Chronic benzodiazepine use in general practice patients with depression: an evaluation of controlled treatment and taper-off

Report on behalf of the Dutch Chronic Benzodiazepine Working Group

FRANS G. ZITMAN and JAAP E. COUVÉE

Background Many patients with depression take benzodiazepine drugs long term despite the absence of continuing therapeutic value.

Aims To evaluate a treatment programme involving gradual discontinuation with or without simultaneous selective serotonin reuptake inhibitor (SSRI) prescribing and to determine the long-term outcome after benzodiazepine withdrawal.

Method Patients went through three phases – change to an equivalent dose of diazepam; subsequent randomisation to either 20 mg of paroxetine or placebo; and gradual reduction of diazepam in depression-free patients – with a follow-up after 2 or 3 years.

Results A total of 230 patients were recruited and 75% in the paroxetine group and 61% in the placebo group were successfully treated after 6 weeks (P=0.067). After 2 or 3 years 13% of patients were still benzodiazepine free: 26% of those who had successfully tapered off benzodiazepine and 6% of the total group.

Conclusions Transfer to diazepam followed by gradual withdrawal is an effective way of discontinuing chronic benzodiazepine use. The addition of SSRI treatment is of limited value.

A substantial proportion of chronic benzodiazepine users are suffering from depression (Rickels *et al*, 1986). For them, benzodiazepines are not considered adequate treatment. The therapeutic value of chronic use is doubtful and benzodiazepines are not recognised as effective antidepressants (Birkenhaeger *et al*, 1995). It has been clinical routine to treat depression first and then taper off the benzodiazepine while antidepressive treatment is continued (Lader, 1994). Such procedures have never been tested in well-designed studies with substantial patient numbers. Moreover, reports evaluating antidepressants in the treatment of benzodiazepine withdrawal show ambiguous results (Rickels *et al*, 1990; Ansseau & De Roeck, 1993; Tyrer *et al*, 1996).

We therefore designed a study testing the feasibility of a discontinuation programme. Our goals were: to compare the efficacy of paroxetine and placebo in the treatment of major depression in a group of chronic users with depression; in the successfully treated patients, to compare paroxetine and placebo in tapering off the benzodiazepine; and to evaluate the long-term efficacy of the programme.

METHODS

Design

Following approval of the medical ethics committee of the University Hospital Nijmegen, The Netherlands, this multi-centre, double-blind, placebo-controlled study was carried out between August 1994 and September 1996. Because this study made use of an electronic case report form, we preferred to use general practitioners (GPs) experienced in the use of such a device. The company that had developed the electronic case report form compiled a list containing the names of 200 GPs. All were invited by means of a letter to consider participation. During the study period

additional centres were recruited. A total of 45 GPs agreed to participate. The practices were well distributed across The Netherlands, representing the average Dutch practice in size and type. The decision to do a follow-up study was taken in December 1997 and the study was executed between March and July 1998. It consisted of complete screening by a research psychologist of psychopharmacological treatment of all participating patients (*n*=230) based on medical records. Retrospectively, GPs were asked by means of a questionnaire to estimate patient numbers at the start of the discontinuation programme as well as the use of the programme in other patients after the study.

Sample size and randomisation

Sample size was estimated by means of power calculation based on the success rate in tapering off: 60–70 patients per group would detect a 25% difference between paroxetine (85%) and placebo (60%), assuming α=0.05 and β=0.20.

Patients were randomised to 20 mg of paroxetine or placebo in a 1:2 double-blind fashion, assuming paroxetine to be twice as effective on antidepressive treatment and to end up with equal numbers in phase III.

A randomisation list (1–330) in blocks of six was obtained by using the random number generator of SPSS/PC+ (SPSS, 1997). Based on this list, study medication (paroxetine, placebo) was blister-packed and wrapped by Genfarma, The Netherlands. Blocks were sequentially distributed to GPs. Unused blocks were reallocated. The list was kept by the Medical Adviser on Safety of the medical department of SmithKline Beecham, The Netherlands. After the database was closed and basic descriptive analyses were done, the actual codes were added to the database.

Study population

Patients were eligible for the study if they met the following criteria: chronic benzodiazepine[1] use, defined as daily use for at least 3 months; a diagnosis of major depressive disorder according to DSM–III–R (American Psychiatric Association, 1987); at least 18 years of age; and written informed consent provided. For diagnostic psychiatric screening we used the Mini International

---

1. For the purposes of this study, zopiclone prescribed as a hypnotic was included in the benzodiazepine group.

Neuropsychiatric Interview (MINI, version 2.1; Lecrubier *et al*, 1997), a semi-structured interview based on DSM–III–R. Excluded were patients with: depression caused by organic factors such as complicated mourning, psychosis, schizophrenia, pregnancy or lactation; child-bearing potential with a lack of adequate contraception; severe concomitant medical conditions; history of seizure disorders; use of other psychotropic medication during the 3 months prior to screening; clinically significant abnormalities in haematology or clinical chemistry; misuse of alcohol or illicit drugs; excessive use of benzodiazepines, defined as more than three times the maximal daily dose; and current suicidal risk.

