Efficacy of antidepressants in treating the negative symptoms of chronic schizophrenia: meta-analysis

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CRD summary
The review concluded that antidepressants plus antipsychotics were more effective in treating negative symptoms of schizophrenia than were antipsychotics alone. The small size of some of the included studies and the fact that details of quality assessment were not reported suggest some caution is warranted when interpreting the authors’ conclusions.

Authors’ objectives
To analyse the efficacy of add-on antidepressants for the treatment of negative symptoms of chronic schizophrenia.

Searching
EMBASE, PubMed, The Cochrane Library, CINAHL and PsycINFO were searched to August 2009. Search terms were reported.

Study selection
Randomised controlled trials (RCTs) that compared the effect of add-on antidepressants with placebo on the negative symptoms of chronic schizophrenia were eligible for inclusion. Trials were excluded if the antidepressant was used to treat an explicit comorbid psychiatric disorder (defined in the review), if the antidepressant was not add-on and if the antidepressant was not normally classified as an antidepressant. Relevant outcomes were the scale for the assessment of negative symptoms (SANS), positive and negative syndrome scale (PANSS) and brief psychiatric rating scale (BPRS). Trials that did not meet the quality criteria were excluded.

The included trials studied citalopram, fluoxetine, fluvoxamine, mianserin, mirtazapine, paroxetine, reboxetine, ritanserin, sertraline and trazodone in patients with schizophrenia. Trial duration ranged from four to 12 weeks. Mean age of patients at study entry ranged from 30 to 62 years. Duration of illness varied from four to 34 years. The proportion of males ranged from 23% to 93%. The severity of negative symptoms ranged from 1.73 to 8.21 and the severity of positive symptoms ranged from 0.46 to 5.66.

Two reviewers independently performed study selection. Disagreements were resolved by consultation with a third reviewer.

Assessment of study quality
Two reviewers independently assessed study quality factors such as blinding, randomisation and comparison with a placebo group. Disagreements between reviewers were resolved by consultation with a third reviewer.

Data extraction
Data were extracted on SANS, PANSS and BPRS scores before trial and after trial. These were used to calculate mean differences and their 95% confidence intervals (CIs).

The authors did not state how many reviewers conducted data extraction. [A: Data were extracted by two reviewers]

Methods of synthesis
A fixed-effect meta-analysis was undertaken to calculate standardised mean differences (SMD) and their 95% confidence intervals (CIs). Random-effects meta-analysis was used when significant statistical heterogeneity was detected. The number needed to treat (NNT) was calculated. Publication bias was assessed using the trim-and-fill method. Subgroup analysis was undertaken for specific medications when there were at least 60 patients in at least two trials. Sensitivity analysis was undertaken using moderator analysis.
Results of the review
Twenty-three trials were included in the review (n=819 patients).

Compared with placebo, antidepressants had a statistically significantly greater effect on negative symptoms (SMD -0.48, 95% CI -0.71 to -0.25; NNT=10; n=819 patients). Subgroup analysis revealed that compared with placebo, negative symptoms were statistically significantly improved with fluoxetine (SMD -0.42, 95% CI -0.77 to -0.07, NNT=11; n=136 patients), trazodone (SMD -0.70, 95% CI -1.19 to -0.22, NNT=6; n=72 patients) and ritanserin (SMD -0.83, 95% CI -1.31 to -0.35, NNT=5; n=73 patients).

Sensitivity analysis did not statistically change the results. Moderator analysis found no association between nine moderator variables. There was evidence of statistical heterogeneity between trials.

Authors’ conclusions
Antidepressants plus antipsychotics were more effective in treating negative symptoms of schizophrenia than antipsychotics alone.

CRD commentary
Inclusion criteria for the review were clearly defined. Several relevant data sources were searched. Attempts were made to control for publication bias. Only trials that met the quality criteria were included, but quality assessment results were not presented. Results for excluded trials were not presented. Attempts were made to reduce reviewer error and bias during study selection; it was unclear whether the same methods were used for data extraction. [A: Data were extracted by two reviewers]. Trials were pooled using random-effects meta-analysis. Statistical heterogeneity was assessed. Many trials had small sample sizes and there may have been clinical heterogeneity across trials. Study quality issues were not considered in the synthesis.

Given these data limitations and the fact that details of study quality are not reported suggest some caution is warranted when interpreting the authors’ conclusions.

Implications of the review for practice and research

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

Research: The authors stated a need for further studies about side effects, adherence, quality of life and cost-effectiveness for the combination of antidepressant and antipsychotic medication. Studies on specific sub-domains of negative symptoms would be useful.

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