Benzodiazepines in generalized anxiety disorder: heterogeneity of outcomes based on a systematic review and meta-analysis of clinical trials

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CRD summary
The authors concluded that, based on withdrawal rates, there was no robust evidence to support the short-term effectiveness of benzodiazepines for generalised anxiety disorder, but there was robust evidence for efficacy. The robustness of the conclusions is difficult to assess in view of the poor reporting of review methods and outcome definitions, as well as the differences between the studies.

Authors' objectives
To evaluate the efficacy and effectiveness of benzodiazepines in patients with generalised anxiety disorder (GAD) using drop-out rates from trials.

Searching
MEDLINE, EMBASE and the Cochrane Controlled Trials Register were searched from inception to January 2005 for reports in any language; the search terms were reported. In addition, reference lists of retrieved papers and the Internet were screened.

Study selection
Study designs of evaluations included in the review
Double-blind randomised controlled trials (RCTs) were eligible for inclusion. The duration of most of the included studies was 4 weeks; in only one was the duration greater than 8 weeks.

Specific interventions included in the review
Studies that compared the benzodiazepines diazepam, lorazepam or alprazolam with placebo were eligible for inclusion in the review.

Participants included in the review
Studies of patients with GAD were eligible for inclusion. The patients in the included studies were aged from 17 to 70 years and most had been diagnosed using the American Psychiatric Association's DSM-III and DSM-III-R criteria; a minority of studies used DSM-IV criteria. Where reported, the majority of studies were of out-patients. The most common exclusion criteria were concomitant psychiatric disorders, consumption or abuse of substances, and other medical conditions.

Outcomes assessed in the review
Inclusion criteria were not specified in terms of the outcomes but it was clear that the review focused on withdrawal rates. The review assessed withdrawal for any reasons, withdrawals due to lack of efficacy and withdrawal due to adverse events (principal outcome measure).

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
Only double-blind RCTs were included. The authors also reported allocation concealment, but they did not state how the validity assessment was performed.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. Data on withdrawals were extracted.
Methods of synthesis
How were the studies combined?
Pooled relative risks (RRs) and 95% confidence intervals (CIs) were calculated using the fixed-effect Mantel-Haenszel method; the DerSimonian and Laird random-effects model was used when moderate heterogeneity was found. Publication bias was assessed using Begg’s funnel plot with pseudo-95% CIs.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the chi-squared and I-squared statistics (chi-squared p>0.05 and I-squared >50% indicated heterogeneity). Potential sources of heterogeneity were sought by examining forest plots. Meta-regression was used to examine the influence on the results of year of publication. Subgroup analysis was used to examine the influence of diagnostic criteria and specific benzodiazepine on the risk of withdrawal for any reason; it is not clear whether these were also post-hoc analyses. Other potential causes of differences between the studies were discussed.

Results of the review
Twenty-three RCTs (n=2,326) were included.

The authors stated that lack of reporting of allocation concealment was the main methodological problem.

Withdrawal for any reason (23 RCTs, n=2,326): statistical heterogeneity was found (chi-squared p=0.007; I-squared 47.4%). There was a reduction in the risk of withdrawal for any reason in patients receiving benzodiazepines compared with placebo (random-effects RR 0.78, 95% CI: 0.62, 1.0, p=0.05).

Withdrawal due to lack of efficacy (20 RCTs, n=2,061): no statistical heterogeneity was found (I-squared 0%; p=0.15). There was a large reduction in the risk of withdrawal due to lack of efficacy in patients receiving benzodiazepines compared with placebo (fixed-effect RR 0.29, 95% CI: 0.18, 0.45, p<0.00001).

Withdrawal due to adverse events (19 RCTs, n=1,950): very little heterogeneity was found (I-squared 26.8%; p=0.15). There was an increase in the risk of withdrawal due to adverse events in patients receiving benzodiazepines compared with placebo (fixed-effect RR 1.54, 95% CI: 1.17, 2.03, p=0.002).

Exploration of heterogeneity.

The risk of withdrawal for any reason associated with benzodiazepines compared with placebo was significantly reduced in studies using DSM-III criteria (11 RCTs) and significantly increased in studies using DSM-IV criteria (3 RCTs); in studies using DSM-III-R criteria there was no significant difference between treatment groups (8 RCTs). No heterogeneity was found for any of these subgroup analyses.

The risk of withdrawal for any reason was significantly reduced in patients receiving diazepam (12 statistically homogeneous RCTs) and alprazolam (4 statistically heterogeneous RCTs) compared with placebo; there was no significant difference between lorazepam and placebo (7 statistically heterogeneous RCTs).

Meta-regression showed that 74% of the variation between studies was accounted for by year of publication, with smaller treatment effects being found in more recent publications.

There was some evidence of publication bias (Begg’s test p<0.012).

Authors’ conclusions
There was no robust evidence to support the short-term effectiveness of benzodiazepines in patients with GAD, but there was robust evidence for efficacy. Differences between the studies with respect to year of publication and other factors may explain these dissimilar results.

CRD commentary
The review question was clear with respect to the participants, intervention, outcomes and study design. Several relevant sources were searched and no language restrictions were applied. No attempts were made to minimise publication bias;
the potential for this was assessed and some evidence of it was found. The methods used to select studies, assess validity and extract the data were not described, so it is not known whether any efforts were made to reduce reviewer error and bias. All of the included studies were double-blind RCTs and so were likely to be of reasonable quality. The methods used to define lack of efficacy in the included studies were not reported and neither were drug doses, thus it was not clear whether studies used comparable definitions and drug doses. Statistical heterogeneity was assessed and potential sources were investigated. The robustness of the conclusion was difficult to assess in view of the lack of reporting of review methods, lack of clear reporting of definitions used for 'loss of efficacy' in the included studies, and differences between the studies.

**Implications of the review for practice and research**
The authors did not state any implications for practice or further research.

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