General practitioners

All participating doctors were trained during interrater sessions in applying the MINI interview and the Hamilton Rating Scale for Depression (HRSD; Hamilton, 1960) and in the use of the electronic case report form. During the study an additional 'booster' training session was performed.

Discontinuation programme

General practitioners were advised to screen all chronic benzodiazepine users for study eligibility. Many asked their pharmacy to prepare a list of chronic users. Eligible patients were entered into three phases.

Phase I: transfer to diazepam

For patients not using diazepam, an equivalent daily dose was calculated based on a conversion table taken from several sources (Bazire, 1994). This table was built into the electronic case report form. Of patients treated with more than one benzodiazepine, the dosages were added. Ten milligrams of diazepam was considered equivalent to: 1 mg alprazolam, 10 mg bromazepam, 0.25 mg brotizolam, 20 mg chlordiazepoxide, 20 mg clobazam, 7.5 mg clorazepate, 1 mg flunitrazepam, 30 mg flurazepam, 1 mg loprazolam, 2 mg lorazepam, 1 mg lormetazepam, 15 mg midazolam, 10 mg nitrazepam, 40 mg oxazepam, 20 mg temazepam and 13 mg zopiclone. The dose could be adapted after 2 weeks. Phase I lasted for 4 weeks, to allow diazepam and its metabolites to reach steady state.

Phase II: antidepressive treatment

Patients were randomised and started treatment with 20 mg of paroxetine once daily or placebo once daily. After 6 weeks patients with a score of 7 or lower on the 17-item HRSD were entered into Phase III.

Phase III: tapering off diazepam

While study medication was continued, diazepam was withdrawn according to a scheme suggested by Rickels *et al* (1990*a*). Daily dose was reduced by 25% in the first and second week. The remaining 50% was tapered off in four steps of 12.5% in weeks 3 and 4. After stopping diazepam, patients continued treatment with the study medication for 2 weeks, followed by 3 weeks of no psychotropic medication. A successful taper-down was defined as benzodiazepine free at week 16.

Measurements

(a) The HRSD was assessed during the visits at weeks 0, 4, 6, 10, 14, 16 and 19 (3 weeks after the end of the taper-off period).

(b) Clinical Global Impression (CGI; Guy, 1976) was assessed on all visits except week 2.

(c) The Spielberger State–Trait Anxiety Inventory – state anxiety sub-scale (STAI–DY1 and 2; van der Ploeg *et al*, 1981) was assessed on all visits except weeks 2, 11 and 13.

(d) The Benzodiazepine Withdrawal Symptom Questionnaire (BWSQ; Tyrer *et al*, 1990) was assessed on all visits except week 2.

(e) Safety assessments: adverse experiences were assessed on all visits except week 0 (screening). Basic haematology and clinical chemistry laboratory tests were taken at week 0 and week 16.

Statistical analyses

The department of Biostatistics and Epidemiology of the University of Utrecht did statistical analyses for the main study. Follow-up data were analysed by a research psychologist of the psychiatric department of the University of Nijmegen. In both analyses, SPSS/PC+ for Windows was used (SPSS, 1997).

All analyses were done on an intention-to-treat basis unless stated otherwise. Descriptive analyses, Pearson's χ^2 test for independent samples, general linear model (GLM) repeated-measures analyses controlled for baseline values, multiple logistic regression analyses and survival analysis (log rank) were used, $P < 0.05$ was taken as the level of statistical significance.

All patients who went through Phase II (antidepressive treatment), irrespective of the outcome, were analysed as 'Phase II patients'. Patients with an HRSD score of 7 or lower who continued into Phase III were coded 'Phase III patients'. Thus, 'Phase III patients' are a subgroup of 'Phase II patients'.

RESULTS

At screening patients had used benzodiazepine for an average of 6 years (range 0.3–27) with an average dose of diazepam equivalents of 9 mg (range 0.5–60 mg). Twenty six per cent of patients had used two benzodiazepines.

A comparison between different subgroups concerning patient characteristics and prognostic factors is given in Table 1. No statistically significant differences between treatment groups were found, indicating a successful randomisation.

Comorbid anxiety disorders (defined as panic disorder, agoraphobia, social phobia, simple phobia, obsessive–compulsive disorder, general anxiety disorder and post-traumatic stress disorder) were diagnosed in 50% of patients, with panic disorder (16.1%), agoraphobia (18.7%), general anxiety disorder (18.7%) and social phobia (14.8%) in the highest frequencies.

Already evident while carrying out the study was the considerable amount of patients refusing consent, as indicated by the fact that 9 (20%) of the 45 practices did not manage to recruit any patients despite considerable numbers of chronic benzodiazepine users.

Estimated retrospectively, each practice had an average of 75 (range 17–250) chronic benzodiazepine users, of whom 12 (16%, range 6–40) had a major depressive disorder. Thus, given our recruitment numbers, 47% of eligible patients did not enter the programme (Fig. 1). A flow diagram of the discontinuation programme and follow-up study, with exact patient numbers, reason for withdrawal/drop-out and efficacy assessments, is shown in Fig. 1.

