Are antipsychotics or antidepressants needed for psychotic depression? A systematic review and meta-analysis of trials comparing antidepressant or antipsychotic monotherapy with combination treatment

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CRD summary
This review concluded that antidepressant-antipsychotic combination-therapy was superior to monotherapy with antidepressants or antipsychotics for the treatment of acute psychotic depression. The uncertain quality and small size of the evidence base limits the reliability of the review. The authors’ recommendation to interpret results in the context of the review’s limitations appears justified.

Authors’ objectives
To evaluate the effects of antidepressants or antipsychotics versus combined therapy with both drug classes for the treatment of psychotic depression.

Searching
PubMed, The Cochrane Library, and PsycINFO were searched from inception to the end of February 2011 for articles in any language. Search terms were reported. Reference lists of relevant articles were searched.

Study selection
Double-blind randomised controlled trials (RCTs) of antidepressant or antipsychotic monotherapy versus antidepressant-antipsychotic combination-therapy for the treatment of adults with major depressive disorder with psychotic features were eligible for inclusion. The primary outcome was study-defined inefficacy. Secondary outcomes included all-cause discontinuation, specific cause discontinuation, global illness severity, specific psychopathology scale scores for depression, anxiety, psychosis, and side-effects.

The included trials had a duration that ranged from four to 16 weeks. First- and second-generation antipsychotics, tricyclic antidepressants, and selective serotonin reuptake inhibitors were included. Psychotic depression was defined by standard criteria in all trials, including Research Diagnostic Criteria, ICD-10, DSM-III or DSM-IV. The mean age of patients in the antidepressant trials was 53.5 years and the proportion of men was 48.9%. The mean age of patients in the antipsychotic trials was 48.4 years and 41.6% were men.

Two reviewers undertook study selection; disagreements were resolved by discussion.

Assessment of study quality
The authors did not state whether any formal quality assessment was undertaken.

Data extraction
Data on inefficacy, discontinuation, psychosis and safety outcomes were extracted and used to calculate relative risks and mean differences, with 95% confidence intervals (CIs). Trial authors were contacted for specific results and additional outcome data.

Two reviewers extracted the data; disagreements were resolved by discussion.

Methods of synthesis
A DerSimonian and Laird random-effects meta-analysis was undertaken to calculate pooled relative risks (RRs) and Hedges g effect sizes, with 95% confidence intervals. To be included in the meta-analysis, data from at least three trials or comparisons had to be available. Statistical heterogeneity was assessed using I² (I² over 50% was considered evidence of substantial statistical heterogeneity). The number needed to treat and the number needed to harm were calculated for statistically significant results.

Sensitivity analysis was undertaken when statistical heterogeneity was detected. Subgroup analysis was undertaken.
according to type of antidepressant and antipsychotic.

**Results of the review**

The authors reported that eight (although nine or ten appeared to be tabulated) acute phase RCTs with ten comparisons were included (762 patients). Four trials provided four comparisons with antipsychotics. Five trials provided six comparisons with antidepressants. Trial sample size ranged from 36 to 259 patients.

Antidepressant-antipsychotic co-therapy significantly reduced inefficacy in the acute phase of psychotic depression compared with antipsychotic monotherapy (RR 0.73, 95% CI 0.63 to 0.84; four comparisons; $I^2=0\%$) and antidepressant monotherapy (RR 0.76, 95% CI 0.59 to 0.98; six comparisons; $I^2=34\%$).

Antidepressant-antipsychotic co-therapy significantly reduced depression in the acute phase compared with antipsychotic monotherapy (Hedges $g$ -0.49, 95% CI -0.75 to -0.23; four comparisons; $I^2=27\%$) but there was no difference when compared with antidepressant monotherapy (five comparisons). Antidepressant-antipsychotic co-therapy significantly reduced Clinical Global Impressions-Severity Illness score in the acute phase compared with antipsychotic monotherapy (Hedges $g$ -0.25, 95% CI -0.49 to -0.02; four comparisons; $I^2=0\%$); data were not available for the antidepressant monotherapy comparison. There was no significant difference in terms of psychosis or anxiety.

The rates of discontinuation and adverse events were similar, except for somnolence which was statistically significantly more likely with antipsychotic-antidepressant co-therapy compared with antidepressant monotherapy (RR 2.79, 95% CI 1.14 to 6.79; three comparisons; $I^2=15\%$).

Further results, including subgroup results, were reported in the review.

**Authors’ conclusions**

Antidepressant-antipsychotic combination therapy was superior to antidepressant monotherapy or antipsychotic monotherapy in the treatment of acute psychotic depression, but the results must be interpreted in the context of the review’s limitations.

**CRD commentary**

Inclusion criteria for the review were clearly defined. Three relevant databases were searched, with no language restrictions. Publication bias was not assessed and could not be ruled out. Attempts were made to minimise reviewer error and bias throughout the review.

Quality assessment did not appear to have been undertaken, which made it difficult to interpreting the reliability of the evidence base. The type of drug varied across the trials, as did the trial duration. The authors noted that most of the drugs studied were older agents. Approximately half of the studies had sample sizes of fewer than 50 patients. Data were pooled using appropriate meta-analysis methods; statistical heterogeneity was assessed. However, the authors were not clear on how they handled a pooled analysis of two trials in the meta-analysis; forest plots indicated that it was imputed as two trials, but the text indicated that it may have been handled as one trial.

Overall, the uncertain quality of the trials and the small size of the evidence base limits the reliability of the results. The authors’ recommendation to interpret the results in the context of the review’s limitations appears justified.

**Implications of the review for practice and research**

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that more studies were needed to confirm the results of this review. Further research to assess specific combinations was needed, as was research to determine the maintenance/relapse prevention efficacy.

**Funding**

National Institute of Mental Health (NIMH) grant; Zucker Hillside Hospital Advanced Centre for Intervention and Services Research for the Study of Schizophrenia.

**Bibliographic details**

Farahani A, Correll CU. Are antipsychotics or antidepressants needed for psychotic depression? A systematic review
and meta-analysis of trials comparing antidepressant or antipsychotic monotherapy with combination treatment. Journal of Clinical Psychiatry 2012; 73(4): 486-496

**PubMedID**
22579147

**DOI**
10.4088/JCP.11r07324

**Original Paper URL**
http://article.psychiatrist.com/dao_1-login.asp?ID=10007825&RSID=63128237627797

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Adult; Antidepressive Agents /administration & dosage /therapeutic use; Antipsychotic Agents /administration & dosage /therapeutic use; Depressive Disorder, Major /drug therapy /psychology; Drug Therapy, Combination; Humans; Psychotic Disorders /drug therapy /psychology; Treatment Outcome

**AccessionNumber**
12012026036

**Date bibliographic record published**
28/07/2012

**Date abstract record published**
27/11/2012

**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.