

A systematic review of atypical antipsychotic drugs in schizophrenia

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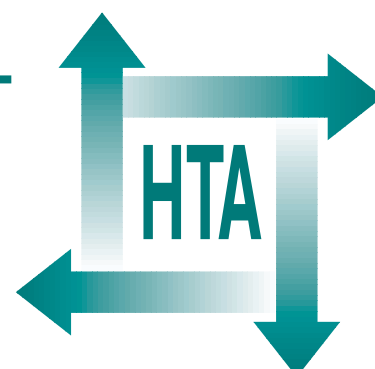
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Executive summary

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Executive summary

Objectives

The clinical effectiveness, safety and cost-effectiveness of 'atypical' antipsychotic drugs in schizophrenia were compared with conventional antipsychotic drugs, placebo and other atypical antipsychotic drugs.

As secondary objectives, the response was investigated in those with 'treatment-resistant' schizophrenia, with predominantly negative symptoms or experiencing their first episode of schizophrenia.

Methods

Data sources

Existing Cochrane reviews were updated with relevant randomised controlled trials (RCTs) found from comprehensive literature searches. Search strategies focused on retrieving RCTs of atypical antipsychotic drugs and non-randomised studies of rare or long-term adverse events. In addition to extensive database searching, ongoing trial registers were searched and the reference lists of retrieved papers scanned.

A systematic review of cost-effectiveness was undertaken using the same sources. In addition, an economic model was constructed using data from the systematic review of clinical effectiveness.

Inclusion criteria

Effectiveness studies

- RCT
- Individuals with schizophrenia, however diagnosed.
- Use of 'atypical' antipsychotic medications.
- Reporting of clinical, economic or social/functional outcomes.

Safety (non-randomised) studies

- Case-control design or at least 2 years follow-up or at least 2000 participants.
- One of following outcomes reported: mortality, tardive dyskinesia, neuroleptic malignant syndrome, agranulocytosis, seizures, weight gain, hepatic dysfunction, cardiac problems.

Two reviewers independently assessed studies for inclusion, any discrepancies being resolved by discussion and, if necessary, a third reviewer.

The inclusion criteria for existing reviews were based on the criteria devised by the NHS Centre for Reviews and Dissemination (CRD) and used in the Database for Abstracts of Reviews of Effectiveness (DARE).

Data extraction

Two reviewers undertook data extraction independently, any discrepancies being discussed and resolved with reference to the original papers and, if necessary, a third reviewer.

Individuals who left studies early were considered to have had a negative outcome, except in the case of death. The impact of including studies with high attrition rates (25–50%) was analysed in a sensitivity analysis. For studies with greater than 50% attrition, all data were excluded other than the outcome 'leaving the study early'.

A validity assessment for RCTs was undertaken using the following criteria: adequacy of randomisation; adequacy of blinding; comparability of groups at baseline; attrition rate; adequacy of description of withdrawals; adequacy of intention-to-treat data analysis; appropriate dose of comparator drug; adequate washout period.

A validity assessment for non-randomised studies was performed using appropriate CRD checklists.

The validity of existing reviews was summarised using criteria for inclusion in the DARE database.

Data synthesis

For binary outcomes, the pooled relative risk and its 95% confidence interval were calculated for all included RCTs; a fixed-effects model was used.

To investigate the possibility of heterogeneity, a chi-squared test was used, together with visual inspection of graphs. A significance level of < 0.10 was interpreted as evidence of heterogeneity. The studies responsible for the heterogeneity were summated and presented separately, and the possible reasons for the heterogeneity explored. ►

Data from all included studies were entered, if possible, into a funnel plot (trial effect against trial size) in an attempt to investigate the likelihood of overt publication bias. If possible, reviewers entered data in such a way that the area to the left of the line of no effect in the resulting graph indicated a favourable outcome for an atypical antipsychotic drug.

For each non-randomised study, the main results and aspects of study design were summarised.

Results

Literature search

A total of 171 RCTs were included, of which 28 comprised wholly or partly commercial-in-confidence data from drug manufacturers.

Additional safety data were found in 52 non-randomised studies, of which seven (all relating to sertindole) were commercial-in-confidence. In addition to 31 published economic evaluations, six commercial-in-confidence evaluations were submitted.

Validity

Evidence for the effectiveness of new atypical antipsychotic drugs compared with older drugs was, in general, of poor quality, based on short-term trials and difficult to generalise to the whole population with schizophrenia. Evidence for the effectiveness of new atypical antipsychotic drugs compared with each other was limited, as was evidence for their cost-effectiveness in the UK compared with each other and with older drugs. Thus the conclusions are based on limited evidence and should be treated with caution.