Phase I: transfer to diazepam (weeks 1–4)

Of the 230 patients entering the study, 40 (17%) used diazepam already. Of the

CHRONIC BENZODIAZEPINE USERS: 2700

Based on retrospective assessments, 36 GPs had an average of 75 patients
(range: 17—250) per practice using benzodiazepines for at least 3 months

---

ELIGIBLE PATIENTS: 436 (16% of 2700)

Based on retrospective assessments, 36 GPs had an average of 12 chronic users
(range: 6—40) per practice with major depression

PHASE I: TRANSFER TO DIAZEPAM (4 weeks)

Parameter: % of patients switched to diazepam successfully
230 (53% of 436) patients gave written informed consent
31[1] (13% of 230) patients dropped out during this phase:

— 8 unsuccessful transfers to diazepam
— 8 patients lost to follow-up
— 8 protocol violations, including non-compliance
— 4 adverse experiences
— 3 other/unknown

162 (85% of 190) were successfully switched to diazepam (40 patients already
used diazepam)

R[1]
N = 199

PHASE II: DEPRESSION TREATMENT WITH PAROXETINE 20 mg
(6 weeks, n = 70)

Parameters: HRSD, STAI-DY1, CGI
22 patients (31% of 70) were withdrawn/dropped out:

— 15 lack of efficacy
— 3 adverse experiences
— 3 other/unknown
— 1 protocol violation, including non-compliance

17 patients (26% of 66) had HRSD >7 after 6 weeks of treatment

PHASE II: DEPRESSION TREATMENT WITH PLACEBO
(6 weeks, n = 129)

Parameters: HRSD, STAI-DY1, CGI
55 patients (43% of 129) were withdrawn/dropped out:

— 49 lack of efficacy
— 4 adverse experiences
— 2 protocol violation, including non-compliance

49 patients (39% of 126) had HRSD >7 after 6 weeks of treatment

---

PHASE III: TAPER OFF DIAZEPAM, PAROXETINE CONTINUED
(6 weeks, n = 48)

Parameter: % of patients who could (not) taper-off diazepam, BWSQ score,
adverse experiences during taper off

— 6 adverse experiences
— 4 protocol violations, including non-compliance
— 2 patient requests/other/unknown
— 1 exacerbation of depression

16 patients (33% of 48) could not taper off diazepam

PHASE III: TAPER OFF DIAZEPAM, PLACEBO CONTINUED
(6 weeks, n = 74)

Parameter: % of patients who could (not) taper-off diazepam, BWSQ score,
adverse experiences during taper off

— 6 adverse experiences
— 5 protocol violations, including non-compliance
— 3 patient requests/other/unknown
— 4 exacerbation of depression

27 patients (36% of 74) could not taper off diazepam

---

35 patients (50% of 70) completed the programme

56 patients (43% of 129) completed the programme

FOLLOW-UP[2] (2.2 years: range 55—1179 days, n = 65)

Parameters: % of patients restarting benzodiazepines, dose, time to restart
benzodiazepines

No follow-up possible: 5 patients (7% of 70)
— 1 patient moved directly after programme end
— 4 patients: 2 GPs retired, 1 refused to cooperate

Lost during follow-up: 9 patients (14% of 65)
— 6 patients moved
— 3 patients died

21 (75% of 28) of successfully tapered-off patients restarted benzodiazepine
use during follow-up period

FOLLOW-UP[2] (2.3 years: range 29—1478 days, n = 119)

Parameters: % of patients restarting benzodiazepines, dose, time to restart
benzodiazepines

No follow-up possible: 10 patients (8% of 129)
— 2 patients moved directly after programme
— 1 patient died directly after programme
— 7 patients: 2 GPs retired, 1 refused to cooperate

Lost during follow-up: 9 patients (8% of 119)
— 7 patients moved
— 2 patients died

