Kayalvili Mugunthan, Treasure McGuire and Paul Glasziou

Minimal interventions to decrease long-term use of benzodiazepines in primary care:

a systematic review and meta-analysis

Abstract

Background
Long-term use of benzodiazepines (BZDs) is common. Not only is such use ineffective, but it also has several risks in addition to dependence, and remains a significant problem among the older population.

Aim
To systematically review randomised controlled trials that evaluate the effectiveness of minimal interventions to reduce the long-term use of BZDs in primary care.

Design and setting
Systematic review and meta-analysis of randomised controlled trials in UK general practices.

Method
Cochrane Central, MEDLINE, and Embase (1967–2010) were searched for trials of minimal interventions (such as a single letter or one consultation from a GP) for patients in primary care with long-term (>3 months) BZD use. Pooled risk differences were calculated with 95% confidence intervals.

Results
From 646 potentially relevant abstracts, three studies (615 patients) met all the inclusion criteria. The pooled risk ratio showed a significant reduction/cessation in BZD consumption in the minimal intervention groups compared to usual care (risk ratio [RR] = 2.04, 95% confidence interval [CI] = 1.5 to 2.8, $P<0.001$; RR = 2.3, 95% CI = 1.3 to 4.2, $P = 0.008$) respectively. Two studies also reported a significant proportional reduction in consumption of BZD from baseline to 6 months in intervention groups compared to the control group. The secondary outcome of general health status was measured in two studies; both showed a significant improvement in the intervention group.

Conclusion
A brief intervention in the form of either a letter or a single consultation by GPs, for long-term users of BZD, is an effective and efficient strategy to decrease or stop their medication, without causing adverse consequences.

Keywords
benzodiazepines; cessation of treatment; long term care; patient education as topic; primary care; reduction.

INTRODUCTION

Long-term use of benzodiazepines (BZDs) is common for anxiety disorders, insomnia, and alcohol withdrawal, as adjuvant therapy in schizophrenia and depression, and as muscle relaxants. Their short-term benefits are well recognised, but their long-term use has risks in addition to dependence: daytime somnolence, blunted reflexes, memory impairment, and an increased risk of falls and hip fractures in older people. In a recent review comparing sedatives with placebo, cognitive events were 4.8 times, adverse psychomotor events 2.6 times, and reports of daytime fatigue 3.8 times more common, respectively.[1] Hence, long-term BZD use is usually inappropriate, and these drugs should be used only in limited circumstances, for short periods.[2,3]

The most common long-term use is for sleeping problems; at least 10% of adults complain of significant insomnia, with incident use of a hypnotic drug increasing with age.[4] In the community, hypnotic use in those aged over 65 years is at least double (14%) that of younger people.[5] It is even higher in older patients attending medical practices, with 26% of women and 6% of men using sleep medications.[6] In North America and the UK, 5% to 33% of older people have been prescribed a BZD or a BZD receptor agonist (zolpidem, zopiclone, zaleplon) for sleep problems.[7,8]

While long-term use is becoming less common, it remains a significant problem. In a study of patients in south-east London, 1.5% of men and 3.5% of women were found to be taking BZDs every day, and an estimated quarter of a million people in the UK took them for over 7 years.[9] In Australia, of the total Pharmaceutical Benefits Scheme (PBS) medicines obtained by doctor-shoppers, 36% were BZDs.[10] Despite an overall fall in BZD prescriptions internationally over the last 20 years, a substantial number of long-term users receive regular prescriptions, especially for hypnotics.[10–15] In 2009 in the UK, there were still 4.2 million benzodiazepine items (used to treat insomnia) dispensed, at a cost of £19 million.[15]

Long-term use is not only ineffective, but is also associated with several undesirable side effects. The risk of adverse events, particularly falls and cognitive impairment, is higher in older people; and the benefits of these drugs may not be justified. Thus, reduction in the long-term use of BZDs in primary care settings is important. As has been demonstrated in several trials, withdrawal of BZDs should be flexible, and a key element is a slow step-down process of about 25% reduction each week. Trials have shown successful reduction with many interventions, but most are resource intensive and require several clinical visits. In some trials, a simple letter was used as the only intervention, which may be more widely applicable. Therefore, this study aimed to systematically review randomised controlled trials that evaluated the effectiveness of minimal intervention to reduce or cease the long-term use of BZDs in adults in primary care.

