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Chronic Benzodiazepine Dependence
A Comparative Study of Abrupt Withdrawal under Propranolol Cover Versus Gradual Withdrawal

T. CANTOPHER, S. OLIVIERI, N. CLEAVE and J. GUY EDWARDS

Thirty-one patients dependent on benzodiazepines were randomly assigned to either slow withdrawal (SW) or abrupt withdrawal under propranolol cover (PW). Of 16 patients in the SW group, 11 successfully withdrew from their drugs, while only 4 out of 15 in the PW group did so. Patients in the SW group had only mild withdrawal symptoms, while those in the PW group suffered more severe symptoms, which lasted around four weeks. In all, 81% of the whole group suffered withdrawal symptoms of some kind. Patients in both groups were significantly less anxious at the end of the study than at baseline. Younger subjects and those who were more severely anxious at the start of the trial had more difficulty in withdrawing than older and less anxious patients.

Following earlier claims that benzodiazepines have a low potential for causing physical dependence (Marks, 1978), it became increasingly realised that dependence occurred in 15–44% of chronic benzodiazepine users. Its existence was demonstrated by a withdrawal syndrome on stopping treatment. Some of the symptoms encountered were identical to those of an anxiety state, while others were atypical; most of the phenomena lasted days or weeks before remitting (Petursson & Lader, 1981*a*; Tyrer *et al*, 1981, 1983; Owen & Tyrer, 1983; Rickels *et al*, 1984; Tyrer, 1988; Edwards *et al*, 1990).

It is now accepted by many that benzodiazepines should not be used for over four weeks in any one course for the treatment of anxiety (Committee on Safety of Medicines, 1988). However, many patients have been on treatment for very much longer than this, and those with dependent, avoidant, and anxious personalities are particularly difficult to withdraw successfully from their drugs (Tyrer *et al*, 1983; Casey & Tyrer, 1986; Ashton, 1984, 1989).

Previous research has compared abrupt with gradual withdrawal, although the latter was in some studies as short as two weeks (Petursson & Lader, 1981*b*; Fontaine *et al*, 1984; Bustro *et al*, 1986*a*,*b*), and abrupt withdrawal with withdrawal during treatment with various pharmacological agents, in particular propranolol (Tyrer *et al*, 1981). Although propranolol ameliorates withdrawal symptoms, slow withdrawal is recommended by most authorities as the method of choice (Lader & Higgitt, 1986; Edwards *et al*, 1990).

However, there is concern that too long a withdrawal phase may decrease the chances of success by "prolonging the agony" (Petursson & Lader, 1984). For this reason withdrawal over one or two months is normally recommended, depending on dose, duration of treatment, and other variables.

In our study we have compared abrupt withdrawal under propranolol cover with a slow withdrawal regime lasting ten weeks in a chronically dependent population of benzodiazepine users. In the process we investigated the prevalence and nature of withdrawal symptoms, and addressed the question of whether patients suffer more severe symptoms when off their drugs than while taking them.

Method

Patients

Thirty-four out-patients were recruited for the study from those attending 58 general practitioners (GPs) in 26 general practices in Portsmouth and Southampton for repeat prescriptions.

Patients who gave informed consent to benzodiazepine withdrawal under the study conditions were included if they were 18–70 years of age, had been taking benzodiazepines for anxiety for at least six months, and were receiving at least 15 mg of diazepam daily or the equivalent doses of other benzodiazepines. Exclusion criteria were: present alcoholism or illicit drug abuse, psychosis, epilepsy or mental handicap; asthma, heart disease, abnormal kidney or liver function; current treatment with other psychotropic drugs; and likely pregnancy during the study period. Patients using only night-time benzodiazepines were also excluded.

Procedure

The trial was of a randomised, double-blind, between-group design, and took place over 17 weeks with a follow-up assessment ten weeks later (six months from the start of the study for each patient).

All patients taking benzodiazepines other than diazepam were changed to diazepam before entering the trial. Equivalent doses were estimated and then adjusted according to clinical need. The study for each patient proceeded only when symptoms had stabilised on two successive assessments following this change. Patients were asked to destroy old unused tablets, and GPs to refrain from prescribing psychotropics during the study.

