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Strategies for discontinuing long-term benzodiazepine use

Meta-analysis

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Background The prevalence of benzodiazepine consumption in European countries remains at 2–3% of the general population despite the well-documented disadvantages of long-term use.

Aims To review systematically the success rates of different benzodiazepine discontinuation strategies.

Method Meta-analysis of comparable intervention studies.

Results Twenty-nine articles met inclusion criteria. Two groups of interventions were identified; minimal intervention (e.g. giving simple advice in the form of a letter or meeting to a large group of people; n=3), and systematic discontinuation (defined as treatment programmes led by a physician or psychologist; n=26). Both were found to be significantly more effective than treatment as usual: minimal interventions (pooled OR=2.8, 95% CI 1.6–5.1); systematic discontinuation alone (one study, OR=6.1, 95% CI 2.0–18.6). Augmentation of systematic discontinuation with imipramine (two studies, OR=3.1, 95% CI 1.1–9.4) or group cognitive–behavioural therapy for patients with insomnia (two studies, OR=5.5, 95% CI 2.3–14.2) was superior to systematic discontinuation alone.

Conclusions Evidence was found for the efficacy of stepped care (minimal intervention followed by systematic discontinuation alone) in discontinuing long-term benzodiazepine use.

Declaration of interest None.

Since the early 1960s benzodiazepines have become widely available, reaching prescription peaks in the 1970s (Lader, 1991). Subsequently more and more data were reported indicating the disadvantages of long-term benzodiazepine use, such as the risk of dependence, a higher risk of accidents and falls, and cognitive disturbances (Taylor *et al*, 1998). In the past few years the prevalence rate of benzodiazepine consumption in most European countries is estimated to be stable or slightly decreasing (Stillwell & Fountain, 2002), but remains at levels varying between 2% and 3% of the general population (Zandstra *et al*, 2002). Although long-term therapeutic use of benzodiazepines is controversial, limited evidence suggests long-term efficacy in specific diagnostic groups such as panic disorder and social phobia (Schweizer *et al*, 1993; Otto *et al*, 2000). The prevalence of these disorders among people who are long-term benzodiazepine users, however, is relatively low (Zandstra *et al*, 2004).

Problems experienced by patients stopping long-term benzodiazepine use initiated the development of treatment strategies for discontinuing these drugs. Russell & Lader (1993) proposed a stepped care approach to address the problem of long-term use. They advised starting with a minimal intervention and, if this failed, gradually intensifying treatment from supervised gradual withdrawal after patient assessment to specialised care including augmentation strategies. In order to summarise the evidence for the individual steps of such programmes, we carried out meta-analyses of the success rates of the different benzodiazepine discontinuation strategies.

METHOD

Identification of studies

An initial search was made of the databases PubMed and PsycINFO for the period 1966 to September 2004 and the Cochrane Library in December 2004, using the keywords BENZODIAZEPINE(S) in combination with WITHDRAWAL, DETOXIFICATION, DEPENDENCE, DISCONTINUATION *or* LONG-TERM. This search was extended by a manual search of the reference lists of all benzodiazepine discontinuation studies and benzodiazepine discontinuation augmentation studies (Fig. 1).

Inclusion criteria

Papers were included in the review if they met the following criteria:

(a) the study had a randomised controlled design;

(b) the outcomes of discontinuation were presented separately for each treatment arm;

(c) long-term benzodiazepine use was defined as daily use for at least 3 months.

Excluded were case series, review papers, double publications, experimental research or clinical trials evaluating the efficacy of benzodiazepine treatment for a fixed period, and animal research. Authors R.C.O.V. and J.E.C. independently checked the inclusion and exclusion criteria of the identified studies.

Selection procedure, data extraction and quality assessment

Included studies were coded twice by R.C.O.V. and J.E.C. Discrepancies in the two coding forms were resolved by consensus after discussion or by referring to the data in the original article. This method yielded one coding form per article. The intervention type was added to the coding form by distinguishing between minimal interventions and systematic discontinuation programmes. Minimal interventions were defined as simple interventions applicable to large groups of people, for example, an advisory letter or a meeting in which patients who are long-term benzodiazepine users are advised to stop taking the drug. Systematic discontinuation programmes were defined as treatment programmes guided by a physician or psychologist. We sub-categorised these treatment programmes into systematic discontinuation alone or discontinuation with either psychotherapy or pharmacotherapy. The coding form consisted of the following items:

