A meta-analytic review of the efficacy of drug treatment in generalized anxiety disorder

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CRD summary
This review assessed the efficacy of drug treatment for generalised anxiety disorder (GAD). The authors concluded that drug treatment, particularly with benzodiazepines, is effective for the short-term treatment of GAD. Poor reporting of review methods, along with a lack of detail on individual studies and study quality, make it difficult to assess the reliability of the authors' conclusions.

Authors' objectives
To assess the efficacy of pharmacological treatment for generalised anxiety disorder (GAD), and to compare the effects of benzodiazepines and azapirones.

Searching
MEDLINE and PsycLIT were searched from inception to May 2002 using the reported search terms. 'Important' journals and secondary sources, such as previous meta-analyses, were handsearched. Unpublished data were sought by searching the Internet and contacting relevant researchers and pharmaceutical companies. Studies were only included if they were published in English or German.

Study selection
Study designs of evaluations included in the review
Studies with at least 4 patients and with a pill-placebo comparison group were eligible for inclusion. No other inclusion criteria were defined for study design. However, all studies included in the review were described as double-blind, which indicates that all were randomised controlled trials.

Specific interventions included in the review
Studies that compared pharmacotherapy with pill placebo for at least 14 days were eligible for inclusion. The non-proprietary drug name had to be provided. The studies most commonly used benzodiazepines (mainly diazepam, alprazolam and lorazepam) and azapirones (mainly buspirone). Studies eligible for inclusion in the review had a pill-placebo comparison group. Most of the included studies did not allow concomitant use of sedatives or other drugs acting on the central nervous system; some studies allowed the use of chloral hydrate.

Participants included in the review
Studies of adults who had been diagnosed with GAD using a diagnostic system, or which described the disorder and the duration of the condition in the participants, were eligible for inclusion. Studies of augmented treatment for patients refractory to other previously used drugs were excluded. Most of the included studies diagnosed patients using the American Psychiatric Association's DSM criteria (versions II, III, III-R and IV) but most did not report using a structured interview to reach the diagnosis.

Outcomes assessed in the review
Studies were eligible if they assessed outcomes using self-report, observer-rated measures, or behavioural tests of anxiety, depression, quality of life, or clinical significance (response) in relation to anxiety. The review did not assess physiological measures. The studies had to report sufficient data to permit calculation of an effect size (standard deviations (SDs), t- or F-values). Response was reported in a variety of ways, including 25% improvement, 50% improvement and (very) much improved. All studies used the Hamilton Rating Scale for Anxiety.

How were decisions on the relevance of primary studies made?
The authors did not state how studies were selected for the review, or how many reviewers performed the selection.
Assessment of study quality
The authors stated that methodological and clinical aspects of the studies were assessed using a coding form. It appeared that criteria on which the studies were assessed included double-blinding, drop-outs, intention-to-treat (ITT) analysis and sample size, since these criteria were used in sensitivity analyses.

Validity appeared to have been assessed using a coding form, but the authors did not explicitly state how many reviewers performed the assessment. However, inter-rater agreement was reported; this suggested that at least two reviewers performed the validity assessment.

Data extraction
The data were extracted using a coding form, but the authors did not explicitly state how many reviewers performed the extraction. Inter-rater agreement was reported; this suggested that at least two reviewers performed the data extraction. The data were extracted on an ITT basis where possible.

For each study, effect sizes were calculated for each assessment scale using Hedge’s g with a correction for small sample size. The methods used to calculate effect sizes using the various forms of data reported in the studies (such as odds ratios, change scores only and tests of statistical significance) were described. For studies examining more than one drug, data were extracted separately for each comparison. For studies with multiple dose treatment arms, data were extracted for the dose showing the highest effect size. Where studies published in recent years did not present sufficient information to calculate an effect size, authors were contacted for additional information.

Methods of synthesis
How were the studies combined?
For each outcome measure, the studies were pooled in a meta-analysis using a random-effects model, and a mean effect size (Hedge’s g) was calculated. A correction for effect size distribution was done for all studies, for each assessment scale, by excluding outliers (defined as 2 SDs smaller or higher than the unweighted mean). The fail-safe N was calculated. Publication bias was assessed using a funnel plot.