K Mugunthan, MBBS, MHst (clinical epidemiology), researcher; **T McGuire**, PhD, BPharm, PostgradDipClinHospPharm, associate professor of Pharmacology; **P Glasziou**, PhD, FRACGP, professor, Faculty of Health Sciences & Medicine, Bond University, Gold Coast, Australia.

Address for correspondence
Kayalvili Mugunthan, Faculty of Health Sciences & Medicine, CREBP, Bond University, Gold Coast, QLD 4229, Australia.

E-mail: kmugunth@bond.edu.au

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How this fits in

This review found that long-term benzodiazepine (BZD) use could be reduced by 'minimal interventions' — a simple tailored letter or consultation. The trials are consistent, but also show that various enhancements do not increase effectiveness. For the tailored letter, the 'number needed to post' is about 12 for one additional person to cease BZD use. Widespread use of this strategy would be clinically and economically worthwhile.

METHOD

This review included primary care studies that were randomised controlled trials, with 'minimal intervention' for BZD withdrawal. Minimal intervention was defined as a letter, self-help information, or short consultation with a GP. These explained:

- concern over the patient's long-term use of hypnotics;
- their potential side effects; and
- advice for patients to gradually reduce or cease their BZD, with less likelihood of withdrawal symptoms.

The patients included in the trials were adults aged over 18 years (males or females) who had long-term benzodiazepine usage (>3 months). Case series, review papers, and duplicate publications were excluded.

Search methods

The Cochrane Central Register of Controlled Trials, MEDLINE and Embase databases (January 1967 to August 2010) were searched. The following medical subject heading (MeSH) search terms were used: [exp]"Substance-Related Disorders" AND [exp] benzodiazepines AND (withdraw* OR discontinu* OR reduc* OR letter OR quit) AND ((Clinical Trial[ptyp] OR Randomized Controlled Trial[ptyp])), with adapted versions for Cochrane and Embase. There were no language or publication restrictions. The references of all identified studies and of relevant systematic reviews were checked. Two review authors and an expert librarian carried out the search.

Data extraction and management

Two review authors independently reviewed and selected trials from searches. Two authors then assessed the trials, rated the study quality, and extracted relevant data. Disagreements were resolved through discussion with the third author. Trial authors were contacted to request missing data or to clarify methods where needed.

The aspects of trial quality assessed were: quality of randomisation; quality of blinding (allocation concealment); and analysis by intention-to-treat (ITT).

Data were extracted using a standardised form. Information included: age and sex of participants; treatment setting; average initial dose of BZDs; number of participants; whether analysis was by ITT; randomisation method; exclusion criteria; outcomes in relation to BZD use; and general health status (for example, measured by a 12-item General Health Questionnaire [GHQ] and/or Short Form [36] Health Survey [SF-36]); adverse effects of withdrawal; and other medicines being used, including those with potential drug interactions.

Meta-analytic calculations were done with Meta-Analyst, with risk ratios (RRs)