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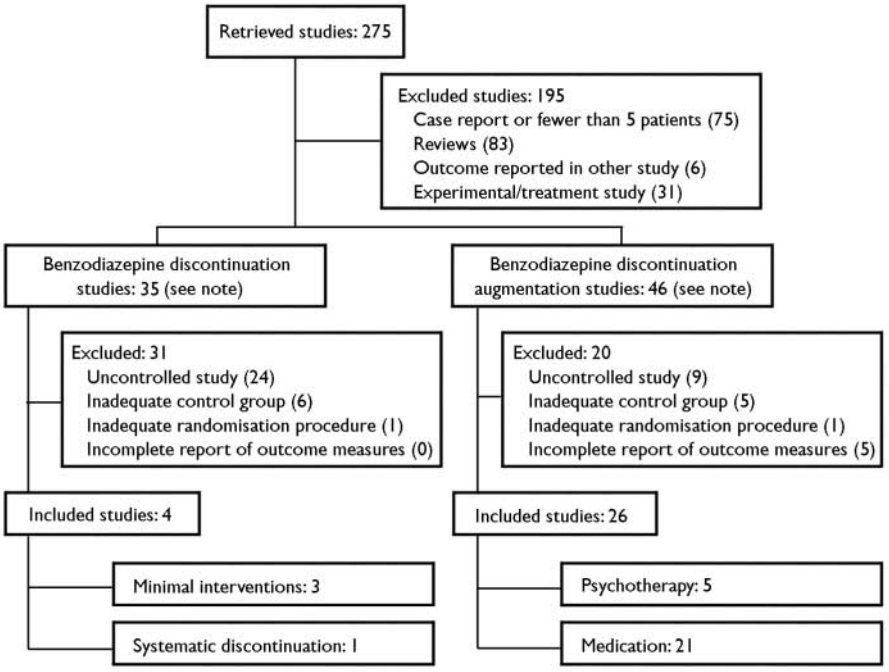

Fig. 1 Search strategy. Note: the study by Oude Voshaar *et al* (2003*a*) was included twice owing to its three-condition randomised controlled design.

(a) inclusion criteria (minimum duration of benzodiazepine use 3.6 or 12 months) and diagnosed benzodiazepine dependence (yes/no);

(b) results at post-treatment outcome;

(c) year of publication;

(d) domain of use (i.e. psychiatric diagnosis or symptoms of included patients);

(e) steps of taper (abrupt, fixed or symptom-guided);

(f) tapered withdrawal after transfer to a long-acting benzodiazepine (yes/no);

(g) history of benzodiazepine use (dosage, type, duration of use);

(h) in-patient treatment (yes/no);

(i) setting (primary care, psychiatric clinic or addiction clinic).

Mean equivalent benzodiazepine dosages were obtained from the articles or calculated in diazepam equivalents (Zitman & Couvée, 2001). If no information was available to calculate the dosage in diazepam equivalents, we categorised the dosages as low (within the therapeutic range, or less than 15 mg), high (above the therapeutic range, or more than 30 mg) or medium (patients using benzodiazepines within and above the therapeutic range, or 15–30 mg).

The quality of the included articles was assessed twice by R.C.O.V., J.E.C. and/or A.J.L.M.v.B. using the Amsterdam–Maastricht consensus list, which covers the Chalmers criteria usually applied in the assessment of study quality (Van Tulder *et al*, 1997; Van Boeijen *et al*, 2005).

Statistical analysis

Since we were interested in the success rates of benzodiazepine discontinuation (binary outcome) and because in some studies data were sparse, we used stratified exact (conditional) methods with odds ratios as fixed-effects association measures. Exact *P*-values for testing significance and homogeneity of odds ratios across studies were calculated, and exact 95% confidence intervals were estimated. In cases in which homogeneity had to be rejected ($P<0.05$) we introduced a random effect in order to account for between-study variability of the odds ratios. In such cases the asymptotic direct pooling method was used for calculating significance levels and confidence limits.

