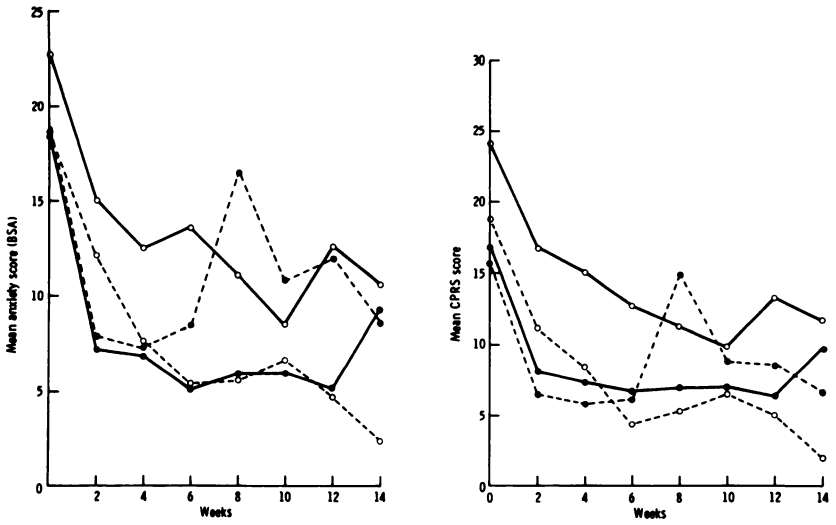


FIG. 1 Mean scores on the BSA and CPRS following early withdrawal (EW) at 6 weeks and late withdrawal (LW) at 12 weeks: diazepam (LW) (●–●) $n = 10$; diazepam (EW) (●---●) $n = 10$; buspirone (LW) (○–○) $n = 12$; buspirone (EW) (○---○) $n = 12$.

for a total of 14 assessments, but it was felt important to analyse their scores as they might have dropped out because of significant withdrawal symptoms. Multivariate repeated-measures ANOVA was carried out on the data at the MRC Biostatistics Unit, Cambridge. Examination of individual withdrawal symptoms was also examined using proportional odds models (Cox, 1970) to determine the significance of any new symptoms arising during the withdrawal period (further information available from authors on request).

### Efficacy

The mean scores of CPRS and BSA ratings in each of the four drug groups are shown in Fig. 1. In the first six weeks, all patients were taking either buspirone or diazepam, and so data from the early and late withdrawal groups were combined. The CPRS and BSA scores showed similar findings, although the changes were most marked on the anxiety scale. Diazepam led to a more rapid improvement in symptoms, and it was not until six weeks of treatment that the patients taking buspirone showed equivalent improvement. There was significantly greater improvement in anxiety (BSA) scores in patients taking diazepam compared with buspirone after two weeks' treatment ($t = 2.2$, d.f. 154, $P < 0.025$).

### Withdrawal symptoms

The most striking finding was the significant increase in symptoms after stopping diazepam after both 6 and 12 weeks (Fig. 1). This was most marked after 6 weeks and highly significant between weeks 6 and 8 ($t = 3.6$, d.f. 225, $P < 0.001$). Between 12 and 14 weeks there was an increase in the diazepam group, which reached significance using a one-tailed but not a two-tailed test ($t = 1.66$, d.f. 225, $P > 0.05$).

Neither group taking buspirone showed a significant increase in symptoms on either the CPRS or BSA scales between weeks 6 and 8 (CPRS $t = 0.6$, d.f. 225, NS) or between weeks 12 and 14 (CPRS $t = 0.25$, d.f. 225, NS). This putative evidence of a significant withdrawal syndrome only occurring with diazepam was confirmed by the analysis of differences between the drugs. At week 8 there was a highly significant difference on all measures between the DEW group and each of the other groups, including BEW (e.g. DEW/BEW: CPRS $t = 3.9$, d.f. 125, $P < 0.005$). There was no significant difference between the late withdrawal groups at week 12.

Unlike some previous investigations (Schweizer *et al*, 1986; Olajide & Lader, 1987) there was no clear association between previous benzodiazepine use, clinical improvement, and withdrawal symptoms. The patients allocated to buspirone who had received previous treatment with benzodiazepines ($n = 13$) had a similar level of improvement after six weeks' treatment (64.9%) as those who had not received benzodiazepines previously (n = 7) (55.6% improvement).

