Long-term outcome of two forms of randomised benzodiazepine discontinuation

R. C. OUDE VOSHAAR, W. J. M. J. GORGELS, A. J. J. MOL, A. J. L. M. VAN BALKOM, J. MULDER, E. H. VAN DE LISDONK, M. H. M. BRETELER and F. G. ZITMAN

Summary About two-thirds of long-term users of benzodiazepines in the population are able to discontinue this drug with the aid of supervised programmes for tapering off. Little is known about the long-term outcome of such programmes, and they have never been compared with usual care. After a 15-month follow-up of a randomised controlled trial comparing such a programme with and without psychotherapy with usual care, we found significantly higher longitudinal abstinence rates in long-term benzodiazepine users who received a benzodiazepine tapering-off programme without psychotherapy (25 out of 69, 36%) compared with those who received usual care (5 out of 33, 15%; P=0.03).

Declaration of interest None.

Almost two-thirds of long-term benzodiazepine users who take part in benzodiazepine discontinuation programmes are able to achieve complete abstinence in the short term (Oude Voshaar *et al*, 2006). The long-term outcome studies that have been published are uncontrolled for the natural course of benzodiazepine usage, and report abstinence rates ranging from 16 to 82% (Ashton, 1987; Golombok *et al*, 1987; Rickels *et al*, 1991; Holton *et al*, 1992; Couvée *et al*, 2002). This paper presents the results of a 15-month follow-up of a previously published randomised controlled trial (RCT) comparing two benzodiazepine tapering-off conditions with a control condition consisting of usual care (Oude Voshaar *et al*, 2003).

METHOD

A total of 180 individuals who had been using benzodiazepine for over 3 months and were unable to quit their usage of the drug by themselves after receiving a discontinuation letter from their general practitioner were randomly allocated to tapering off with cognitive–behavioural group therapy (CBT; n=73), tapering off alone (n=73) or usual care (n=34) in general practice. A detailed description of the interventions and interview assessments at baseline and end of treatment is given elsewhere (Oude Voshaar *et al*, 2003).

The present paper describes: a 15-month follow-up; the use of prescription data instead of self-reported benzodiazepine usage, with a significantly lower drop-out rate as a consequence; and data on the prescribing of other drugs during follow-up. All patients gave their informed consent to participate in the follow-up study. Drug prescription data were prospectively obtained from the computerised medical records, and included date of issue, Anatomical Therapeutic Chemical classification code (ATC code; World Health Organization Collaborating Centre for Drugs Statistics Methodology, 1996) and name of the drug, number of tablets and dose. Gender, date of birth and the administration number of individual participants were extracted to link the prescription data with the results of the RCT. The primary outcome measure, benzodiazepine abstinence, was based on the computerised prescription data. We analysed the prevalence rates of benzodiazepine abstinence and the mean daily dosages in diazepam equivalents of all issued benzodiazepine prescriptions over predefined 3-month periods using χ^2-tests, Cox regression analysis and repeated-measures analysis of variance (ANOVA). The secondary outcome measure was the prescription of psychotropic drugs other than benzodiazepines.

In addition to the prescription data, we also performed a follow-up assessment at 15 months (n=143) which was identical to the baseline (n=180) and outcome (n=141) assessments of the RCT. In this report, we present the outcome and follow-up assessment data for self-reported benzodiazepine usage.

RESULTS

Computerised drug prescription data were available for 170 of the 180 participants for the whole study period. However, owing to patient withdrawal from the interview assessments, data on self-reported benzodiazepine usage were available for only 143 participants at the 15-month follow-up. Baseline characteristics did not differ across the three conditions. Patients used benzodiazepines on average for 13.5 years (s.d.=9.6) at a mean dosage of 8.4 mg (s.d.=8.3) diazepam equivalents before receiving the discontinuation letter from their general practitioner, and at a mean dosage of 5.9 mg (s.d.=8.3) thereafter. The mean age was 63 years (s.d.=12), and 119 of the participants (70%) were female.