RESULTS

The initial search yielded 5264 reference titles in PubMed, 1260 in PsychINFO and 666 in the Cochrane Library. Of these, 275 titles were identified by R.C.O.V. and J.E.C. as having possible relevance to discontinuation of long-term benzodiazepine use. (The full reference list is presented in data supplement 1 to the online version of this paper.) After screening of the abstracts and if necessary the full text, 246 papers were excluded (Fig. 1) and 29 papers met the inclusion criteria (Tyrer *et al*, 1981; Lader & Olajide, 1987; Ashton *et al*, 1990; Cantopher *et al*, 1990; Jones, 1990; Udelman & Udelman, 1990; Garcia-Borreguero *et al*, 1991; Schweizer *et al*, 1991; Di Costanzo & Rovea, 1992; Lader *et al*, 1993; Otto *et al*, 1993; Bashir *et al*, 1994; Cormack *et al*, 1994; Schweizer *et al*, 1995; Tyrer *et al*, 1996; Lemoine *et al*, 1997; Hantouche *et al*, 1998; Garfinkel *et al*, 1999; Petrovic *et al*, 1999; Rickels *et al*, 1999, 2000; Cialdella *et al*, 2001; Zitman & Couvée, 2001; Gerra *et al*, 2002; Vorma *et al*, 2002; Baillargeon *et al*, 2003; Oude Voshaar *et al*, 2003*a*; Rynn *et al*, 2003; Morin *et al*, 2004).

Table 1 lists the scores for methodological quality of the included studies measured with the Amsterdam–Maastricht consensus list. The sumscore (range 0–18) can be considered to be a proxy of study quality. For studies evaluating psychotherapy augmentation strategies, however, the maximum score is 17. The quality of the included studies ranged from 8 to 17, corresponding with a moderate to excellent study quality. Recency of the study correlated moderately with better quality (Spearman's rank correlation coefficient 0.44, $P=0.02$). Patient numbers and demographic characteristics of the samples in the included papers are summarised in Table 2. The numbers of patients leaving the studies were relatively low, which can be explained by the fact that patient withdrawal was classified as discontinuation failure in the 14 studies reporting intention-to-treat analyses (Table 1). No difference was found in withdrawal rates between studies of different treatment modalities. Compared with those using benzodiazepine in the general population, minimal intervention studies included a higher proportion of women and the participants had a relatively higher age (Zandstra *et al*, 2002). Age and gender distribution of patients recruited in the only controlled study of systematic discontinuation alone was comparable with that of long-term benzodiazepine users in the population, as found by Zandstra *et al* (2002). Systematic discontinuation studies with augmentation strategies, on the contrary, included a lower proportion of women and a relatively lower age compared with the 'average' person using benzodiazepines in the population. The characteristics of the included studies

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Table 1 Validity scores of included studies assessed with the Amsterdam–Maastricht consensus list

	Jones (1990)	Cormack *et al* (1994)	Bashir *et al* (1994)	Oude Voshaar *et al* (2003*a*)	Otto *et al* (1993)	Vorma *et al* (2002)	Baillargeon *et al* (2003)	Morin *et al* (2004)	Tyrer *et al* (1981)	Lader & Olajide (1987)
Validity criteria										
Adequate randomisation procedure	0	+	+	+	+	+	+	+	0	+
Concealed random allocation of treatments	–	+	–	+	–	+	–	0	–	–
Baseline similarity tested	+	–	–	+	+	+	+	+	–	–
Control for co-interventions in design	–	–	–	–	+	+	+	+	0	0
Check for adherence to interventions	+	–	–	+	–	+	+	+	–	+
Valid outcome measures	–	+	–	+	+	+	+	+	–	+
Relevant outcome measures	+	+	+	+	+	+	+	+	+	+
Outcome assessor masked	–	0	0	+	0	0	0	0	0	+
Care provider masked	–	–	–	–	–	–	–	–	+	+
Patient masked	–	–	–	–	–	–	–	–	+	+
Withdrawals (proportion; inequality between groups; reasons for withdrawal reported)	+	+	+	+	+	+	+	+	+	+
Identical timing of outcome assessment for all intervention groups	+	+	+	+	+	+	+	+	–	+
Intention-to-treat analysis	0	–	–	+	+	+	+	+	+	+
Descriptive criteria										
Specification of eligibility criteria	+	+	+	+	+	+	+	+	+	+
Description of the interventions	+	+	+	+	+	+	+	+	+	+
Follow-up	–	–	+	–	+	0	+	+	+	–
Adverse effects	0	–	+	+	+	–	+	+	+	+
Statistical criteria										
Sample size presented at randomisation and outcome	0	–	+	+	+	+	+	+	+	0
Presentation of point estimates and distribution measures	+	0	+	+	+	+	+	+	0	0
Total score (range 0–19)	8	9	10	15	14	14	15	15	10	13

+, Present; –, absent; 0, not reported.