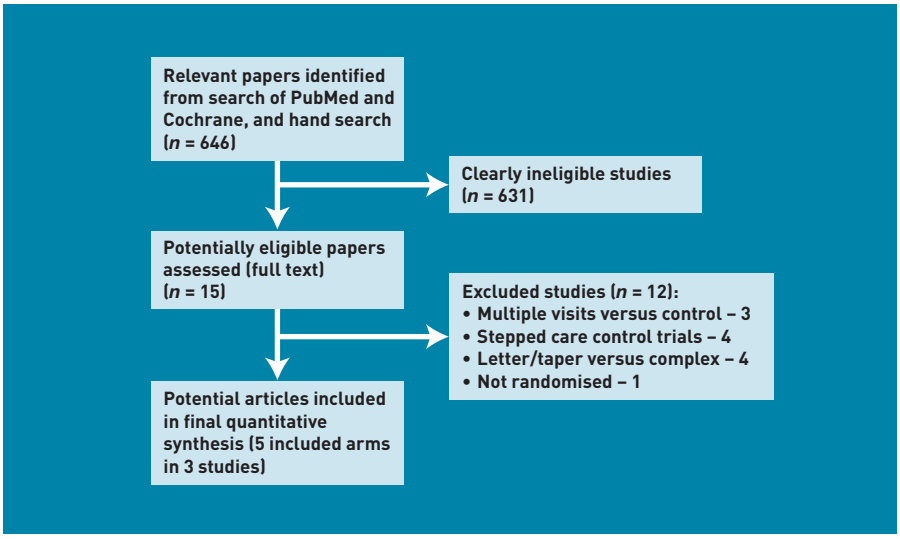

Figure 1. Flow chart of search and study selection.

Table 1. Key features of included BZD-withdrawal trials

Study characteristics	Bashir *et al*, 1994[16]	Cormack *et al*, 1994[17]	Heather *et al*, 2004[18]
Number of participants	109	222	284
Setting; patients	UK general practice; patients with long-term BZD use	UK general practice; patients with long-term BZD use	UK general practice; patients with long-term BZD use
Follow-up	6 months	6 months	6 months
Interventions	One consultation from GP + self-help booklet[a] to reduce gradually/ stop drug	Group 1: single letter from GP[b]; group 2: letter[b] + 4-monthly information sheets[a] on reducing medication and coping with withdrawal	Group 1: letter from GP to reduce gradually/ stop drug[b]; group 2: consultation and self-help booklet[a]
Comparison	Allowed to continue usual dose	Allowed to continue usual dose	Allowed to continue usual dose
Outcome measures			
BZD usage	Prescription records	Prescription records	Prescription records
Health questionnaire	GHQ	—	GHQ and SF-36
Methodological quality of studies			
Adequate randomisation?	Yes (used date of birth with baseline equality)	Yes	Yes
Baseline similarity?	No	Unclear	Yes
Groups treated equally?	Yes	Unclear	Unclear
Loss to follow-up	3.7% (BZD reduction), 15% (GHQ)	5.8%	3.9% (BZD reduction), 30% (GHQ)
Outcomes measures blind or objective?	Unblinded but objective prescription records	Unblinded but objective prescription records	Unblinded but objective prescription records

[a]Sample not provided; [b]sample provided. BZD = benzodiazepines. GHQ = general health questionnaire. SF = short-form.

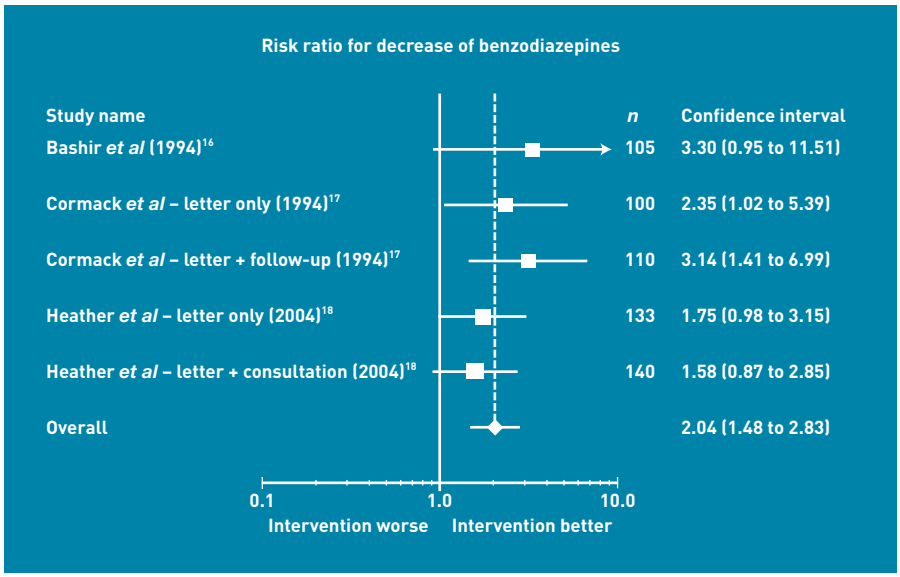

Figure 2. Risk ratio for decrease of benzodiazepine use.

calculated using a random effects model. A pooled risk difference was also estimated, to allow a number needed to treat (NNT) to be calculated.