There was no evidence for the effectiveness of atypical versus typical antipsychotic drugs for individuals with concurrent substance abuse problems or comorbid mental illness, such as depression. There are few implications for those with related disorders such as schizoaffective and schizophreniform disorders, other than that ziprasidone, risperidone or olanzapine may be effective.

Effectiveness/safety

Atypical versus typical antipsychotic drugs

Effectiveness in controlling psychotic episodes

Risperidone, amisulpride, zotepine, olanzapine and clozapine were all more effective than typical comparators in relieving overall symptoms of schizophrenia. Quetiapine and sertindole were no more or less effective than typical antipsychotic drugs in alleviating overall symptoms of psychosis.

Attrition

In general, fewer individuals from atypical drugs groups left trials early than from typical drugs groups; the exceptions were ziprasidone and zotepine, which suggests that patients found atypical antipsychotic drugs more acceptable.

Side-effects

Movement disorders: all new antipsychotic drugs appeared to cause fewer movement disorder side-effects than typical antipsychotic treatments, although issues such as dose or definition and reporting of symptoms limited the confidence that can be placed in these results.

Sedation: clozapine increased daytime sleepiness (somnolence) or drowsiness compared with typical antipsychotic drugs. Treatment with olanzapine, amisulpride, sertindole and perhaps risperidone, caused less somnolence or drowsiness than typical comparator drugs; the other atypical antipsychotic drugs were no more or less sedating than their typical comparators.

Autonomic effects: side-effects, such as increased salivation, increased temperature and rhinitis (blocked nose), were seen in both clozapine- and sertindole-treated groups. For quetiapine, there was increased incidence of dry mouth. Olanzapine was associated with fewer autonomic effects than typical antipsychotic drugs. Other atypical antipsychotic drugs had similar numbers of autonomic side-effects to their typical comparators.

Gastrointestinal effects: atypical antipsychotic drugs were not significantly better or worse than typical drugs with regard to rates of nausea and vomiting, except for ziprasidone, which caused increased nausea and vomiting, and olanzapine, which caused less nausea and vomiting.

Weight gain: amisulpride, risperidone and sertindole caused weight gain. Ziprasidone, zotepine and, possibly, clozapine and olanzapine did not. It had been suggested that for those with schizophrenia, weight gain impacted negatively on their quality of life but this information was based on a telephone survey which was not rigorous in design.

Prolactin-related problems: for most atypical antipsychotic drugs, the problems related to hyperprolactinaemia, such as gynaecomastia, galactorrhoea, impotence and infertility, were not reported (the exceptions were amisulpride, risperidone and sertindole). This seems to reflect a lack of awareness or concern by those

conducting trials about the distressing nature of such side-effects. The adverse events related to hyperprolactinaemia reported for amisulpride, risperidone and sertindole showed no statistically significant differences from their typical comparators.

Cardiotoxic effects: at least two atypical antipsychotic drugs had potentially fatal effects on cardiac conductance. In the UK, sertindole was withdrawn from the market in 1999 (except for patients already stabilised on it) and, in a long-term follow-up study of clozapine, recipients reported cardiomyopathy or myocarditis at a rate of approximately 3 per 1,000 in physically healthy young adults. However, in non-randomised studies of mortality for both drugs compared with other antipsychotic treatments, an excess in the number of cardiac deaths was not reported.

Atypical versus atypical antipsychotic drugs

The following differences were observed.

- More people taking amisulpride, compared with risperidone, experienced 'agitation'.
- Fewer people treated with clozapine, compared with risperidone, suffered movement disorders, impotence, dry mouth or insomnia.
- Fewer individuals treated with olanzapine, compared with clozapine, suffered nausea and vomiting, orthostatic dizziness, hypersalivation and constipation.
- Compared with olanzapine or risperidone, clozapine caused more fatigue, nausea and vomiting, excess salivation, tachycardia, orthostatic dizziness, constipation and leucocytosis.
- Olanzapine caused more weight gain and dry mouth than risperidone but fewer movement disorders.
- Quetiapine may have been more likely to improve depression than risperidone.
- Zotepine was perhaps more likely to cause movement disorders than clozapine or risperidone.
- Amisulpride may be more effective than risperidone in terms of 'response'.

Treatment-resistant illness

Clozapine was more effective than typical antipsychotic drugs in treating those with treatment-resistant illness.