The longitudinal abstinence rate based on prescription data for participants who received tapering off plus CBT (20 out of 68, 29%) was not significantly superior to that for those who received usual care (5 out of 33, 15%; χ^2=2.4, d.f.=1, P=0.12), whereas the opposite was the case for participants who received tapering off alone (25 out of 69, 36%, χ^2=4.8, d.f.=1, P=0.03 in favour of tapering off alone; see data supplement to the online version of this paper). The two active treatment groups only differed significantly at 1–3 months of follow-up (χ^2=4.6, d.f.=1, P=0.03), in favour of tapering off alone. The 'survival curve' to the first benzodiazepine prescription after the intervention period confirmed these findings (Gehan–Breslow test: 9.31; d.f.=2, P=0.02). Of the participants who restarted benzodiazepine treatment during follow-up, 90% (113 out of 126) restarted within the first 9 months.

Self-reported abstinence in the month before the 15-month follow-up assessment was not significantly different between the three groups (tapering off plus CBT, 30 out of 58, 52%; tapering off alone, 37 out of 59, 63%; usual care, 11 out of 26, 42%; χ^2=3.3, d.f.=2, P=0.19). Kappa for the agreement of computerised benzodiazepine prescription outcome at 13–15 months and self-reported outcome at 15 months was 0.73 (P<0.001). Most discrepancies were found in participants who used benzodiazepines intermittently during follow-up.

https://doi.org/10.1192/bjp.bp.105.012039 Published online by Cambridge University Press

A repeated-measures ANOVA showed that among participants who did not achieve continued abstinence, those who received active treatment used significantly lower dosages at follow-up compared with those who were assigned usual care ($F=6.5$, d.f.=1, $P=0.01$). A significant time × group interaction (active treatment *v.* usual care) indicated that this difference decreased during follow-up ($F=5.3$, d.f.=1, $P=0.02$).

The prescription of antidepressants, analgesics, antipsychotics and anti-epileptic drugs remained stable, and patients were not prescribed hypnotic or anxiolytic drugs other than benzodiazepines during follow-up.

DISCUSSION

Although relatively low 15-month longitudinal rates for abstinence from benzodiazepines were found (29% for tapering off plus CBT and 36% for tapering off alone), comparison with the control group confirmed the long-term efficacy of tapering off alone. The high point prevalence of benzodiazepine abstinence in the 3-month follow-up periods (see data supplement to the online version of this paper) suggests that a number of participants used the drug intermittently.

Our longitudinal abstinence rates are relatively high compared with the values of 16% and 18% found by Couvée *et al* (2002) and Holton *et al* (1992) respectively. It is unlikely that this is due to a shorter follow-up period, because most relapses (>90%) occur within the first 9 months. Two feasible explanations can be suggested. First, there were differences in the populations studied, as Holton *et al* (1992) included referred participants in a psychiatric setting, and Couvée *et al* (2002) included a subgroup of long-term benzodiazepine users with depression. The results of several studies suggest that people with depression experience greater difficulty in stopping benzodiazepine use (Lader, 1994). Second, because of the prospective nature of our study, both general practitioners and participants were aware that they would be followed-up, whereas the follow-up in the other studies was retrospective.

The self-reported abstinence rates during the last month of follow-up (52% for tapering off plus CBT *v.* 63% for tapering off alone) replicate the findings of Rickels *et al* (1991) and Golombok *et al* (1987), who found self-reported cross-sectional success rates at follow-up of 58% and 54% respectively. Owing to the intermittent usage of benzodiazepines during follow-up, cross-sectional success rates overestimate the longitudinal effects. The significance of self-reported cross-sectional success rates is questionable, since we included a control, in contrast to Rickels *et al* (1991) and Golombok *et al* (1987), but found no significant differences in the self-reported success rate between active treatment and the control group.

One study showed a longitudinal abstinence rate of 82% (Ashton, 1987). This study differed from the others in that it was an evaluation of a patient-tailored withdrawal programme with tapering off periods of up to 15 months at a tertiary clinical pharmacology unit that offered pharmacological as well as psychological support during tapering off. It is impossible to provide such highly specialised care in a primary care setting.

In line with the findings of the primary care study by Couvée *et al* (2002), the participants in our study were not prescribed more antidepressants or other psychotropic drugs. This is in contrast to the results of Rickels *et al* (1991), who found an increase in the use of antidepressants by individuals in psychiatric care who were taking part in their tapering-off programme.