#### Identification of withdrawal syndrome

In previous studies the number of individuals having withdrawal symptoms has been determined by two methods: an increase from pre-withdrawal anxious symptoms of 50% or greater, followed by resolution; and the presence of two or more completely new symptoms after withdrawal (Tyrer *et al*, 1981, 1983). In this study we also have the advantage of having pre-treatment scores, which allowed separation of withdrawal symptoms into two groups: one in which symptoms after withdrawal *exceeded* those before treatment (overshoot group), and those in whom there was a similar pattern of withdrawal but pre-treatment scores were

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TABLE II
*Significant differences in individual symptom scores from the CPRS between treatment groups after early and late withdrawal*

| *CPRS variables* | *Significantly higher frequency in DEW group at week 8* | *Significantly higher frequency in DLW group at week 14* | *Significantly higher frequency in BLW group at week 14* |
|---|---|---|---|
| Sadness | + | | |
| Hostile feelings | | + | |
| Inability to feel | + | + | |
| Worrying over trifles | + | | |
| Indecision | | + | |
| Lassitude | + | | + |
| Fatiguability | + | | |
| Concentration difficulties | + | | |
| Aches and pains | + | | |
| Muscular tension | + | | |
| Derealisation | + | + | |
| Observed agitation | + | | + |

TABLE III
*Proportions of patients experiencing withdrawal syndrome after stopping treatment using different criteria of definition*

| *Definition of withdrawal syndrome* | *Drug* | *No. of patients satisfying definition of withdrawal syndrome* n | % |
|---|---|---|---|
| Temporary increase in symptoms beyond initial scores (overshoot)[1] | Diazepam | 2 | 20 |
| | Buspirone | 1 | 10 |
| Temporary increase in symptoms to less than initial score (rebound)[1] | Diazepam | 3 | 30 |
| | Buspirone | 3 | 30 |
| New symptom emergence (two or more) | Diazepam | 6 | 30 |
| | Buspirone | 1 | 5 |

1. These groups include all patients who had an increase in CPRS or BSA symptoms of 50% or more after withdrawal, followed by return to no more than 25% of pre-withdrawal scores. For these groups only the early withdrawal patients are included.

not exceeded (rebound group). As data before withdrawal included symptoms both before and during treatment, it was also possible to determine which symptoms were truly new ones after withdrawal, rather than rely on patients' testimony retrospectively.

Examination of the 65 variables in the CPRS showed that 12 showed significant differences at the 5% level or greater between the four treatment groups (Table II). All except two of these were found only in the patients treated with diazepam, and most of the symptoms showing differences were those of anxiety that are included in the BSA. However, some of the symptoms (sadness, inability to feel, lassitude, and concentration difficulties) are found more often in depressed patients (Montgomery & Åsberg, 1979), and one symptom, derealisation, is a perceptual disturbance that is typical of benzodiazepine withdrawal.

Additional new symptoms reported during weeks 13 and 14 included hypersensitivity to noise, light, touch, and smell, muscle twitching, muscle pain, vomiting, diarrhoea, perceptual abnormalities independent of depersonalisation and derealisation, headache, and throbbing sensations. These were most common in the diazepam group.

Comparison of the three different methods of identifying withdrawal symptoms are summarised in Table III. The results are very similar to those following withdrawal after longer periods of treatment, with approximately a third of patients taking diazepam showing a withdrawal syndrome (Tyrer *et al*, 1981, 1983).

Definition of withdrawal symptoms as a temporary increase in symptoms occurring within two weeks of withdrawal yielded similar numbers in groups treated with buspirone and diazepam. As the data taken as a whole showed buspirone to cause few or no withdrawal symptoms, this particular definition of a withdrawal syndrome may be defective, whereas that including new symptoms is more in keeping with other results (i.e. 6:1 ratio of diazepam to buspirone in predicting withdrawal symptoms). Nevertheless, the finding of a temporary increase in symptoms in three of the ten patients in the BEW group suggests that buspirone should not be regarded as entirely free from dependence potential.