Patient, investigator, and pharmacist all remained blind to treatment by the use of a coded prescribing/dispensing system. There were no changes in appearance or number of tablets for any patients throughout the study.

At the first recorded visit (week −3) and a week later (week −2) baseline assessments were made. At week −2 the tablets were changed to the trial format (i.e. active diazepam plus propranolol placebo). At this point patients were randomly allocated to one of two treatment groups, one to be treated by slow withdrawal (SW) and the other by abrupt withdrawal under propranolol cover (PW). Visits then took place at fortnightly intervals for the next 16 weeks, with withdrawal starting at week 0. At week 0 in the PW group, diazepam was replaced by diazepam placebo and propranolol placebo by active propranolol (40 mg t.d.s.). The SW group had active diazepam replaced by diazepam placebo in a stepwise manner from week 0 to week 10, while propranolol placebo was continued throughout. In both groups, active drugs were stopped at week 10 and placebo stopped at week 12. No other medication was allowed during the trial.

TABLE I
Baseline characteristics of the sample

	SW group (n = 16)	*PW group (n = 15)*
Age: years (means)	47.3 (14.0)	44.4 (12.3)
Females	10	12
Males	6	3
Social class		
I, II	3	3
III	6	4
IV, V	7	8
Marital status		
married	7	11
single	5	1
widowed/separated/divorced	4	3
Ethnic background		
white British/Irish	14	13
other	2	2
Past psychiatric history		
neurosis other than anxiety or depression	4	3
depression	0	2
antisocial behaviour	1	1
illicit drug abuse	2	1
Use of benzodiazepines		
Duration: years (means)	7.7 (6.0)	11.3 (7.4)
No. of previous attempts at withdrawal (means)	2.2 (2.5)	1.5 (1.4)
Starting dose of diazepam: mg/day (means)	19.1 (8.5)	20.9 (8.0)
Drug taken		
diazepam	10	8
lorazepam	5	4
chlordiazepoxide	1	2
temazepam	0	3
nitrazepam	1	1
clobazam	1	0
triazolam	1	0
flurazepam	0	1
Baseline assessments (means of weeks −3 and −2)		
Hamilton anxiety	14.4 (4.8)	18.5 (3.3)
visual analogue	60.7 (16.5)	40.9 (16.6)
HAD depression	5.3 (2.8)	8.6 (3.5)
global severity	3.6 (1.0)	4.3 (0.6)
alcohol consumption: g/week	44.4 (36.6)	14.3 (30.4)

Standard deviations are shown in parentheses where appropriate.

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During the study patients received general support and advice from the researchers, but they were given no specific psychological, behavioural, or cognitive therapy.

At each visit assessments on the following scales were carried out:

(a) Hamilton Rating Scale for Anxiety (Hamilton, 1959)
(b) Hospital Anxiety and Depression (HAD) scale (Zigmond & Snaith, 1983)
(c) a visual analogue scale of the three worst symptoms which originally led to taking anti-anxiety drugs
(d) a withdrawal symptom check-list (defined as a symptom either appearing or significantly worsening during the withdrawal phase, disappearing or returning to its original level before the end of the study, and having no other apparent cause)
(e) a global assessment of severity of illness (Kearns *et al*, 1982)
(f) a quantitative record of other substances used including alcohol, nicotine and caffeine
(g) pulse rate and blood pressure.

All measures were rated with respect to the preceding two weeks. All unused tablets were surrendered before allocation to the withdrawal groups, and compliance was monitored by measuring plasma drug levels at weeks 0, 4, 8, and 12. Patients were followed up by the researchers and the ratings were repeated six months after the start of withdrawal.

Drop-outs

Patients unable to tolerate withdrawal dropped out of the study, with no further data collected, and were returned to the care of their GP with advice given on future management.

Statistics

The means and distribution of scores for each assessment were tabulated and plotted over time for each of the two treatment groups (means of all the three visual analogue scales were used in the analyses). Within-group differences were analysed using Fisher's least significant difference test (Miller, 1981), with an α level of 0.05.