34 (74% of 46) successfully tapered-off patients restarted benzodiazepine
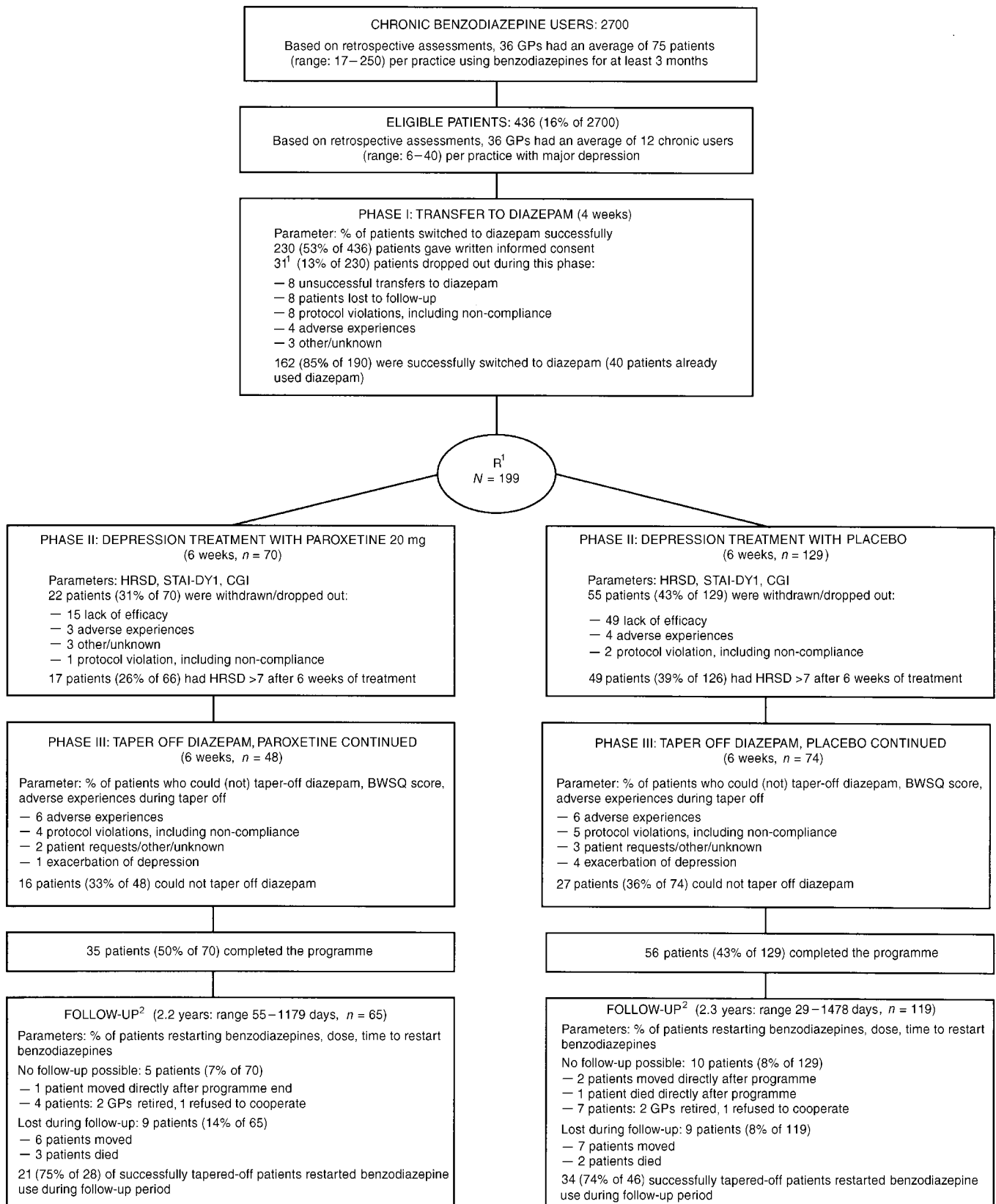use during follow-up period

---

Fig. I Flow diagram of discontinuation programme and follow-up study, patient numbers, reasons for withdrawal/drop-out, primary efficacy assessments and intervention outcome. I. Ratio of randomisation was 2:I in favour of placebo. 2. Non-randomised patients (n=31) were also included in the follow-up study. BWSQ, Benzodiazepine Withdrawal Symptom Questionnaire; CGI, Clinical Global Impression; GP, general practitioner; HRSD, Hamilton Rating Scale for Depression; STAI–DYI, Spielberger State–Trait Anxiety Inventory – state anxiety sub-scale.

Table 1 Characteristics of patients per group

	Total (n=230)	Paroxetine (n=70)	Placebo (n=129)	Dropped out before/at visit 5 (n=108)	Continued at visit 5 (n=122)	Success in tapering off (n=79)	No success in tapering off (n=37)
Gender: males	61 (27%)	19 (27%)	36 (28%)	27 (25%)	34 (28%)	17 (21%)	15 (41%)
Age (years)	56 (24–84)	55 (24–84)	57 (25–84)	54 (25–84)	58 (24–84)	58 (34–82)	58 (24–74)
Quetelet index	25.5 (16–41)	25.3 (19–38)	25.5 (16–39)	25.2 (17–41)	25.7 (16–38)	25.9 (20–38)	25.1 (16–37)
Benzodiazepine use (years)	6.1 (0.3–27)	5.5 (0.3–27)	6.4 (0.3–25)	4.8 (0.3–25)	6.1 (0.3–27)	5.2 (0.3–27)	7.3 (0.3–21)
Benzodiazepine category							
Short-acting	163 (71%)	48 (68%)	90 (70%)	79 (73%)	84 (69%)	55 (69%)	24 (65%)
Long-acting	49 (21%)	18 (26%)	28 (22%)	21 (19%)	28 (23%)	15 (20%)	13 (35%)
Other[1]	18 (8%)	4 (6%)	11 (9%)	8 (7%)	9 (7%)	9 (11%)	0
Use of two benzodiazepines at screening	59 (26%)	17 (24%)	35 (27%)	30 (27%)	29 (24%)	19 (24%)	7 (19%)
Diazepam equivalence (daily dose: mg)	9 (0.5–60)	9 (1–30)	9 (0.5–60)	10 (1–50)	8 (0.5–60)	7 (0.5–20)	10 (2–30)
HRSD at screening	17.3 (5–32)	17.2 (5–24)	17.4 (8–32)	18.3 (6–34)	16.4 (5–28)	17.0 (6–28)	15.4 (5–28)
Psychiatric comorbidity							
Depression only	132 (57%)	39 (56%)	71 (55%)	59 (54%)	71 (59%)	48 (61%)	21 (57%)
Depression+anxiety disorder	98 (43%)	31 (44%)	58 (45%)	50 (46%)	50 (41%)	31 (39%)	16 (43%)

