Selective serotonin reuptake inhibitor (SSRI) add-on therapy for the negative symptoms of schizophrenia: a meta-analysis

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CRD summary
This review found that selective serotonin re-uptake inhibitor augmentation does not improve the negative symptoms of schizophrenia. These findings are likely to be reliable.

Authors' objectives
To investigate the effect of selective serotonin re-uptake inhibitor (SSRI) add-on therapy on the negative symptoms of schizophrenia.

Searching
MEDLINE, PsycINFO (1967 to 2005) and Current Contents (1993 to 2005) were searched; the keywords were reported. Published review articles and reference lists were screened for additional relevant studies. Pharmaceutical companies were contacted for unpublished data.

Study selection
Study designs of evaluations included in the review
Randomised, double-blinded, parallel-group trials were eligible for inclusion.

Specific interventions included in the review
Placebo-controlled studies that compared SSRI add-on therapy with antipsychotic treatment were eligible for inclusion. Studies on monoamino oxidase inhibitors, or tricyclic, dual-action or atypical antidepressants were excluded. The SSRIs assessed in the included studies were fluoxetine, fluvoxamine, sertraline, citalopram and paroxetine. The antipsychotics, where reported, were clozapine, olanzapine, typical antipsychotics or mixed antipsychotics. Treatment duration ranged from 4 weeks to 4 months.

Participants included in the review
Studies of patients with a diagnosis of schizophrenia-spectrum disorder were eligible for inclusion. Studies were excluded if schizophrenia patients were diagnosed with co-morbid obsessive-compulsive disorder. The patients in the included studies were chronic and non-chronic patients and in-patients and out-patients.

Outcomes assessed in the review
Studies that assessed negative symptoms using the Scale for the Assessment of Negative Symptoms (SANS) or the Positive and Negative Syndrome Scale-negative subscale (PANSS-N) before and after follow-up were eligible for inclusion. Studies with incomplete or unavailable data were excluded; authors were contacted for missing data.

How were decisions on the relevance of primary studies made?
Decisions on inclusion were achieved through consensus.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
Two reviewers independently extracted the data, with any disagreements resolved through consensus. Data were extracted as effect sizes for the difference in negative symptoms between patients treated with add-on SSRI and placebo before and after treatment. Effect size estimates were calculated, based on sample size, means and standard deviations. Full data without attrition were extracted in preference to intention-to-treat data.

Methods of synthesis
How were the studies combined?
Random-effects models were used to calculate summary effect sizes based on Hedges' g.

How were differences between studies investigated?
Heterogeneity was assessed using the Q statistic. Significant heterogeneity was considered to be present if the p-value was less than 0.10. Subgroup analyses were carried out besides other sensitivity analyses by pooling effect sizes separately according to the following groupings: antipsychotic type (typical, atypical or mixed), SSRI medication (fluoxetine versus others), psychiatric setting (in-patient versus out-patient), severity of illness (chronic versus non-chronic), psychiatric assessment (PANSS-N versus SANS) and treatment duration (<12 weeks versus at least 12 weeks).

Results of the review
Eleven studies (393 patients at end point) were included.

There were no overall differences between the treatment groups: the pooled Hedges' g was 0.178 (p=0.191). There was some evidence of heterogeneity (p=0.078). The only subgroup analysis that provided a significant composite effect size estimate for negative symptoms was that for patients with chronic schizophrenia (Hedges' g 0.386, p=0.014).

Authors' conclusions
SSRI augmentation does not improve the negative symptoms of schizophrenia.

CRD commentary
The review addressed a focused question that was supported by clearly defined inclusion criteria. The literature search was adequate and included some attempts to identify unpublished studies. Appropriate steps were taken to minimise bias in the extraction of data, but the process employed for the selection of studies was less clear. A formal quality assessment was not undertaken but the review was limited to double-blind studies. The reliability of the findings of the primary studies therefore remains unclear, although given that all included studies were double-blind randomised controlled trials this is less problematic than it would be for less reliable study designs. Appropriate methods were used to pool study results and the results were clearly presented. Overall, the authors' conclusions are likely to be reliable.

Implications of the review for practice and research
Practice: The authors stated that the review findings do not support the combination of antipsychotics and SSRIs for the treatment of negative symptoms of schizophrenia.

Research: The authors did not state any implications for further research.

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