RESULTS

Of 646 potentially relevant abstracts retrieved, 25 relevant abstracts were selected for detailed evaluation by two reviewers. Fifteen potentially useful full-text articles were retrieved for further evaluation, and only three papers that fulfilled the main inclusion criteria were finally included for review.[16–18] Two of these trials were three-arm studies that included two active interventions. Hence, five interventions were available (Figure 1).

The studies (Table 1) had a high proportion of women (>60%), and participants' mean age was above 60 years. The BZD dosage in all included trials was expressed in terms of diazepam equivalents, either 5 mg or 10 mg. The numbers of patients lost to follow-up in all three studies were low. No difference was found in withdrawal rates between studies of different treatment modalities.

Reduction or cessation of benzodiazepine use

All three studies reported statistically significant reductions in BZD consumption with the minimal intervention group compared to control groups (Figure 2). Effect sizes varied minimally between studies: there was no significant heterogeneity (I^2 = 0.0 %, P = 0.59). The pooled results indicated a relative benefit increase, with twice the reduction in BZD consumption in the intervention groups — either letter or letter and short consultation groups — compared to the control group (RR = 2.04 95% confidence interval [CI] = 1.5 to 2.8, P<0.001). In the pooled analysis of cessation of BZD use (Figure 3), the intervention group appeared to be superior, with twice the rate of cessation of the usual care group. The RR for cessation in BZD use was 2.3 (95% CI = 1.3 to 4.2, P = 0.008). There was no significant heterogeneity (I^2 = 0.0%, P = 0.79). To allow calculation of a NNT, the pooled risk difference was also calculated, which was a difference of 0.08 (95% CI = 0.03 to 0.13), and hence the NNT was 12.

Of the three studies, two reported the proportional BZD reduction from baseline to 6-month follow-up period.[17,18] There was an observed 20–35% reduction in the intervention group compared to the control group (10–15%). The standard deviation of proportional reduction was only available for two studies,[17,18] and is summarised in Table 2.

Secondary outcome

In the study by Bashir *et al*, at the 6-month follow-up period, the proportion of patients who suffered from psychiatric morbidity, according to the GHQ, was 11% lower in the intervention compared to the control group (3%).[16] The intervention group that reported reduction in BZD usage showed a modest psychiatric improvement over the trial

Table 2. Reduction in benzodiazepine use across studies

	Bashir *et al*, 1994[16]		Cormack *et al*, 1994[17]			Heather *et al*, 2004[18]		
	Letter	Control	Letter	Letter + follow-up	Control	Letter	Letter + consultation	Control
Number	50	55	65	75	69	88	95	89
Decreased BZD	9	3	24	37	11	36	35	21
Ceased BZD	9	3	15	10	4	9	10	6
Proportional BZD reduction over 6 months			0.32	0.37	0.1	0.24	0.22	0.16
Standard deviation of reduction			0.43	0.41	0.44	0.93	0.94	0.93

BZD = benzodiazepine.