A logistic regression was carried out with a dependent indicator variable corresponding to whether or not the patient dropped out of the trial because of withdrawal symptoms. The variables considered were age, sex, social class, length of time on benzodiazepines, original benzodiazepine, number of previous attempts at withdrawal, baseline alcohol and cigarette consumption, and baseline scores on each scale.

Results

Of the 34 patients entering the study, three dropped out before being randomly allocated to the withdrawal groups and were excluded from the analysis. There were 15 patients in the PW group and 16 in the SW group. Their characteristics are shown in Table I.

Despite the random allocation, patients in the PW group had higher baseline scores on all symptom scales than did the SW group. However, this difference was considerably reduced by week 0.

Patients in both groups were chronically and severely dependent, with a mean time on benzodiazepines of over nine years for the sample as a whole, and each patient having made one or more previous attempts to withdraw from benzodiazepines. About half those entering the study were successfully withdrawn from diazepam, but these were unevenly spread between the two groups: 11 out of 16 in the SW group were successful, compared with only 4 out of 15 in the PW group (difference 42.1%, 95% confidence interval 7.7–74.6%, χ^2 test, 1 d.f., $P=0.019$).

Only two patients dropped out of the SW group because of withdrawal symptoms; the others did so before the withdrawal phase because of anticipatory anxiety in two cases, and because of unrelated events in the other. All of the patients who dropped out of the PW group did so because of withdrawal symptoms. Taking both groups together, 12 out of the 16 patients who dropped out did so within four weeks of withdrawal. All subjects who completed the withdrawal remained drug free at six-month follow-up.

Eleven of the SW group suffered withdrawal symptoms, which were mostly mild, while 14 of the PW group suffered such symptoms, ranging in intensity from mild to severe. None of our patients had bizarre perceptual disturbances, convulsive seizures, or psychotic symptoms during withdrawal. Withdrawal symptoms suffered included: anxiety (psychic and physical manifestations) (12 patients), sleep loss (9), depression (8), restlessness (4), headache (4), nausea (3), aches and pains (3), irritability (2), emotional lability (2), and paraesthesia (2).

The rating scales all showed the same picture when the means for each group were plotted (Fig. 1). From weeks -3 and -2 to week 0 both groups showed an improvement in all symptoms and the graphs converge. A temporary but significant ($P<0.05$) worsening on all the symptom scales occurred between week 0 and week 2 in the PW group (Table II), but not in the SW group. By week 14 (and at six-month follow-up) both groups had improved on all scales compared with baseline, although this trend reached significance only in the Hamilton anxiety and global severity scales of the SW group (mean changes: 4.7, 1.5 respectively; lower 95% confidence limits: 2.7, 0.6; upper 95% limits: 6.7, 2.5 respectively).

The figures after week 4 in the PW group should be interpreted with caution owing to the high drop-out rate. When the mean changes in each scale between baseline and week 2 were compared, the PW group showed larger mean changes on all measures, although this difference between the groups only reached significance ($P<0.05$) in the case of the Hamilton anxiety scale (mean difference: 6.0; lower 95% confidence limit: 0.99, upper 95% limit: 11.07). When data from only those who successfully completed the withdrawal phase were analysed, the differences between the groups disappeared. However, the non-significant trend toward improvement from the start to the end of the trial in the whole sample remained. The only significant changes ($P<0.05$) between weeks 12 and 14