Negative symptoms

In most trials, the effect of new atypical antipsychotic drugs on negative symptoms was not addressed, which is surprising given the claims

made by many manufacturers for their efficacy in treating these symptoms. Clozapine was found to be more effective than typical antipsychotic drugs in improving negative symptoms in those whose illnesses were resistant to conventional treatment. Zotepine also seemed to be more effective on negative symptoms.

First-episode schizophrenia

In one trial of risperidone in first-episode schizophrenia, participants responded similarly to all those with schizophrenia for all the major outcomes of interest. In a trial of olanzapine versus haloperidol, olanzapine was reported to be more effective than haloperidol in treating a subgroup with first-episode psychosis and caused fewer extrapyramidal symptoms; however, the quality of the report was poor. There was no evidence relating to other antipsychotic drugs in first-episode illness.

Schizoaffective disorder

In one trial of risperidone versus haloperidol for treatment of schizoaffective disorder, no differences were found between groups with regard to mental state but risperidone was associated with fewer movement disorder side-effects. In another trial, olanzapine was found to be significantly more effective than haloperidol in improving mental state in a subgroup with schizoaffective disorder.

Cost-effectiveness

Amisulpride was more effective than haloperidol and, if ziprasidone remains unlicensed, represents the most cost-effective atypical antipsychotic drug.

Clozapine was more cost-effective than haloperidol and appeared from the model to be cost-effective compared with other atypical antipsychotic drugs; however, the cost of weekly blood monitoring was not included and the total cost figure is likely to be significantly higher in practice.

Olanzapine was the cheapest atypical antipsychotic drug but may be less effective than the others (not statistically significant). Some side-effects, such as weight gain associated with olanzapine treatment, were not included in the estimation of quality-adjusted life-years (QALYs), hence the effectiveness of olanzapine may have been overestimated.

Quetiapine was not more cost-effective than haloperidol and, compared with other atypical drugs, it was not a cost-effective treatment option (differences are not, however, statistically significant).



Risperidone had the highest costs after amisulpride but was also associated with higher QALYs than other atypical antipsychotic drugs. It did not appear to be superior and was dominated by ziprasidone.

Sertindole was dominated by chlorpromazine (apart from in final-line therapy for which it has better outcomes). Its costs and QALYs were both lower than those for haloperidol. Sertindole did not seem to be superior to other atypical drugs and is dominated (higher costs and lower number of QALYs) by ziprasidone.

Zotepine was cheaper but less effective than haloperidol. It did not appear to be superior to other atypical antipsychotic drugs.

Conclusions

The evidence for the effectiveness of the new atypical antipsychotic drugs was, in general, of poor quality, based on short-term trials and difficult to generalise to the whole population with schizophrenia. Thus all conclusions are based on limited evidence and should be treated with caution. Further research is needed.

However, individuals with schizophrenia may have found new atypical antipsychotic drugs (except for zotepine and ziprasidone) more acceptable than their typical comparators as, in general, fewer of them left trials early. Apart from clozapine for those with treatment-resistant illness, none of the new atypical antipsychotic drugs stands out as being more effective than the others. They all seemed to have slightly different side-effect profiles, which may have varying importance for those with schizophrenia and their carers.

Cost-effectiveness

Given the uncertainty about the validity of the clinical data for typical antipsychotic drugs and what is an acceptable cost/QALY, it was not possible to reach any definite conclusions as to whether the additional costs and benefits represent value for money.

Recommendations for research

1. More useful research is urgently needed: long-term trials involving large numbers of people, less rigid inclusion criteria, and outcomes relevant to those with schizophrenia and their carers should all be of primary concern. Less rigid, more pragmatic trial protocols may help to both decrease trial attrition rates and to increase the generalisability of the results. Outcomes related to prolactin problems and sexual side-effects are particularly poorly reported at present. Funding that is as free of conflicts of interest as possible is justified.
2. Large, long-term RCTs in which atypical antipsychotic drugs are compared with each other would be useful, particularly risperidone versus olanzapine and zotepine versus clozapine.
3. Trials of all atypical antipsychotic drugs, along with other aspects of care, should be undertaken in those with first-episode schizophrenia, treatment-resistant schizophrenia, schizoaffective disorder and predominantly negative symptoms. RCTs are also needed on effects in children and the elderly; on the effectiveness and safety of using more than one antipsychotic drug simultaneously; on whether differences in gender or ethnicity influence response to antipsychotic drugs; and on the impact of adjunctive psychosocial treatments on antipsychotic effectiveness.
4. Future systematic reviews of this topic should include trials in which clinician-determined switching of medication is allowed within the time frame of the study in reaction to poor response or serious side-effects.

Publication

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