1. Zopiclone, zolpidem and brotizolam.
HRSD, Hamilton Rating Scale for Depression.

remaining 190 patients, 162 (85%) were successfully transferred to diazepam (Fig. 1). For patients who dropped out during this phase, we checked at the level of individual drugs for differences in successful transfer. No differences were found: alprazolam, 2/13 patients; bromazepam, 4/16; brotizolam, 1/11; chlordiazepoxide, 1/3; clobazam, 0/3; clorazepate, 0/8; flunitrazepam, 0/2; flurazepam, 0/4; loprazolam, 0/5; lorazepam, 2/16; lormetazepam, 1/5; midazolam, 0/4; nitrazepam, 2/7; oxazepam, 12/72; temazepam, 2/18; zopiclone, 1/6. Three patients who already use diazepam dropped out during this phase.

Phase II: antidepressive treatment (weeks 5–10)

Analysis of responder rates (HRSD score ≤7) between treatment groups in the first 6 weeks of treatment is given in Table 2a. In the paroxetine group 74% of patients and in the placebo group 61% were treated successfully (P=0.067). However, at screening we found four patients with HRSD scores of ≤7, of whom two discontinued before randomisation. At randomisation, 18 patients had an HRSD score of ≤7. This group had an average of 12.4 (range 5–22) at screening, were rated mild to moderately ill and had used 7.5 mg of diazepam for 3 years. In a subsequent multiple logistic regression analysis, we excluded these 'Phase I responders'. Using

Table 2 Intention-to-treat analysis in number of patients (%): efficacy of paroxetine v. placebo

(a) Treatment of depression

	HRSD scores	
	≤7	>7
Paroxetine (n=66)	49 (74%)	17 (26%)
Placebo (n=126)	77 (61%)	49 (39%)

Dichotomised Hamilton Rating Scale for Depression (HRSD) scores at the end of Phase II (n=192): Pearson's χ^2 test, P=0.067.

(b) Discontinuation of diazepam

	Taper off diazepam	
	Success	Failure
Paroxetine (n=48)	32 (67%)	16 (33%)
Placebo (n=74)	47 (64%)	27 (36%)

Successful v. non-successful taper-off at the end of Phase III: Pearson's χ^2 test, P=0.72.

HRSD score (>7 and ≤7) as a binary independent variable with correction for gender and diazepam dose, we again found no significant difference between treatment groups (P=0.07).

Figure 2a,b gives an overview of average HRSD and STAI–DY1 scores. The patient-rated STAI–DY1 shows a significant decrease in the paroxetine-treated group

compared with placebo (P=0.009). The CGI did not show a statistically significant effect (P=0.10).

Thus, patient's depression score improved significantly during the first weeks of treatment, but we did not find paroxetine to be better than placebo. In contrast, the state anxiety score decreased significantly in patients treated with paroxetine but did not in placebo-treated patients.

In the analysis of the antidepressive effect for patients during the first 12 weeks of treatment, a GLM repeated-measures analysis with the HRSD at randomisation as a covariate showed a significant difference of HRSD between paroxetine and placebo (Fig. 2c). The STAI–DY1 showed comparable results (Fig. 2d). The CGI did not show a statistically significant effect (P=0.24). During or at the end of Phase II, 22 (31%) patients in the paroxetine group and 55 (43%) in the placebo group were withdrawn or dropped out (Fig. 1).

Phase III: diazepam withdrawal (weeks 11–16)

The main result during Phase III is that 32 (67%) of the patients on paroxetine and 47 (64%) of the patients on placebo successfully tapered off diazepam (Table 2b; P=0.72). The withdrawal symptoms were analysed by two measures: an increase of BWSQ scores, with week 10 as point of reference, and reported adverse experiences.
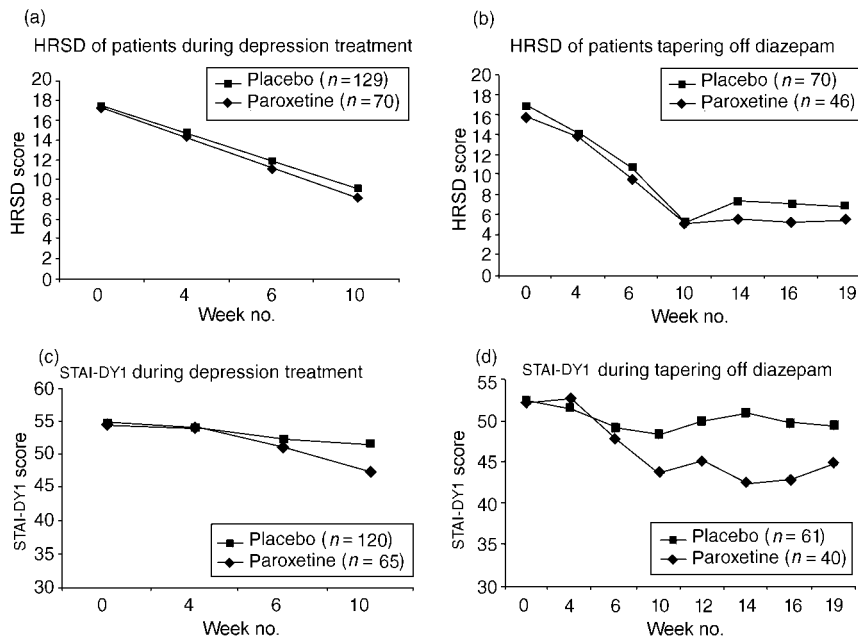
Fig. 2 Hamilton Rating Scale for Depression (HRSD) of patients during depression treatment (a) and of patients tapering off diazepam (b), and Spielberger State–Trait Anxiety Inventory (STAI–DYI) during depression treatment (c) and during tapering off diazepam (d). General linear model (GLM) repeated-measures analyses: (a) NS; (b,c) $P=0.009$; (d) $P<0.001$.