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Table 1 (continued) Validity scores of included studies assessed with the Amsterdam–Maastricht consensus list

	Ashton *et al* (1990)	Cantopher *et al* (1990)	Udelman & Udelman (1990)	Garcia-Borreguero *et al* (1991)	Schweizer *et al* (1991)	Di Costanzo & Rovea (1992)	Lader *et al* (1993)	Schweizer *et al* (1995)	Tyrer *et al* (1996)	Lemoine *et al* (1997)
Validity criteria										
Adequate randomisation procedure	+	+	+	0	+	+	+	+	+	+
Concealed random allocation of treatments	–	–	0	–	–	+	–	–	–	–
Baseline similarity tested	+	+	+	–	+	+	–	–	–	+
Control for co-interventions in design	+	+	+	+	–	0	0	–	–	0
Check for adherence to interventions	+	+	+	–	+	+	+	+	–	+
Valid outcome measures	+	+	+	+	+	+	+	+	0	+
Relevant outcome measures	+	+	+	+	+	+	+	+	+	+
Outcome assessor masked	+	0	0	–	0	+	0	0	0	0
Care provider masked	+	+	+	–	+	0	+	+	+	+
Patient masked	+	+	+	–	+	+	+	+	+	+
Withdrawals (proportion; inequality between groups; reason for withdrawal reported)	+	+	+	+	+	+	+	+	+	+
Identical timing of outcome assessment for all intervention groups	+	+	0	0	+	+	+	+	+	+
Intention-to-treat analysis	0	–	+	+	–	+	0	0	0	+
Descriptive criteria										
Specification of eligibility criteria	+	+	+	+	+	+	+	+	+	+
Description of the interventions	+	+	+	+	+	+	+	+	+	+
Follow-up	+	0	–	–	–	–	–	+	–	+
Adverse effects	+	+	+	+	+	0	+	+	+	+
Statistical criteria										
Sample size presented at randomisation and outcome	+	+	0	0	+	–	–	+	–	–
Presentation of point estimates and distribution measures	0	+	0	+	+	+	+	+	+	+
Total score (range 0–19)	16	15	13	9	14	14	12	14	10	15

+, Present; –, absent; 0, not reported.

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Table 1 (continued) Validity scores of included studies assessed with the Amsterdam–Maastricht consensus list

	Garfinkel *et al* (1999)	Hantouche *et al* (1998)	Petrovic *et al* (1999)	Rickels *et al* (1999)	Rickels *et al* (2000)	Cialdella *et al* (2001)	Zitman & Couvée (2001)	Gerra *et al* (2002)	Rynn *et al* (2003)
Validity criteria									
Adequate randomisation procedure	+	+	0	+	+	+	+	+	+
Concealed random allocation of treatments	–	0	–	–	–	–	+	–	–
Baseline similarity tested	+	+	–	+	+	+	+	+	+
Control for co-interventions in design	–	+	–	–	–	+	–	–	0
Check for adherence to interventions	+	+	–	+	+	+	+	+	+
Valid outcome measures	+	+	+	+	+	+	+	+	+
Relevant outcome measures	+	+	+	+	+	+	+	+	+
Outcome assessor masked	+	+	0	+	+	+	0	–	+
Care provider masked	+	0	–	0	+	+	+	–	+
Patient masked	+	+	+	+	+	+	+	+	+
Withdrawals (proportion; inequality between groups; reasons for withdrawal reported)	+	+	+	+	+	+	+	–	+
Identical timing of outcome assessment for all intervention groups	+	+	+	+	+	+	+	+	+
Intention-to-treat analysis	+	0	+	0	–	0	+	0	–
Descriptive criteria									
Specification of eligibility criteria	0	+	+	+	+	+	+	+	+
Description of the interventions	+	+	+	+	+	+	+	+	+
Follow-up	+	–	–	–	+	–	+	+	+
Adverse effects	+	+	+	+	+	+	+	+	+
Statistical criteria									
Sample size presented at randomisation and outcome	+	+	+	+	–	+	+	0	–
Presentation of point estimates and distribution measures	+	+	+	+	0	+	+	0	+
Total score (range 0–19)	16	15	11	14	14	16	17	10	15

+, Present; –, absent; 0, not reported.