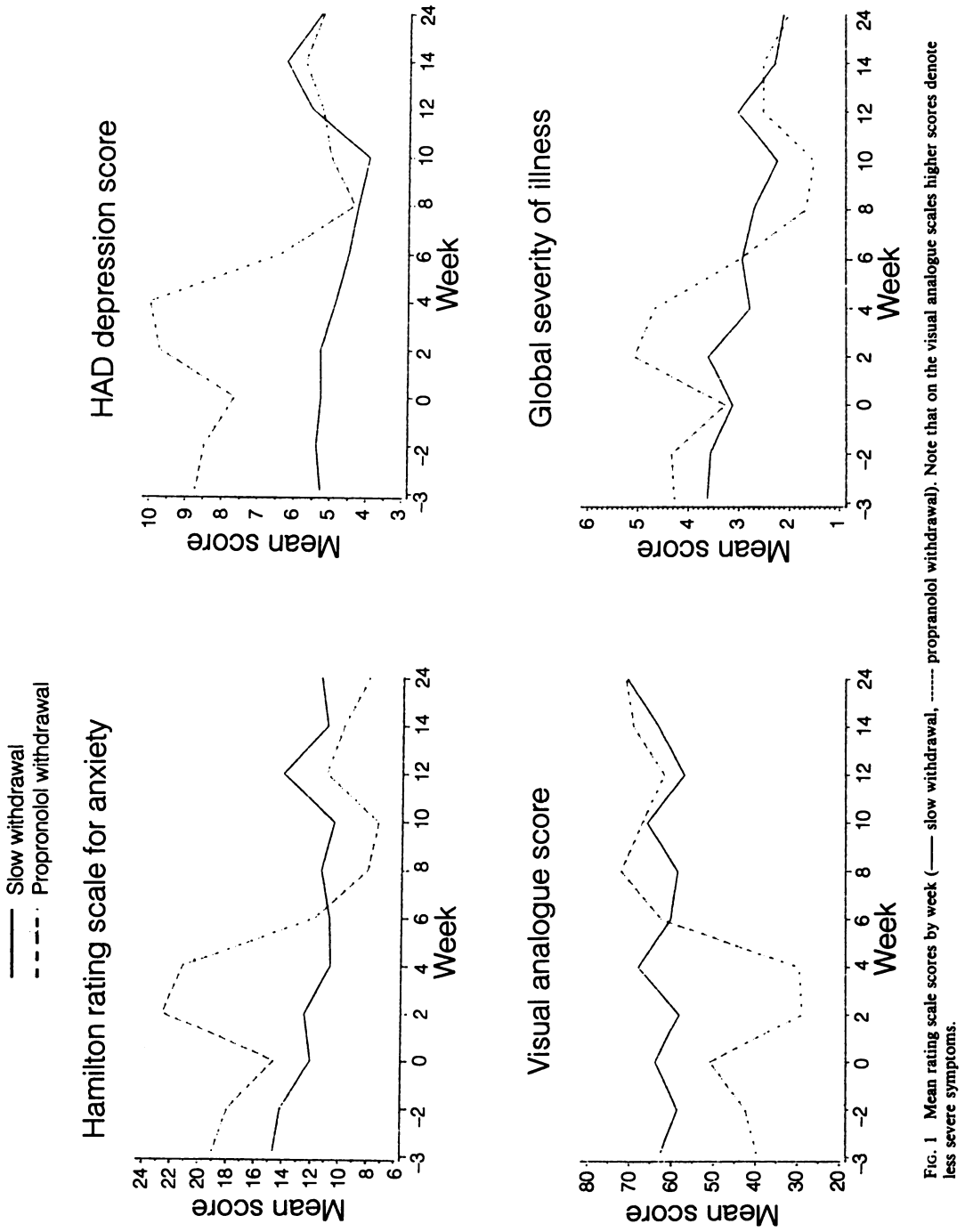

FIG. 1 Mean rating scale scores by week (—— slow withdrawal, ------ propranolol withdrawal). Note that on the visual analogue scales higher scores denote less severe symptoms.

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TABLE II
PW group — changes in rating scales from week 0 to week 2

	Mean difference	*s.e. mean*	*Lower 95% limit*	*Upper 95% limit*
Hamilton anxiety	−8.00	2.469	−13.3	−2.7
Visual analogue	21.93	8.472	3.8	40.0
HAD depression	−2.21	1.034	−4.4	0.0
Global severity	−1.80	0.490	−2.8	−0.8

(between taking placebo only and taking no tablets) were improvements in anxiety and global severity ratings in the SW group. No significant change in any measure occurred between week 14 and six-month follow-up in either group.

An analysis of variance for the period week 2 to week 12 (the withdrawal period) showed no significant linear or quadratic time trends for either group.