Overall, 61% *v.* 65% of patients in the success and no-success groups, respectively, reported an increase in number and/or severity of symptoms during the diazepam withdrawal phase. In the no-success patients the average BWSQ scores showed an increase of three points (6.5–9.5) in the last phase of tapering down. In the success group, the score remained unchanged (mean=6.5, s.d.=6.6, $P=0.036$).

Adverse experiences had two peaks concerning the time of onset: one peak around visit 3 (transfer to diazepam and start of study medication) and another 3 weeks after taper-off start. The latter is of interest here. Adverse experiences during taper-down with an incidence of 5% or more were insomnia (13%), anxiety (6%), headache (5%) and agitation (5%). Interesting is the difference of reported insomnia/sleep disorder between paroxetine-treated patients (8%) and placebo-treated patients (23%). The difference, if any, between success and no-success patients focuses on agitation. Increases in the average HRSD score (from 5.6 to 9.6) and the STAI–DY1 score (45 to 54) were found in the non-success group but not in the success group.

No serious adverse experiences occurred during the taper-down phase.

Follow-up period

Follow-up assessments, achieved for 207 patients (90% of main study patients),

were done on average 2.3 years (range 29 days to 3 years) after patients had ended the discontinuation programme.

Twenty-six patients (13%) who started the programme remained benzodiazepine-free throughout the follow-up period: of these, 19 (26%) were among the patients who successfully completed the programme; one was from the unsuccessful group (i.e. who still used diazepam at week 16); and six had dropped out before/at week 10.

Survival curves until benzodiazepine restart for the success *v.* no-success group show a significant difference (Fig. 3). Table 3 shows the characteristics of benzodiazepine use during the follow-up period. Patients who successfully finished the discontinuation programme were less likely to restart; if they did restart this was at a later stage, for shorter periods, in lower dosages and fewer patients tended to resume their old habit of chronic use (defined as benzodiazepine use >95% of follow-up period). Compared with the characteristics at baseline (Table 2) the successful taper-off group had used benzodiazepines in lower doses and for shorter periods. At the time of follow-up, 52% of patients used benzodiazepine. The difference between the successful (42%) and unsuccessful group (69%) was significant ($P=0.028$).

After study completion 64% of GPs used the discontinuation protocol for other patients. On average, they had treated

another five patients per practice: 71% reported to be satisfied with the results.

DISCUSSION

To our knowledge this is the first time a sample of chronic benzodiazepine users suffering from depression has been investigated separately in a benzodiazepine discontinuation programme. Moreover, it is the largest intervention study trying to deal with the problem of chronic use.

When we planned this study, it was our goal to develop and test a tool for GPs, that could help them in treating the depression as well as long-term benzodiazepine dependence in one programme.

Short-term efficacy of the programme

Transfer to diazepam

In the 13% of patients who dropped out during this phase, we failed to detect any differences between individual drugs in transferring to diazepam. There have been some reports that coming off lorazepam might be more difficult, but our data do not support this (Murphy & Tyrer, 1991).

Treatment of depression

Evaluating the depression treatment phase we found the mean HRSD score of our sample to be relatively low: 17.4 at screening and 14.8 at randomisation. We did not set a severity entry criterion in order to be as close as possible to the day-to-day setting of the general practice. The HRSD is not a diagnostic tool and a severity limit may have pushed up the scores. It is also known that training health care professionals in structured interviews like the MINI can anticipate some overrating. After all, setting a psychiatric diagnosis can be a difficult process in many patients. Given these results, one could argue that not all of our patients had major depressive disorder, but given the high comorbidity of anxiety disorders as well as the high anxiety scores on the STAI we are convinced that this group of patients needs adequate treatment and not just a daily dose of benzodiazepines.

Seventy-four per cent of patients with an HRSD score of 7 or lower after 6 weeks of treatment with paroxetine is comparable to that of efficacy studies in other populations of patients suffering from depression (Dunner & Kumar, 1998). Our results,

however, differ from those studies with respect to a placebo response of 61%.

