The effects of atypical antipsychotic drugs on neurocognitive impairment in schizophrenia: a review and meta-analysis

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Authors' objectives
To critically review studies of the impact of atypical antipsychotics on cognitive deficits in patients with schizophrenia.

Searching
MEDLINE and Psychological Abstracts were searched, and relevant articles published between 1990 and April 1998 were then reviewed. Data from a paper in press, which described additional measures in an already published study, were also included.

Study selection
Study designs of evaluations included in the review
The authors do not specifically state the study design inclusion and exclusion criteria used to select studies for inclusion. The study designs included in the review were open-label studies and randomised double-blind studies. Unpublished studies were excluded.

Specific interventions included in the review
Atypical antipsychotic medications were compared with conventional antipsychotic treatment. These included clozapine, 150 to 900 mg daily; risperidone, 2 to 11 mg daily; zotepine, 150 to 450 mg daily; ziprasidone, aripiprazole and haloperidol, 3 to 40 mg daily; and fluphenazine, 6 mg to a mean of 37.8 mg daily.

Participants included in the review
The inclusion criterion was patients with schizophrenia. Studies investigating the effects of atypical antipsychotics on neurocognitive functioning in geriatric patients with schizophrenia were excluded from the analysis. The participants in the included studies were patients with schizophrenia, schizoaffective disorders, or an unspecified psychosis.

Outcomes assessed in the review
Neuropsychological and neurocognitive function were assessed. The actual outcomes included in the review were reported neurocognitive improvements, and neurocognitive improvements following correction for multiple comparisons in the following test measures: attention subprocesses, executive function, working memory, learning and memory, visuospatial analysis, verbal fluency, digit-symbol substitution and fine motor function.

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 reviewers performed the selection.

Assessment of study quality
Methodological quality was assessed using standards for the assessment of cognitive change in schizophrenia. These included pharmacological status at baseline; multiple study arms with random assignment; double-blind conditions; adequate duration of trial; clinically appropriate dosing strategies; appropriate content, properties and number of neurocognitive measures; appropriate sample size; and discrimination between cognitive enhancement and generalised clinical change. The authors do not state how the papers were assessed for quality, or how many of the reviewers performed the quality assessment.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction.
Methods of synthesis
How were the studies combined?
The probabilities (p values) from two or more independent studies were combined using Fisher's method (see Other Publications of Related Interest no.1). Two meta-analyses were conducted to address the question of whether atypical antipsychotics improved neurocognitive performance in general. The first analysis combined the results from the 3 double-blind studies, whilst the second combined the results of the 12 open-label studies.

The authors made some corrections for multiple comparisons in each arm using an experimental p value (p<0.05), but did not finish the procedure. When a given study included multiple test measures, the average p value for that study was used in the statistical procedure. If multiple test measures were included in a single domain of cognitive functioning, the average p value for that domain was used in the statistical procedure.

Meta-analyses were also conducted to examine the effect of novel antipsychotic medications on specific domains of cognitive function. These combined all the studies that reported data for each domain. Corrections for multiple comparisons were not made in these meta-analyses, since this would have required setting a p value for each domain.

How were differences between studies investigated?
Heterogeneity does not appear to have been investigated.

Results of the review
Fifteen studies were included: 3 randomised and double-blind studies and 12 open-label studies, one of which included multiple study arms with random allocation. There were 10 studies of clozapine, 4 of risperidone, 1 of zotepine, 1 of ziprasidone, and 1 of aripiprazole. The number of participants was unclear.

Methodological quality results:
pharmacological status at baseline was determined in 14 of the 15 studies;
4 studies used multiple study arms with random assignment;
3 studies used double-blind conditions;
14 studies were of adequate trial duration;
12 studies used clinically appropriate dosing strategies;
7 studies included neurocognitive batteries that were appropriate, while 3 additional studies used measures that were acceptable, yet limited in scope;
5 studies used an appropriate sample size; and 9 studies showed discrimination between cognitive enhancement and generalised clinical change.

