Clinical and cost-effectiveness of different classes of antipsychotic drug treatments

Randomised controlled trials of conventional antipsychotic versus new atypical drugs, and new atypical drugs versus clozapine, in people with schizophrenia responding poorly to, or intolerant of, current drug treatment

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Executive summary

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Executive summary

Objectives

The aim of the study was to determine the clinical and cost-effectiveness of different classes of antipsychotic drug treatment in people with schizophrenia responding inadequately to, or having unacceptable side-effects from, their current medication.

Methods

Design

Two pragmatic, randomised controlled trials (RCTs) were undertaken. The first RCT (band 1) compared the class of older, inexpensive conventional drugs with the class of new atypical drugs in people with schizophrenic disorders, whose current antipsychotic drug treatment was being changed either because of inadequate clinical response or owing to side-effects. The primary hypothesis was that, in this population, the additional acquisition costs of the new atypical drugs would be offset by improvements in health-related quality of life and/or savings in the use of other health and social care services, compared with conventional drugs.

The second RCT (band 2) compared the new (non-clozapine) atypical drugs with clozapine in people whose medication was being changed because of poor clinical response to two or more antipsychotic drugs. The primary hypothesis was that, in this population, the additional acquisition costs of clozapine would be offset by improvements in health-related quality of life and/or savings in the use of other services, compared with the new atypical drugs.

Both RCTs were four-centre trials with concealed randomisation and three follow-up assessments over 1 year, blind to treatment. The trial was designed to minimise extra work for the referring clinician.

Setting

In general, the study was carried out in adult mental health settings in 14 NHS trusts in Greater Manchester, Nottingham and London.

Subjects

In total, 227 participants (40% of the planned sample) were randomised into the band 1 comparison and 136 (98% of the planned sample) were randomised into band 2. Participants were aged 18–65 years and one or more randomisations resulted from referrals by 95 general adult psychiatrists.

Interventions

Participants were randomised to a class of drug. The managing clinician selected the individual drug within that class, except for the clozapine arm in band 2. The class of new atypical drugs included risperidone, olanzapine, quetiapine and amisulpride. The class of conventional drugs included older drugs, including depot preparations. As in routine practice, clinicians and participants were aware of the identity of the prescribed drug, but clinicians were asked to try, as much as was compatible with good practice, to keep their participating patient on the randomised medication for at least the first 12 weeks. If the medication needed to be changed, the clinician was asked to prescribe another drug within the same class, if possible.

Main outcome measures

The primary outcome was the Quality of Life Scale (QLS). Secondary clinical outcomes included symptoms [Positive and Negative Syndrome Scale (PANSS)], side-effects and participant satisfaction. Economic outcomes were costs of health and social care and a utility measure.

Results

Recruitment to band 1 was less than anticipated (40%) and diminished during the course of the trial. This appeared largely to result from the loss of perceived clinical equipoise (clinicians progressively becoming more convinced of the superiority of new atypicals). Good follow-up rates and a higher than expected correlation between QLS score at baseline and at follow-up meant that the sample as recruited had 75% power to detect a difference in QLS score of 5 points between the two treatment arms at 52 weeks. The sample was recruited approximately as planned to ▶

band 2. Follow-up assessments were completed at week 52 in 81% of band 1 and 87% of band 2 participants.

Band 1

The intention-to-treat comparison of conventional versus new atypical drugs showed that, in people with schizophrenia whose medication was being changed because of intolerance or inadequate response, there was no disadvantage in terms of quality of life or symptoms over 1 year in commencing conventional antipsychotic drugs rather than new atypical drugs. Inspection of the data showed that, on the QLS and symptom measures, those participants in the conventional arm showed a trend towards greater improvements. This suggests that the failure to find the predicted advantage for new atypicals was not due to inadequate recruitment and statistical power in this sample. Participants reported no clear preference for either class of drug. There were no statistically significant differential outcomes for participants entering band 1 for reasons of treatment intolerance to those entering because of broadly defined treatment resistance.

Net costs of care over the year varied widely, with a mean of £18,850 in the conventional drug group and £20,123 in the new atypical group, not a statistically significant difference. Of these costs, 2.1% and 3.8% were due to antipsychotic drug costs in the conventional and atypical group, respectively. There was a trend towards participants in the conventional drug group scoring more highly on the utility measure at 1 year.

