Pharmacologic treatments effective in both generalized anxiety disorder and major depressive disorder: clinical and theoretical implications

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Authors' objectives
To assess the efficacy of anxiolytics (alprazolam and azapirones) in major depressive disorder (MDD) and of antidepressants in generalized anxiety disorder (GAD), thereby exploiting the possible theoretical and clinical implications of this efficacy.

Searching
MEDLINE was searched from January 1980 to September 1997 for English language peer-reviewed articles using the following keywords: depressive disorders, anxiety disorders, generalized anxiety disorder, antidepressants, antianxiety agents, benzodiazepines and buspirone. Bibliographies of identified studies were examined.

Study selection
Study designs of evaluations included in the review
Randomised, double-blind trials (RCT) with a sample size of 30 patients or more that compared anxiolytics and antidepressants in the acute treatment of GAD or MDD were included.

Specific interventions included in the review
The following therapies were studied: benzodiazepines including alprazolam, diazepam, and lorazepam; tricyclic antidepressants (TCA) including desipramine, amitryptilline, imipramine, and doxepin); azapirones (including buspirone, ipsapirone, and gepirone); and placebo. Duration of treatment ranged from 4 to 8 weeks.

Participants included in the review
Adult patients with generalised anxiety disorder (GAD) or major depressive disorder (MDD) who were not being simultaneously treated with psychotherapy were studied. Outpatients and inpatients with the following diagnoses were included: major depression (Feighner's criteria, American Psychiatric Association DSM-III, or ICD-9); neurotic, reactive, secondary depression; neurotic depression; endogenous and recurrent depression; primary anxiety; and generalised anxiety disorder (American Psychiatric Association DSM-III or DSM IV).

Outcomes assessed in the review
The following outcomes were assessed: Hamilton Rating Scale- Depression (HRS-D) scores including change in mean total score; HRS-A depression component subscores; and HRS-D dysphoric mood items; HSCL-depression scale; CGI; and Beck DI scores.

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

Assessment of study quality
Mention was made of some aspects of validity but no formal assessment was undertaken.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the authors performed the data extraction.
**Methods of synthesis**

How were the studies combined?
The studies were combined in a narrative review.

How were differences between studies investigated?
Potential causes of differences between studies were discussed.

**Results of the review**

Alprazolam vs placebo and/or tricyclic antidepressants in depression (10 double blind controlled RCTs, 2154 patients).

Alprazolam vs tricyclic antidepressants in depression (20 double blind controlled RCTs, 2930 patients).

Azapirones in major depressive disorder (3 double blind, placebo controlled RCTs studied buspirone; one studied isapirone (34 patients); one studied gepirone (130 patients); and 4 studies examined the use of drugs for primary anxiety or GAD (613 patients).

Flaws in the primary studies include heterogeneity of study sample, exclusion of patients with significant psychomotor retardation or endogenous depression, short duration of medication, high drop-out rates and absence of intention to treat analysis. No studies addressed the long term efficacy of alprazolam.

Alprazolam vs placebo in depression (10 RCTs with mean alprazolam dose from 2.4 to 3.9 mg /day, range 1.0 to 8.5 mg /day): alprazolam was superior to placebo in eight RCTs, and of equal efficacy in two RCTs.

Alprazolam vs tricyclic antidepressants in depression (20 RCTs): only one RCT demonstrated alprazolam to be significantly superior to TCA and in this study the TCA group had a significantly greater number of previous depressive episodes. Eleven of the sixteen RCTs showing alprazolam to be of equal efficacy to TCA had serious methodological flaws. Five methodologically sound studies showed alprazolam to be of equal efficacy to TCA. Three RCTs showed amitriptylline to be significantly more effective than alprazolam but flaws included exclusion of patients who had previously failed to respond to TCA and differences in prognostic indicators between treatment arms at baseline.

Azapirones in depression (2 RCTs plus 1 review that included these two studies and one other trial compared buspirone and placebo): Results from one RCT were reported to be difficult to interpret due to extremely high drop-out rates (70%). The review was not assessed for quality and showed buspirone to be significantly more effective than placebo. The authors consider that it is unclear whether the antidepressant properties of azapirone are clinically significant.