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Table 2 Demographic characteristics of the population in the selected studies

Intervention	Studies *n*	Participants			Gender ratio M : F	Age, mean (years)
		Total *n*	Withdrew *n*	Completed *n*		
Minimal intervention	3	601	75	526	1 : 5	71
Systematic discontinuation alone[1]	1	107	23	84	1 : 2.6	62
Systematic discontinuation with psychotherapy[1]	5	357	40	317	1 : 1.4	56
Systematic discontinuation with pharmacotherapy	21	1333	130	1188	1 : 1.3	52

1. The study by Oude Voshaar *et al* (2003*a*) is included twice because it was a three-condition, controlled study.

according to the main items of the coding form are given in data supplement 2 to the online version of this paper.

Findings of the meta-analysis

The three minimal intervention studies including 298 patients were homogeneous (P=0.76). The pooled odds ratio was 2.8 (95% CI 1.6–5.1). We found only one study that evaluated systematic discontinuation alone using a randomised controlled design (Oude Voshaar *et al*, 2003*a*) which showed an odds ratio of 6.1 (95% CI 2.0–18.6). (Further information is presented in data supplement 2 to the online version of this paper.)

All psychotherapy augmentation strategies evaluated the effect of cognitive–behavioural therapy. These studies appeared to be heterogeneous in outcome values ($P<0.001$), which could be explained by the cofactors setting, benzodiazepine dosage, group *v*. individual therapy and diagnosis (see Table 2). However, the studies of Baillargeon *et al* (2003) and Morin *et al* (2004) appeared to be comparable with respect to all variables evaluated with the coding form. Both studies evaluated group cognitive–behavioural therapy as an augmentation to systematic discontinuation alone using a fixed taper programme in a psychiatric out-patient setting among patients using low-dose benzodiazepines for insomnia. A *post hoc* heterogeneity analysis confirmed this finding (P=1.00) and a pooled odds ratio of 5.5 (95% CI 2.3–14.2) was found.

We found five pharmacological augmentation strategies with the compounds propranolol, buspirone, carbamazepine, trazodone and imipramine which were each evaluated at least twice. Statistical homogeneity was found for the studies evaluating carbamazepine (P=0.22), trazodone (P=0.35) and imipramine (P=0.051). The pooled analysis of studies evaluating the addition of imipramine found a significantly higher discontinuation success rate (P=0.03); augmentation with carbamazepine resulted in a higher success rate of borderline significance (P=0.06); whereas no significant effect was found for the addition of trazodone (P=0.12). The studies evaluating augmentation with propranolol and buspirone were heterogeneous in odds ratios (P=0.02 and P=0.004 respectively). The heterogeneity in odds ratios of the two studies evaluating propranolol was explained by differences in the steps of the tapering procedure, transfer to a long-acting benzodiazepine before dosage tapering, baseline benzodiazepine dosage, type of benzodiazepine and finally the diagnosis of included patients. The heterogeneity in odds ratios of the five studies evaluating buspirone was explained by the transfer to a long-acting agent, hospitalisation, baseline benzodiazepine dosage, type of benzodiazepine used before tapering, and diagnosis of included patients. Closer inspection did not reveal combinations of studies evaluating the addition of buspirone that might be homogeneous. Using a random-effects model we also did not find significant effects of the addition of propranolol (P=0.77) and buspirone (P=0.59).

DISCUSSION

The main finding of our meta-analysis was that minimal interventions are effective strategies for reducing benzodiazepine consumption, yielding an odds ratio of 2.8 in comparison with patients receiving usual care. More-intensive treatment in the form of systematic discontinuation with or without therapeutic augmentation was only once compared with usual care (Oude Voshaar *et al*, 2003*a*), with the finding of an odds ratio for patients receiving systematic discontinuation alone of 6.1. Although the clinical relevance was limited by the fact that systematic discontinuation alone was evaluated in one study only, the 62% success rate of systematic discontinuation alone in this study was comparable with the median success rate of 58% (range 25–100) in the control groups of studies evaluating systematic discontinuation augmentation strategies which consisted of systematic discontinuation alone or systematic discontinuation with placebo. Moreover, two large and well-designed (but uncontrolled) studies of benzodiazepine discontinuation also found discontinuation success rates of 62% (Rickels *et al*, 1990; Schweizer *et al*, 1990). The three minimal intervention studies, as well as the study by Oude Voshaar *et al* (2003*a*), were conducted in general practice. Therefore, evidence for treatment of patients referred for help with benzodiazepine discontinuation is scarce.