We did not find that the addition of psychotherapy to a tapering-off programme was efficacious among benzodiazepine users in the general population. Most previously published benzodiazepine discontinuation studies that have assessed the efficacy of additional psychotherapy were uncontrolled and evaluated a maximum of 21 patients per treatment arm (Oude Voshaar *et al*, 2006). However, well-designed RCTs on the efficacy of additional psychotherapy showed significantly superior short-term effects in some specific patient groups, namely those with panic disorder (Otto *et al*, 1993) and insomnia (Baillargeon *et al*, 2003; Morin *et al*, 2004), but not in others, such as multidrug users (Vorma *et al*, 2002).

R. C. OUDE VOSHAAR, MD, PhD, Department of Psychiatry, Radboud University Medical Centre Nijmegen; W. J. M. J. GORGELS, MD, Department of General Practice and Family Medicine, Radboud University Medical Centre Nijmegen; A. J. J. MOL, MSc, Department of Psychiatry, Radboud University Medical Centre Nijmegen; A. J. L. M. VAN BALKOM, MD, PhD, Department of Psychiatry and Institute for Research in Extramural Medicine, VU University Medical Centre, Amsterdam; J. MULDER, Ing, E. H. VAN DE LISDONK, MD, PhD, Department of General Practice and Family Medicine, Radboud University Medical Centre Nijmegen; M. H. M. BRETELER, PhD, Department of Clinical Psychology and Personality, Radboud University, Nijmegen; F. G. ZITMAN, MD, PhD, Department of Psychiatry, Leiden University Medical Centre, Leiden, The Netherlands

Correspondence: Dr R. C. Oude Voshaar, Department of Psychiatry, Radboud University Medical Centre Nijmegen, PO Box 9101, 6500 HB Nijmegen, The Netherlands. E-mail: r.oudevoshaar@psy.umcn.nl

(First received 7 April 2005, accepted 5 May 2005)

REFERENCES

Ashton, H. (1987) Benzodiazepine withdrawal: outcome in 50 patients. *British Journal of Addiction*, **82**, 665–671.

Baillargeon, L., Landreville, P., Verreault, R., *et al* (2003) Discontinuation of benzodiazepines among older insomniac adults treated with cognitive–behavioural therapy combined with gradual tapering: a randomized trial. *Journal of the Canadian Medical Association*, **11**, 1015–1020.

Couvée, J. E., Timmermans, E. A. & Zitman, F. G. (2002) The long-term outcome of a benzodiazepine discontinuation program in depressed outpatients. *Journal of Affective Disorders*, **70**, 133–141.

Golombok, S., Higgitt, A., Fonagy, P., *et al* (1987) A follow-up study of patients treated for benzodiazepine dependence. *British Journal of Medical Psychology*, **60**, 141–149.

Holton, A., Riley, P. & Tyrer, P. (1992) Factors predicting long-term outcome after chronic benzodiazepine therapy. *Journal of Affective Disorders*, **24**, 245–252.

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

Morin, C. M., Bastien, C., Guay, B., *et al* (2004) Randomized controlled trial of supervised tapering and cognitive–behavior therapy to facilitate benzodiazepine discontinuation in older adults with chronic insomnia. *American Journal of Psychiatry*, **161**, 332–342.

Otto, M. W., Pollack, M. H., Sachs, G. S., *et al* (1993) Discontinuation of benzodiazepine treatment: efficacy of cognitive–behavioral therapy for patients with panic disorder. *American Journal of Psychiatry*, **150**, 1485–1490.

Oude Voshaar, R. C., Gorgels, W. J. M. J., Mol, A. J. J., *et al* (2003) Tapering off long-term benzodiazepine use with or without group cognitive–behavioural therapy: three-condition randomised controlled trial. *British Journal of Psychiatry*, **182**, 498–504.

Oude Voshaar, R. C., Couvée, J. E., Van Balkom, A. J. L. M., *et al* (2006) Strategies to discontinue long-term benzodiazepine use: a meta-analysis. *British Journal of Psychiatry*, in press.

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

Vorma, H., Naukkarinen, H., Sarna, S., *et al* (2002) Treatment of out-patients with complicated benzodiazepine dependence: comparison of two approaches. *Addiction*, **97**, 851–859.

World Health Organization Collaborating Centre for Drugs Statistics Methodology (1996) *Guidelines ATC Classification and DDD Assignment* (1st edn). Oslo: WHO/Norwegian Institute of Public Health.

https://doi.org/10.1192/bjp.bp.105.012039 Published online by Cambridge University Press