Antidepressants in generalised anxiety disorder (GAD): results were reported from one review based on 18 trials (described as usually not placebo controlled, variable with respect to composition, medication dosage, trial duration, and statistical rigour) and four other RCTs. The validity of the review was not assessed. One RCT (242 patients studied for 8 weeks) compared imipramine, chlordiazepoxide and placebo and found imipramine to be significantly more effective than the other therapies. One RCT (60 patients studied for 6 weeks) compared alprazolam and imipramine and found them to be of equal efficacy. One RCT (230 patients studied for 8 weeks) compared imipramine, trazodone and diazepam and found only imipramine to be significantly more effective than placebo. One RCT (81 patients studies for 8 weeks) compared paroxetine, imipramine and 2- chlordesmethyldiazepam and found there to be no statistically significant difference between treatments.

**Authors’ conclusions**

Alprazolam, at doses double those generally recommended for anxiety disorder, appear to be as effective as tricyclic antidepressants in the acute treatment of mild to moderate major depressive disorder. Alprazolam was also found to have a more rapid onset of action than TCAs, particularly for the improvement of anxiety, somatization and insomnia. Two azapirones (buspirone and gepirone) have demonstrated a modest acute antidepressant effect in preliminary studies albeit only in a depressed outpatient sample with considerable anxiety at baseline. Various antidepressant drugs (imipramine, trazodone, paroxetine) were shown to have, at the least, comparable efficacy to benzodiazepines in the acute treatment of generalized anxiety disorder.
The non specificity of treatment response suggests that:

1. GAD and MDD are different expressions of a similar disorder with a common neurobiological substrate.
2. Discrete diagnostic entities that respond to independent pharmacological effects of the same drugs.
3. A combination of the two (heterogeneity hypothesis).

The most relevant clinical finding is the efficacy of antidepressants in the acute treatment of generalized anxiety disorder.

CRD commentary
The aims and inclusion criteria were stated. Some aspects of validity were assessed though no formal assessment was undertaken and some relevant information from the primary studies was clearly presented in tabular format (available from the authors). The authors report the following problems with the primary studies: subtherapeutic doses of antidepressants; exclusion of patients with significant psychomotor retardation, endogenous depression, involutional depression; short trial duration; poor outcome measures; no intention to treat analysis; high drop out rates; heterogeneous study samples; small sample size; no clear exclusion criteria; and very high alprazolam dose. The authors mention the following limitations of the review: the findings for antidepressants were based on the results of few studies; alprazolam may not be as effective as tricyclic antidepressants in more severely depressed patients; and all possible reasons elicited for the non specificity of treatment response in GAD and MDD remain speculative.

By limiting the literature search to English language articles identified in one database, other relevant studies may have been omitted. No details were given of methods used to select primary studies or extract data. Side effects of drugs were not assessed. No evidence was presented on speed of onset of action of therapies or outcomes such as insomnia and somatization. Trials were all of short duration with the longest duration being 8 weeks. Fuller details of the studies comparing interventions for generalized anxiety disorder would have been helpful.

In view of the methodological flaws in the primary studies, the conclusions should be interpreted with caution.

Implications of the review for practice and research
Practice: The authors do not report any clinical implications of the review.

Research: The authors consider that the following questions remain to be answered: How does buspirone compare with standard antidepressants (including newer agents) in the treatment of both GAD and MDD? In which subsets of GAD and MDD patients are standard antidepressants, buspirone and alprazolam most effective? At what doses? For which symptom clusters? Can their efficacy be maintained for several months?

Bibliographic details

Indexing Status
Subject indexing assigned by NLM

MeSH
Adult; Anti-Anxiety Agents /therapeutic use; Antidepressive Agents /therapeutic use; Antidepressive Agents, Tricyclic /therapeutic use; Anxiety Disorders /physiopathology /drug therapy /classification; Benzodiazepines; Depressive Disorder /physiopathology /drug therapy /classification; Pyrimidines /therapeutic use; Randomized Controlled Trials as Topic; Serotonin Agonists /therapeutic use

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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.