A total of 17 different augmentation strategies were evaluated. Although these studies were conducted in a variety of settings, the age and gender distribution of patients in the samples suggests selective recruitment towards younger, male patients. Six augmentation strategies were evaluated in at least two studies each; for imipramine, carbamazepine and trazodone augmentation the studies were homogeneous. Of these three agents, only for imipramine was a significantly superior effect on benzodiazepine discontinuation success rate found (P=0.03); the effect of carbamazepine did not reach significance (P=0.06). A *post hoc* analysis showed that

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group cognitive–behavioural therapy had additive value for patients using low-dose benzodiazepines (<15 mg diazepam equivalent) for insomnia. Finally, the following strategies showed significantly higher benzodiazepine discontinuation success rates in single studies: group cognitive–behavioural therapy for patients with panic disorder, melatonin therapy for patients with insomnia, and for long-term benzodiazepine use generally also sodium valproate or flumazenil (Otto *et al*, 1993; Garfinkel *et al*, 1999; Rickels *et al*, 1999; Gerra *et al*, 2002).

Limitations

Large generalisations from our meta-analysis are limited owing to heterogeneity of the included studies. We strove to explain heterogeneity with variables that have previously been suggested to be associated with discontinuation outcome (Ashton *et al*, 1990; Rickels *et al*, 1990, 2000; Schweizer *et al*, 1990, 1998; Murphy & Tyrer, 1991; Oude Voshaar *et al*, 2003*b*). However, the current state of knowledge precludes any firm conclusion as to the effects of these variables. In addition, more important variables might not have been identified or measured in the included studies, such as a clear DSM–IV Axis I diagnosis (American Psychiatric Assocation, 1994) or personality characteristics. For example, in a relatively large, uncontrolled study (n=165) personality factors were found to explain 24% of the variance in discontinuation outcome (Schweizer *et al*, 1998).

Clinical implications

Although establishing the efficacy of individual treatment strategies is clinically relevant, stepped care approaches are even more important for treatment planning in the case of treatment-resistant benzodiazepine dependence. This meta-analysis was conducted in order to establish the clinical evidence for the individual steps in a stepped care approach in order to discontinue long-term benzodiazepine use. Following the stepped care approach proposed by Russell & Lader (1993), we now know that use of the first two steps – namely starting with a minimal intervention strategy, followed by systematic discontinuation alone for cases resistant to treatment in primary care – is supported by the results of randomised controlled trials. With respect to this statement, it has to be mentioned that the single study evaluating systematic discontinuation alone was conducted among people with long-term benzodiazepine use who did not respond to a minimal intervention strategy (Oude Voshaar *et al*, 2003*a*; Gorgels *et al*, 2005). However, much research has still to be conducted in this field; for example, we do not know which variables and treatment characteristics are associated with a favourable outcome. The taper schedules described in published studies vary from abrupt discontinuation (Rickels *et al*, 1990), to 25% weekly reduction of dosage (Schweizer *et al*, 1990; Oude Voshaar *et al*, 2003*a*), discontinuation in steps of about one-eighth of the daily dose every 2 weeks (Russell & Lader, 1993) to, finally, symptom-guided withdrawal with the time needed for withdrawal varying from about 4 weeks to a year or more (Ashton, 1987). However, different taper schedules have never been directly compared in a randomised controlled study. We also do not know which strategy should be followed if the first two steps fail. Although augmentation was not evaluated among patients who failed to discontinue their benzodiazepine use by systematic discontinuation alone, our meta-analysis found a higher discontinuation success rate after the addition of imipramine and carbamazepine in general, or group cognitive–behavioural therapy for patients with insomnia. Moreover, adding sodium valproate or flumazenil and adding melatonin or group cognitive–behavioural therapy in specific patient groups (e.g. those with panic disorder) can be an option. It should be noted that these suggestions are based on small, single studies (patient numbers n=27 to n=40). Future research should evaluate more rigorously stepped care programmes and promising augmentation strategies.

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REFERENCES

American Psychiatric Assocation (1994) *Diagnostic and Statistical Manual of Mental Disorders* (DSM–IV). Washington, DC: APA.

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

Ashton, C. H., Rawlins, M. D. & Tyrer, S. P. (1990) A double-blind placebo-controlled study of buspirone in diazepam withdrawal in chronic benzodiazepine users. *British Journal of Psychiatry*, **157**, 232–238.