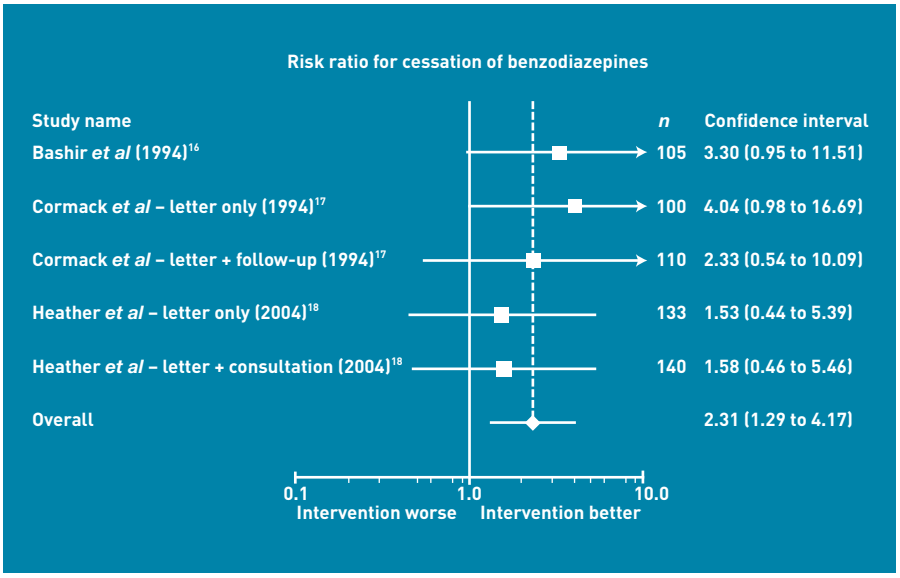

Figure 3. Risk ratio for cessation of benzodiazepines.

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Provenance

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Competing interests

The authors have declared no competing interests.

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period, according to the GHQ. In comparison, the control group had unchanged qualitative and quantitative symptoms over the 6 months. In the study by Heather *et al*, there was no significant difference between study groups on the SF-36 overall scores.[18] However, there was a significant difference in changes on the SF-36 subscore ('mental') in patients who had undergone a true reduction and those who had not ($\chi^2 = 7.0$; $P = 0.008$), with 'true reducers' showing a mean increase of 5.4, compared to a decline of 2.2 in those who were not 'true reducers'. Similarly, there was no significant change in GHQ-total score between follow-up and initial assessment, nor any significant differences between groups in relation to changes in somatic symptoms, anxiety, or insomnia (on GHQ subscales). There was a modest correlation ($\rho = 0.20$; $P = 0.011$) between changes in BZD intake and changes in GHQ-B (anxiety and insomnia).

DISCUSSION

Summary

The three trials identified in this review found that a simple letter intervention could reduce BZD usage in older patients on long-term BZDs. The effect was substantial, with one cessation of benzodiazepines for every 12 letters sent. There appeared to be no additional advantage in either self-help information or a short consultation with a GP.

Strengths and limitations

There were some minor flaws in all trials: one study had weak randomisation methods and some baseline inequality; all had minor loss to follow-up. However, these flaws seem unlikely to explain the size of the effects seen. A fourth paper was excluded because of lower quality, but showed similar results.[19] However, the consistency of the results across different measures and different studies is reassuring.

Comparison with existing literature

This review is consistent with a previous review, which found that a number of interventions are able to reduce BZD use.[20] Most of these interventions, however, involved levels of skill and resource usage that would not be feasible for widespread use. The letter interventions used were similar in the trials, and were adapted from the first study by Cormack *et al*.[17] In their letters, both Cormack *et al* and Heather *et al* explained why BZDs should not be continued for prolonged periods. However, the recommended method of discontinuation was slightly different (Appendix 1). The main barrier to implementation will be GP practices' ability to generate a list of patients for whom the letter is appropriate. However, when this is not possible, GPs could consider simply giving the letter to appropriate patients when they consult.

Implications for practice and research

Given the problems of cognitive impairment and falls induced by BZDs and other hyposedatives, the routine and widespread use of this simple letter intervention appears warranted. While only a modest percentage of patients will reduce or cease their BZD, the minimal effort required suggests it would have a high benefit-to-effort ratio. However, further research is needed to find

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Appendix 1. Key elements of primary care practitioners' letters to reduce hypnotic use

- Explain your concern over the individual patient's long-term use of a hypnotic/s — ideally name the specific drug(s) and possibly the extent of use over a defined period.
- Highlight potential side effects when taken over a prolonged period.
- Ask the patient to consider a reduction in their use.
- Include advice on how to feasibly, gradually, and safely reduce or cease use.

OR

- Include advice on how to gradually reduce or cease use in a manner that is not only feasible but can also decrease the likelihood of withdrawal symptoms.
- Invite the patient to discuss the issue further with you.