No significant changes in alcohol or cigarette consumption occurred in either group. Propranolol did not cause a clinically significant fall in blood pressure in any patient. The plasma diazepam and desmethyldiazepam estimations confirmed that compliance with the treatment regimen was good in both groups.

Age, baseline anxiety score, and treatment group (SW v. PW) each had individually significant effects ($P<0.05$) on the probability of successful withdrawal. Although treatment group and baseline anxiety level were not entirely independent because of an imbalance in matching, the relationship between outcome and treatment group remained significant ($P<0.05$) after controlling for baseline anxiety. That is, the difference in outcome between the groups was not entirely accounted for by the variation in baseline anxiety states — there was a treatment group effect in addition.

Discussion

While recognising the differences between the two groups at baseline, it seems that, even in this chronically and severely dependent sample, slow withdrawal over ten weeks was successful in the majority of cases and led to relatively mild withdrawal symptoms. Abrupt withdrawal, even under the cover of propranolol, led to more severe symptoms and a lower success rate. The withdrawal syndrome lasted between four and six weeks and consisted mainly of an increase in anxiety, which in many cases was sufficiently severe to cause failure to continue with the withdrawal process. The differences between the groups disappeared when the withdrawal symptoms of only those who were successfully withdrawn were analysed.

Our results throw some doubt on the role of propranolol in benzodiazepine withdrawal. Slow withdrawal was successful in most cases while propranolol alone did not lead to any great measure of success in effecting withdrawal. Whether propranolol in combination with slow withdrawal may be useful is beyond the scope of our study.

There was no evidence from our findings that "prolonging the agony" led to treatment failure after the first few weeks, while those who succeeded in withdrawing stayed drug free for at least six months. We therefore advocate a slow, though flexible, withdrawal regime (lasting months) for most patients undergoing this process.

Around 80% of our sample suffered withdrawal symptoms of some kind. This is a higher figure than found in most previous studies (Owen & Tyrer, 1983), and probably reflects the severity of dependence in our patients, who had all previously tried unsuccessfully to withdraw from their drugs.

Our results support the work of Ashton (1984), who suggested that the most anxious patients are more difficult to withdraw from benzodiazepines. In these patients specific treatment of the underlying anxiety using behavioural or other non-pharmacological techniques before withdrawal could be helpful.

Contrary to expectation, in our sample older patients were more often successful in withdrawing from benzodiazepines than younger ones. A possible explanation for this is that an older liver metabolises diazepam more slowly than a younger one (Klotz *et al*, 1975), thereby producing a more gradual removal of the benzodiazepine and its active metabolites from the body. Any inference from this finding must be tentative, but future research should re-examine the prevalent assumption that older patients invariably suffer more difficulties during withdrawal.

Those who were successfully withdrawn in our study were no worse, and may even have been better, on every measure when off their benzodiazepines than they were at baseline. This could be due to relief from unwanted effects or the result of non-specific counselling. Such counselling can be carried out easily in general practice without taking up much time, and could be helpful before withdrawal, as many patients are worried that they will suffer a long-term worsening of symptoms when deprived of their drug. The successful withdrawal of many of our patients with the help of non-specific counselling questions the assumption that all benzodiazepine-dependent patients need more sophisticated and time-consuming psychological treatment. We believe that all doctors can help most of their patients to become free of benzodiazepines by the use of

simple support and advice, alongside gradual withdrawal.

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*Tim Cantopher, BSc, MB, BS, MRCPsych, *Consultant Psychiatrist, Abraham Cowley Unit, St Peter's Hospital, Guildford Road, Chertsey, Surrey KT16 0PZ and Honorary Senior Research Fellow, Department of Psychiatry, St George's Hospital Medical School, London*; Stefano Olivieri, DMS, MD, MRCPsych, *Consultant Psychiatrist, Park Prewett Hospital, Basingstoke, Hants RG24 9LZ*; Nancy Cleave, BA, MSc, *Statistician, Department of Statistics and Computational Mathematics, Liverpool University, Liverpool L69 3BX*; J. Guy Edwards, MB, BCh, FRCPsych, DPM, *Consultant Psychiatrist, Royal South Hants Hospital, Southampton, Hants SO9 4PE*

*Correspondence