Baillargeon, L., Landreville, P., Verreault, R., *et al* (2003) Discontinuation of benzodiazepine among older insomniac adults treated with cognitive–behavioural therapy combined with gradual tapering: a randomized trial. *Canadian Medical Association Journal*, **169**, 1015–1020.

Bashir, K., King, M. & Ashworth, M. (1994) Controlled evaluation of brief intervention by general practitioners to reduce chronic use of benzodiazepines. *British Journal of General Practice*, **44**, 408–412.

Cantopher, T., Olivieri, S., Cleave, N., *et al* (1990) Chronic benzodiazepine dependence. A comparative study of abrupt withdrawal under propranolol cover versus gradual withdrawal. *British Journal of Psychiatry*, **156**, 406–411.

Cialdella, P., Boissel, J. P. & Belon, P. (2001) Homeopathic specialties as substitutes for benzodiazepines: double-blind *v.* placebo study. *Thérapie*, **56**, 397–402.

Cormack, M. A., Sweeney, K. G., Hughes-Jones, H., *et al* (1994) Evaluation of an easy, cost-effective strategy for cutting benzodiazepine use in general practice. *British Journal of General Practice*, **44**, 5–8.

Di Costanzo, E. & Rovea, A. (1992) [The prophylaxis of benzodiazepine withdrawal syndrome in the elderly: the effectiveness of carbamazepine. Double-blind study *v.* placebo] (in Italian). *Minerva Psychiatrica*, **33**, 301–304.

Garcia-Borreguero, D., Bronisch, T., Apelt, S., *et al* (1991) Treatment of benzodiazepine withdrawal symptoms with carbamazepine. *European Archives of Psychiatry and Clinical Neuroscience*, **241**, 145–150.

Garfinkel, D., Zisapel, N., Wainstein, J., *et al* (1999) Facilitation of benzodiazepine discontinuation by melatonin: a new clinical approach. *Archives of Internal Medicine*, **159**, 2456–2460.

Gerra, G., Zaimovic, A., Giusti, F., *et al* (2002) Intravenous flumazenil versus oxazepam tapering in the treatment of benzodiazepine withdrawal: a randomized, placebo-controlled study. *Addiction Biology*, **7**, 385–395.

Gorgels, W. J. M. J., Oude Voshaar, R. C., Mol, A. J. J., *et al* (2005) Discontinuation of long-term

https://doi.org/10.1192/bjp.189.3.213 Published online by Cambridge University Press

benzodiazepine use by sending a letter to users in family practice: a prospective controlled intervention study. *Drug and Alcohol Dependence*, **78**, 49–56.

Hantouche, E. G., Guelfi, J. D. & Comet, D. (1998) [Alpha-beta L-aspartate magnesium in treatment of chronic benzodiazepine misuse: controlled and double-blind study versus placebo] (in French). *Encéphale*, **24**, 469–479.

Jones, D. (1990) Weaning elderly patients off psychotropic drugs in general practice: a randomised controlled trial. *Health Trends*, **22**, 164–166.

Lader, M. (1991) History of benzodiazepine dependence. *Journal of Substance Abuse and Treatment*, **8**, 53–59.

Lader, M. & Olajide, D. (1987) A comparison of buspirone and placebo in relieving benzodiazepine withdrawal symptoms. *Journal of Clinical Psychopharmacology*, **7**, 11–15.

Lader, M., Farr, I. & Morton, S. (1993) A comparison of alpidem and placebo in relieving benzodiazepine withdrawal symptoms. *International Clinical Psychopharmacology*, **8**, 31–36.

Lemoine, P., Touchon, J. & Billardon, M. (1997) [Comparison of 6 different methods for lorazepam withdrawal. A controlled study, hydroxyzine versus placebo] (in French). *Encéphale*, **23**, 290–299.

Morin, C. M., Bastien, C., Guay, B., *et al* (2004) Randomized clinical 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.

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.

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.

Otto, M. W., Pollack, M. H., Gould, R. A., *et al* (2000) A comparison of the efficacy of clonazepam and cognitive–behavioral group therapy for the treatment of social phobia. *Journal of Anxiety Disorders*, **14**, 345–358.

Oude Voshaar, R. C., Gorgels, W. J. M. J., Mol, A. J. J., *et al* (2003*a*) 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., Mol, A. J. J., Gorgels, W. J. M. J., *et al* (2003*b*) Cross-validation, time course and predictive validity of the Benzodiazepine Dependence Self-Report Questionnaire in a benzodiazepine discontinuation trial. *Comprehensive Psychiatry*, **44**, 247–255.