In the state anxiety measure (STAI–DY1) we did not find any placebo response. We would have expected that transfer from short-acting benzodiazepine in 70% of patients to diazepam would have given some anxiolysis during the day, but we found no decrease in anxiety during Phase I. Moreover, although these patients were treated for 6 years with benzodiazepines, their anxiety level of 54 during Phase I was comparable to that of psychiatric outpatients, whereas in normal populations scores are 30–40 on this scale (van der Ploeg *et al*, 1981). Patients treated with paroxetine for 6 weeks were significantly less anxious. This confirms the results of many clinical studies that have shown the efficacy of selective serotonin reuptake inhibitors (SSRIs) in the treatment of anxiety disorders.

In summary, we found paroxetine to be more effective in treating anxiety than depression. Perhaps the relatively low depression scores versus the high anxiety scores at screening ('Law of Initial Value'; Uhlenhuth *et al*, 1997) might clarify this, but we are not able to explain this inconsistency completely.

Unfortunately, no MINI was done at the end of the programme to check for possible changes in psychopathology.

Discontinuation of diazepam

The short-term effect of the programme showed that after treating the depression adequately 65% of these primary care patients, either on paroxetine or placebo, were successful in stopping benzodiazepine use. This percentage is comparable to the 66% reported by Schweizer *et al* (1990), who used a comparable tapering-off procedure without concomitant treatment to ameliorate withdrawal symptoms, and in a non-selected group of chronic users. Several publications report that a substantial proportion of chronic benzodiazepine users are depressed, and that these patients have greater difficulty in stopping benzodiazepine use (Lader, 1994). Our data suggest that if patients are treated for their depression successfully, they end up with comparable success rates of taper-off.

Of the patients who entered the tapering-off phase, 63% reported withdrawal symptoms. Although figures of prevalence of withdrawal symptoms across studies have been reported from zero to 100%, in

low-dose, long-acting benzodiazepine use with gradual taper this is 40–80% (Rickels *et al*, 1990; Schweizer *et al*, 1990). As in the findings of Schweizer *et al* (1990), no serious withdrawal effects were noted, indicating that the procedure is safe in this

group of chronic low-dose users. We estimated that 50% of patients refused informed consent. Although we did not assess the reasons for their unwillingness to participate, this result might indicate medication craving, as suggested by Linden *et al*

Fig. 3 Follow-up survival time until first use of benzodiazepine after the discontinuation programme. Log rank survival analysis; $P < 0.001$.

Table 3 Characteristics of benzodiazepine use during follow-up ($n=207$)

	Patients successfully tapered off $n=74$ (68%)	Patients not successfully tapered off $n=35$ (32%)	
Number of patients restarting use of benzodiazepine at any point during the follow-up	55 (74%)	34 (97%)	$P < 0.001$[a]
Days to first use after the intervention programme	190	67	$P < 0.001$[b]
Number of patients immediately on benzodiazepines	11 (15%)	21 (60%)	
Mean days	235	175	
Median	208	39	
Range	6–767	8–779	
No. of patients using benzodiazepines > 95% of follow-up time	12 (16%)	23 (68%)	$P < 0.001$[a]
Mean dosage in diazepam equivalents	8.55	12.28	$P = 0.07$[b]
Median	6.00	10.00	
s.d.	7.00	9.84	
Range	0.05–28	2.0–40.0	

a χ^2 test.
b Kruskal–Wallis.

(1998), who found that two-thirds of chronic benzodiazepine users rejected a drug holiday.

Comparing paroxetine with placebo during discontinuation, we found that patients treated with paroxetine were less depressed, less anxious and complained less of insomnia/sleep disorder compared with placebo. Surprisingly, this did not result in higher taper-off success rates. In both groups, two-thirds of patients managed to taper off diazepam.

To our knowledge, lack of a beneficial effect of an antidepressant in successfully tapering off benzodiazepine in chronic users in general has been demonstrated in one study (Tyrer *et al*, 1996). Two other studies reported positive effects of imipramine and trazodone (Rickels *et al*, 1990; Ansseau & De Roeck, 1993). The conclusions of these studies have been based on small patient numbers.

Diazepam dose, duration of chronic use, incidence and severity of withdrawal symptoms and concomitant effective anti-depressive treatment do not fully explain why a patient can or cannot taper off benzodiazepine. Other factors, not measured in this study, must be of importance. It has been well reported already that personality traits might be relevant in explaining the difficulties in stopping benzodiazepines (Murphy & Tyrer, 1991; Seivewright *et al*, 1991).

Long-term efficacy of the programme

Our main result, showing the long-term effect of the programme, is that about 2 years after participation two-thirds of patients proved to have stopped their old habit of daily benzodiazepine use. Moreover, 13% managed to remain benzodiazepine free. If patients successfully completed the programme they had a better outcome, but a substantial number of patients who dropped out of the programme early or did not successfully taper off managed to change their benzodiazepine use. All this confirms the findings of Holton & Tyrer (1990), that a substantial number of patients who have been on benzodiazepine chronically in the past can restart and stop their medication without much difficulty.

The finding of 48% benzodiazepine free at the time of follow-up with a difference of 58% and 31%, respectively, between the success and no-success groups replicates the findings of the only comparable study

reported by Rickels *et al* (1991). They found 73% *v*. 39%, respectively, of patients benzodiazepine free after 3 years.