## Discussion

The results suggest that buspirone is effective in reducing anxiety, but acts more slowly than diazepam; this is in agreement with other studies (Tyrer & Owen, 1984; Jacobson *et al*, 1985). Despite suggestions that buspirone has less sedative, anticonvulsant, and muscle-relaxant properties than benzodiazepines (Riblet *et al*, 1984; Cohn & Wilcox, 1986), our analysis of individual CPRS and BSA scores showed no evidence that relief of anxiety was qualitatively different with buspirone compared with diazepam.

The delayed onset of action with buspirone is likely to pose clinical problems. Despite their dependence potential, benzodiazepines are extremely effective antianxiety drugs in the short term, and patients have come to expect a rapid relief of symptoms after taking any antianxiety drugs. It would therefore seem prudent to warn patients about the possibility of delay in efficacy when buspirone is prescribed.

The results following withdrawal of buspirone after 6 and 12 weeks' treatment suggest that it has

little or no dependence potential after such a period. However, this does not mean that buspirone has no risk of dependence, because the period of treatment was relatively short. However, when taken with other evidence, particularly a study by Rickels *et al* (1985, 1989), in which buspirone was withdrawn after six months' treatment without any adverse effects being observed, it is reasonable to conclude that buspirone has significantly less potential for dependence than the benzodiazepines.

The most surprising aspect of the results was the high incidence of withdrawal phenomena in patients treated with diazepam for this relatively short period, particularly in the early withdrawal group. Patients also showed an increase in symptoms after stopping diazepam at 12 weeks, but as the study ceased after 14 weeks' assessment is is impossible to know what proportion of these patients suffered withdrawal and who suffered relapse. It is nevertheless surprising that withdrawal effects after 12 weeks were apparently less marked than after 6 weeks of treatment with diazepam, and no satisfactory explanation for this can be given. However, after 12 weeks' treatment the major antianxiety effects of diazepam are conferred by its long-acting metabolite, nordiazepam, and the resulting smooth fall in plasma concentration after withdrawal appears to offer some protection against withdrawal symptoms (Tyrer *et al*, 1981). However, this hypothesis cannot be confirmed, as we did not measure diazepam or nordiazepam blood levels.

The withdrawal symptoms after 6 and 12 weeks' treatment are indistinguishable from those of pathological anxiety, although there is a relative excess of symptoms normally found in depression and perceptual disturbances. Although in some patients the symptoms were marked, all patients taking diazepam who continued beyond two weeks' treatment completed the study, despite experiencing marked symptoms of withdrawal in some instances. There was therefore 100% success rate in achieving withdrawal with diazepam. Despite the higher incidence of withdrawal problems with diazepam, 8 of the 11 drop-outs in the study were taking buspirone. All except one of these 8 patients were taking active drug when they dropped out of the study, and none did so while taking placebo. This suggests that buspirone may have some additional effects that hinder treatment compliance. There is some evidence of dysphoria after acute treatment with buspirone (Lader, 1982), and our findings suggest that this may extend into longer-term therapy. The higher incidence of suicidal thoughts of patients taking buspirone and who subsequently dropped out supports this notion.

The results of this study, reinforced by those of others (Fontaine *et al*, 1984; Power *et al*, 1985; Griffith *et al*, 1986) support the general principle that intermittent rather than regular treatment with benzodiazepines is preferable (Tyrer & Murphy, 1987), and that in the treatment of anxiety "benzodiazepines ideally should be prescribed for no more than one month" (Royal College of Psychiatrists, 1988). Once duration of treatment has reached this critical stage, dependence becomes a potential risk and, if withdrawal symptoms are to be avoided, gradual rather than sudden cessation of treatment is preferable.

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*Siobhan M. Murphy, MRCPsych, *formerly Research Fellow and Honorary Senior Registrar, Mapperley Hospital, Nottingham NG3 6AA, now Senior Registrar at St George's Hospital, Blackshaw Road, London SW17*; Robert Owen, MRCPsych, *Consultant Psychiatrist, Pastures Hospital, Mickleover, Derbyshire*; Peter Tyrer, MD, MRCP, FRCPsych, *Mapperley Hospital, Nottingham NG3 6AA, now at St Charles' Hospital, Exmoor Street, London W10 6DZ*

*Correspondence