Petrovic, M., Pevernagic, D., Van den Noortgate, N., *et al* (1999) A programme for short-term withdrawal from benzodiazepines in geriatric hospital inpatients: success rate and effect on subjective sleep quality. *International Journal of Geriatric Psychiatry*, **14**, 754–760.

Rickels, K., Schweizer, E., Case, W. G., *et al* (1990) Long-term therapeutic use of benzodiazepines. I. Effects of abrupt discontinuation. *Archives of General Psychiatry*, **47**, 899–907.

Rickels, K., Schweizer, E., Garcia, E. F., *et al* (1999) Trazodone and valproate in patients discontinuing long-term benzodiazepine therapy: effects on withdrawal symptoms and taper outcome. *Psychopharmacology (Berlin)*, **141**, 1–5.

Rickels, K., DeMartinis, N., Garcia-Espana, F., *et al* (2000) Imipramine and buspirone in treatment of patients with generalized anxiety disorder who are discontinuing long-term benzodiazepine therapy. *American Journal of Psychiatry*, **157**, 1973–1979.

Russel, V. J. & Lader, M. H. (eds) (1993) *Guidelines for the Prevention and Treatment of Benzodiazepine Dependence*. London: Mental Health Foundation.

Rynn, M., Garcia-Espana, F., Greenblatt, D. J., *et al* (2003) Imipramine and buspirone in patients with panic disorder who are discontinuing long-term benzodiazepine therapy. *Journal of Clinical Psychopharmacology*, **23**, 505–508.

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

Schweizer, E., Rickels, K., Case, W. G., *et al* (1991) Carbamazepine treatment in patients discontinuing long-term benzodiazepine therapy. Effects on withdrawal severity and outcome. *Archives of General Psychiatry*, **48**, 448–452.

Schweizer, E., Rickels, K., Weiss, S., *et al* (1993) Maintenance drug treatment of panic disorder. I. Results of a prospective, placebo-controlled comparison of alprazolam and imipramine. *Archives of General Psychiatry*, **50**, 51–60.

Schweizer, E., Case, W. G., Garcia-Espana, F., *et al* (1995) Progesterone co-administration in patients discontinuing long-term benzodiazepine therapy: effects on withdrawal severity and taper outcome. *Psychopharmacology (Berlin)*, **117**, 424–429.

Schweizer, E., Rickels, K., De Martinis, N., *et al* (1998) The effect of personality on withdrawal severity and taper outcome in benzodiazepine dependent patients. *Psychological Medicine*, **28**, 713–720.

Stillwell, G. & Fountain, J. (2002) *Benzodiazepine Use – A Report of a Survey of Benzodiazepine Consumption in the Member Countries of the Pompidou Group*. Geneva: World Health Organization.

Taylor, S., McCracken, C. F., Wilson, K. C., *et al* (1998) Extent and appropriateness of benzodiazepine use. Results from an elderly urban community. *British Journal of Psychiatry*, **173**, 433–438.

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

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

Udelman, H. D. & Udelman, D. L. (1990) Concurrent use of buspirone in anxious patients during withdrawal from alprazolam therapy. *Journal of Clinical Psychiatry*, **51** (suppl.), 46–50.

Van Boeijen, C. A., Van Balkom, A. J. L. M., Van Oppen, P., *et al* (2005) Efficacy of self-help manuals for anxiety disorders in primary care, a review. *Family Practice*, **22**, 192–196.

Van Tulder, M. W., Assendelft, W. J. J., Koes, B. W., *et al* (1997) Methodologic guidelines for systematic reviews in the Cochrane Collaboration Back Review Group for Spinal Disorders. *Spine*, **22**, 2323–2330.

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.

Zandstra, S. M., Führer, J. W., Van de Lisdonk, E. H., *et al* (2002) Different study criteria affect the prevalence of benzodiazepine use. *Social Psychiatry and Psychiatric Epidemiology*, **37**, 139–144.

Zandstra, S. M., Van Rijswijk, E., Rijnders, C. A., *et al* (2004) Long-term benzodiazepine users in family practice: differences from short-term users in mental health, coping behaviour and psychological characteristics. *Family Practice*, **21**, 266–269.

Zitman, F. G. & Couvée, J. E. (2001) 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. *British Journal of Psychiatry*, **178**, 317–324.

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