The number of patients restarting benzodiazepine in the first 6 months might suggest the need for follow-up treatment to consolidate the reasons for stopping. In patients with panic disorder, for example, Spiegel & Bruce (1997) found behavioural psychotherapy efficacious in preventing benzodiazepine restart.

The overall satisfaction of GPs who treated patients according to the discontinuation programme was demonstrated by its use in other patients and their appraisal of the programme after 2 or 3 years.

ACKNOWLEDGEMENTS

FRANZ G. ZITMAN, PhD, LUMC, Departments of Psychiatry, Leiden, and UMC St Radbond, Nijmegen, The Netherlands; JAAP E. COUVÉE, MSc, Medical Department, SmithKline Beecham Farma bv, Rijswijk, The Netherlands

Correspondence: F.G. Zitman, LUMC, Department of Psychiatry, BIP, PO Box 9600, 2300 RC Leiden, The Netherlands. Tel: +31 71 526 3448; fax: +31 71 524 8156; e-mail: f.g.zitman@lumc.nl

REFERENCES

American Psychiatric Association (1987) *Diagnostic and Statistical Manual of Mental Disorders* (3rd edn, revised) (DSM–III–R). Washington, DC: APA.

Ansseau, M. & De Roeck, J. (1993) Trazodone in benzodiazepine dependence. *Journal of Clinical Psychiatry*, **54**, 189–191.

Bazire S. (1994) *Psychotropic Drug Directory.* Salisbury: Mark Allen Publishing.

Birkenhaeger, T. D., Moleman, P. & Nolen, W. A. (1995) Benzodiazepines for depression? A review of the literature. *International Clinical Psychopharmacology*, **10**, 181–195.

Dunner, D. & Kumar, R. (1998) Paroxetine: a review of clinical experience. *Pharmacopsychiatry*, **31**, 89–101.

Guy, W. (1976) *ECDU Assessment Manual for Psychopharmacology.* Revised DHEW Pub. (ADM). Rockville, MD: National Institute for Mental Health.

Hamilton, M. A. (1960) Rating scale for depression. *Journal of Neurology, Neurosurgery and Psychiatry*, **23**, 56–62.

Holton, A. & Tyrer, P. (1990) Five year outcome of patients withdrawn from long term treatment with diazepam. *British Medical Journal*, **300**, 1241–1242.

Lader, M. (1994) Anxiety or depression during withdrawal of hypnotic treatments. *Journal of Psychosomatic Research*, **38**, 113–123.

Lecrubier, Y., Sheehan, D. V., Weiller, E., et al (1997) The Mini International Neuropsychiatric Interview (MINI). A short diagnostic structured interview: reliability and validity according to the CIDI. *European Psychiatry*, **12**, 224–231.

Linden, M., Baer, T. & Geiselmann, B. (1998) Patient treatment insistence and medication craving in long-term low-dosage benzodiazepine prescription. *Psychological Medicine*, **28**, 721–729.

Murphy, S. M. & Tyrer, P. (1991) A double-blind comparison of the effects of gradual withdrawal of lorazepam, diazepam and bromazepam in benzodiazepine dependence. *British Journal of Psychiatry*, **158**, 511–516.

Rickels, K., Case, W. G., Schweizer, E. E., et al (1986) Low-dose dependence in chronic benzodiazepine users: a preliminary report on 119 patients. *Psychopharmacology Bulletin*, **22**, 407–415.

__, __, __, et al (1990) Benzodiazepine dependence: management of discontinuation. *Psychopharmacology Bulletin*, **26**, 63–68.

__, Case, W. G., Schweizer, F., et al (1991) Long-term benzodiazepine users 3 years after participation in a discontinuation program. *American Journal of Psychiatry*, **148**, 757–761.

Schweizer, E., Rickels, K., Case, W. G., et al (1990) Longterm therapeutic use of benzodiazepines: II Effects of gradual taper. *Archives of General Psychiatry*, **47**, 908–915.

Seivewright, H., Tyrer, P. & Seivewright, N. (1991) A three-year follow-up of psychiatric morbidity in urban and rural primary care. *Psychological Medicine*, **21**, 495–503.

Spiegel, D. A. & Bruce, T. J. (1997) Benzodiazepines and exposure-based cognitive behavior therapies for panic disorder: conclusions from combined treatment trials. *American Journal of Psychiatry*, **154**, 773–781.

SPSS (1997) *SPSS version 8.0.* Chicago: SPSS Inc.

Tyrer, P., Murphy, S. & Riley, P. (1990) The benzodiazepine withdrawal symptom questionnaire. *Journal of Affective Disorders*, **19**, 53–61.

__, Ferguson, B., Hallström, C., et al (1996) A controlled trial of dothiepin and placebo in treating benzodiazepine withdrawal symptoms. *British Journal of Psychiatry*, **168**, 457–461.

Uhlenhuth, E. H., Matuzas, W., Warner, T. D., et al (1997) Methodological issues in psychopharmacological research: growing placebo rates in recent therapeutic trials? *Psychopharmacology Bulletin*, **33**, 31–39.

van der Ploeg, H. M., Defares, P. B. & Spielberger, C. D. (1981) *ZBV, een nederlandstalige bewerking van de Spielberger State–Trait Anxiety Inventory.* Lisse: Swets & Zeitlinger.