How were differences between studies investigated?
A sensitivity analysis was conducted by repeating the analysis after excluding all studies not presenting means and SDs, and by repeated meta-analysis using a fixed-effect model. Heterogeneity was examined using the Q-test for homogeneity of effect size, and by repeating the meta-analysis after excluding the most extreme effect sizes. Effect sizes were also calculated for baseline data from studies reporting means and SDs. Multiple regression, (adjusted for diagnostic criteria, fixed or flexible drug dose, analysis of completers or ITT, drop-out rates and sample size) was used to assess the difference in effect size between benzodiazepines and azapirones. The influence of the following moderator variables on results for anxiety were examined using regression analysis: sample size; completers versus ITT analysis; fixed and flexible doses; diagnostic criteria; and drop-out rates. In addition, assessor-rated outcomes were compared with self-rated outcomes.

Results of the review
Forty-eight (double-blind) studies were included. It was not possible to readily calculate the number of participants, since numbers were reported for each comparison rather than for each individual study.

Inter-rater agreement for the coding of extracted data was no lower than 0.5 for any variable; the overall rate was 0.75.

The funnel plot showed asymmetry, thus suggesting the possibility of publication bias. The fail-safe N was 42 additional studies.

There was no significant difference between treatment and placebo groups at baseline for anxiety (g = -0.06) or depression (g = -0.06).

Pharmacotherapy reduced anxiety (72 comparisons; effect size 0.31, 95% confidence interval, CI: 0.26, 0.37) and depression (26 comparisons; effect size 0.31, 95% CI: 0.20, 0.42) compared with placebo. The results for random-
effects models are reported. No significant heterogeneity was detected for fixed-effect models (Q=87.27 and Q=27.77 for anxiety and depression, respectively).

Pharmacotherapy improved the response rate (44 studies; random effect size 0.52, 95% CI: 0.40, 0.65). Significant heterogeneity was detected for the fixed-effect model (Q=121.22, P<0.10).

The mean effect size for anxiety increased after excluding all effect sizes not calculated using means and SDs.

The results were similar to the main meta-analysis when including only effect sizes calculated from the Hamilton Rating Scale for Anxiety. The multiple regression analysis showed no significant difference between benzodiazepines and azapirones for anxiety (g=0.32 versus g=0.30, Beta 0.05) or depression (g=0.28 versus g=0.22, Beta -0.08).

The mean unweighted drop-out rate was significantly greater with azapirones compared with benzodiazepines (30.7% versus 20.5%, P<0.05). The mean unweighted drop-out rate with pill placebo was 30.2%.

The sample size was associated with the effect size; smaller studies showed larger effect sizes. There was no significant difference between assessor-rated and self-reported outcomes.

**Authors' conclusions**
Drug treatment, particularly with benzodiazepines and azapirones, is effective for the short-term treatment of generalised anxiety disorder, but no drug class is superior in reducing symptoms.

**CRD commentary**
The review addressed a clear question that was defined in terms of the participants, intervention and outcomes; inclusion criteria for study design were restricted to a minimum sample size and the inclusion of a pill-placebo comparison group. Two named electronic databases were searched, but there were no details of the journals searched or how secondary sources were identified. Attempts were made to locate unpublished studies, thus reducing the potential for publication bias; the authors used appropriate methods to assess its presence and found evidence suggesting its presence. The restriction to studies published in either of two languages might have resulted in the omission of other relevant studies, a possibility the authors discussed. 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 errors and bias, although it appeared that such methods were used in the data extraction and validity assessment. The authors also apparently assessed validity since the influence of various methodological criteria on the results was examined. However, since the quality of the individual studies was not reported, it was difficult to assess the reliability of the results.

Very little information on the individual included studies was given, and the designs of the included studies were not explicitly reported. Statistical heterogeneity was assessed and the studies were pooled using meta-analysis; without adequate details of the individual studies, the appropriateness of pooling studies cannot be judged. The heterogeneity shown for the meta-analysis of clinical response was not explored, although some potential reasons were discussed. The influence of various methodological variables on the results was examined. Comparisons between benzodiazepines and azapirones, although adjusted for various factors, were based on indirect comparisons and the results may not be definitive. Incomplete reporting of review methods and the lack of details on individual studies and study quality make it difficult to assess the reliability of the authors' conclusions.

**Implications of the review for practice and research**
Practice: The authors stated that in view of the potential for addiction and other adverse effects, benzodiazepines should be prescribed for short-term use only.

Research: The authors stated that future research should consider adequate double-blinding, assess outcomes using a questionnaire in addition to the Hamilton Anxiety Scale (such as the Penn State Worry Questionnaire), and assess quality of life.
Bibliographic details

PubMedID
15738745

Indexing Status
Subject indexing assigned by NLM

MeSH
Anti-Anxiety Agents /therapeutic use; Anxiety Disorders /drug therapy /psychology; Clinical Trials as Topic; Humans

AccessionNumber
12005003881

Date bibliographic record published
31/12/2006

Date abstract record published
31/12/2006

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.