Band 2

The intention-to-treat comparison of new atypicals compared with clozapine in people with more narrowly defined treatment resistance showed an advantage for commencing clozapine in quality of life (QLS) at trend level ($p = 0.08$) and in symptoms (PANSS), which was statistically significant ($p = 0.01$), at 1 year. Clozapine showed approximately a 5-point advantage on PANSS total score. Clozapine showed a trend towards having fewer total extrapyramidal side-effects. Participants reported at 12 weeks that their mental health was significantly better with clozapine than with new atypicals ($p < 0.05$).

Net costs of care varied widely, but were higher than in band 1, with a mean of £33,800 in the clozapine group and £28,400 in the new atypical group. Of these costs, 4.0% and 3.3%, respectively, were due to antipsychotic drug costs. The increased costs in the clozapine group appeared to reflect the licensing requirement for inpatient admission for commencing the drug. There was a trend towards higher mean participant utility scores in the clozapine group.

The small number of deaths in the study appeared unrelated to class of drug treatment. There were no deaths on clozapine.

Conclusions

Band 1

In people with schizophrenia whose medication is being changed because of intolerance or broadly defined treatment resistance, there is no disadvantage in terms of quality of life and symptoms, or associated costs of care, over 1 year in commencing conventional antipsychotic drugs rather than new atypical drugs. Conventional drugs were associated with non-significantly better outcomes and lower costs. A trial of a conventional drug is recommended in patients unresponsive to or intolerant of current medication. This result is not accounted for by inadequate power or by patterns of drug discontinuation. Drug costs represented a small proportion of the overall costs of care (less than 5%).

Band 2

In people with schizophrenia whose medication is being changed because of narrowly defined treatment resistance, there is a statistically significant advantage in terms of symptoms but not quality of life over 1 year in commencing clozapine rather than new atypical drugs, but with increased associated costs of care.

Implications for healthcare

This trial does not allow any statements to be made about the relative safety, efficacy and cost of new atypicals versus conventionals as first line drugs. Thus, no comment is made on National Institute for Health and Clinical Excellence (NICE) guidance as to the availability of new atypical drugs for first line treatment. The results suggest that conventionals, which are substantially cheaper, still have a place in the treatment of patients unresponsive to or intolerant of current medication.

The NICE guidance on antipsychotic drug treatment for schizophrenia recommends the wider use of clozapine in treatment-resistant schizophrenia in the NHS. The results from this non-commercially sponsored trial in ▶

clinician-defined treatment resistance in the NHS show some advantage to clozapine over new atypical drugs and provide support to this aspect of NICE guidance, but with increased service costs. These increased costs associated with clozapine will diminish with the new licensing for outpatient initiation.

Further analysis

Further planned analyses of this data set include an examination of the effects of injectables, the impact and determinants of polypharmacy, and an examination of QLS validity and determinants of QLS score in schizophrenia.

Recommendations for research

The following areas are recommended for future research:

- a randomised trial of current antipsychotic treatment guidance using atypical versus conventional drugs in the context of careful management of schizophrenia
- the development of valid measures of utility in serious mental illness
- a randomised trial of low-dose 'conventional' treatment such as sulpiride versus a new atypical in first episode schizophrenia
- further examination of QLS validity and determinants of QLS score in schizophrenia
- an investigation into the possible financial and other mechanisms of rewarding clinician participation in trials.

Publication

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The HTA Programme was set up in 1993. Its role is to ensure that high-quality research information on the costs, effectiveness and broader impact of health technologies is produced in the most efficient way for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined to include all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care, rather than settings of care.

The HTA Programme commissions research only on topics where it has identified key gaps in the evidence needed by the NHS. Suggestions for topics are actively sought from people working in the NHS, the public, service-users groups and professional bodies such as Royal Colleges and NHS Trusts.

Research suggestions are carefully considered by panels of independent experts (including service users) whose advice results in a ranked list of recommended research priorities. The HTA Programme then commissions the research team best suited to undertake the work, in the manner most appropriate to find the relevant answers. Some projects may take only months, others need several years to answer the research questions adequately. They may involve synthesising existing evidence or conducting a trial to produce new evidence where none currently exists.

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Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

The research reported in this monograph was commissioned by the HTA Programme as project number 96/19/06. The contractual start date was in May 1999. The draft report began editorial review in July 2003 and was accepted for publication in April 2005. As the funder, by devising a commissioning brief, the HTA Programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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