After correcting for multiple comparisons, 2 of the 3 randomised double-blind studies demonstrated significant neurocognitive improvement on at least one test measure, following treatment with atypical antipsychotic medication compared with conventional antipsychotics. Seven of the 12 open-label studies demonstrated improvement following treatment with atypical antipsychotics. Overall, 9 of the 15 studies demonstrated improvement.

The meta-analysis of the 3 double-blind studies indicated that atypical antipsychotics were significantly more effective...
than conventional antipsychotics at improving cognitive functioning (chi-squared 14.82, \(p=0.022\)). The meta-analysis of the 12 open-label studies also indicated that atypical antipsychotics were significantly more effective than conventional antipsychotics at improving cognitive functioning (chi-squared 47.59, \(p=0.002\)). Meta-analytical procedures that included all 15 studies also supported the effect of atypical antipsychotics on cognition (chi-squared 62.41, \(p=0.0004\)).

Results for the meta-analyses examining the effect of novel antipsychotic medication on specific domains of cognitive function were reported in the paper. In the double-blind studies, these meta-analyses indicated that atypical antipsychotics produce significant improvement in attention, executive functions and visuospatial analysis. In the open-label studies, they indicated improvements in executive function, working memory, visuospatial analysis, verbal fluency, digit-symbol substitution and fine motor functions.

**Authors’ conclusions**

The authors concluded that ‘despite a conservative statistical approach, correcting the results of each study for the number of statistical comparisons made, the meta-analysis conducted in this study suggests that atypical antipsychotics, when compared with conventional antipsychotics, improve cognitive functions in patients with schizophrenia.’ The strongest responders to novel antipsychotics were verbal fluency, digit-symbol substitution, fine motor functions, and executive functions; attention subprocesses were found to be responsive; and learning and memory functions were found to be the least responsive.

The authors also concluded that it was difficult to determine conclusively the pattern of specific cognitive improvements that could be expected with any specific atypical antipsychotic treatment, because of the limited number of studies included in the analysis. The authors stated that ‘none of the 15 studies that we reviewed met all of the recently developed standards for the assessment of cognitive change in schizophrenia. Most important, only 3 of the 15 studies used double-blind methodology. The strong impact of the various rater biases inherent in open-label studies of patients with schizophrenia, underscored recently in the Department of Veterans Affairs collaborative study of clozapine (see Other Publications of Related Interest no.2), should lead us to temper our enthusiasm for the results of the open-label studies reviewed here’.

**CRD commentary**

The review question was clearly stated, although the authors did not specifically state the inclusion criteria relating to the outcomes and study designs used to select studies. The literature search was adequate, but it made no attempt to identify unpublished research and provided no details of any language restrictions employed. The quality assessment of primary studies was adequate. No information regarding the review process was provided, e.g. how many reviewers were involved, whether decisions were made independently, whether reviewers were blinded to source, and how disagreements were resolved.

The details of the studies were well reported and the data analysis used suitable methods. However, heterogeneity was not assessed and studies did not appear to have been weighted. Bearing in mind the different interventions used, the different comparators and the different dosages, there was likely to have been heterogeneity between studies. Thus, it would not have been appropriate to pool the data. Publication bias was also not assessed.

The authors’ conclusions were adequate and follow from the results of the meta-analyses. The authors presented their conclusions in light of methodological limitations and biases of the primary studies being evaluated. Given these limitations, the conclusions should be treated with some caution.

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

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

Research: The authors state that, as a result of these initial studies, several large-scale comprehensive investigations of the effect of atypical antipsychotics on cognitive impairment in schizophrenia are underway. In addition, over the next few years, the results of large-scale clinical trials will begin to refine our understanding of the extent to which specific cognitive deficits in schizophrenia can be improved by the drugs currently available. In the meantime, however, data from studies of the pharmacology of cognitive function in animals and normal humans can help establish the directions...
for the next generation of cognitive-enhancing medications for patients with schizophrenia.

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