Randomized controlled trial of the effect on quality of life of second- vs first-generation antipsychotic drugs in schizophrenia: Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 1)


Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The study compared first-generation (typical) antipsychotic (FGAs) drugs with second-generation (atypical) antipsychotics (SGAs) (other than clozapine). The FGAs comprised chlorpromazine hydrochloride, flupenthixol, haloperidol, loxapine, methotrimeprazine, sulpiride, trifluoperazine hydrochloride, zuclopenthixol, and the depot preparations of fluphenazine decanoate, flupentixol decanoate, haloperidol decanoate, pipothiazine palmitate and zuclopenthixol decanoate. The SGAs comprised risperidone, olanzapine, amisulpride, zotepine and quetiapine fumarate. Ziprasidone was not included as a comparator as it was not licensed in the authors’ setting.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients with schizophrenia, aged between 18 and 65 years, whose psychiatrist chose to change current FGA or SGA drug treatment due to adverse effects or insufficient response. Further inclusion criteria were Diagnostic and Statistical Manual of Mental Disorders-IV schizophrenia, schizoaffective disorder, or delusional disorder. The patients included in the study were suffering for at least one month from positive psychotic symptoms. Patients under substance misuse, those suffering from medical disorders causally correlated with positive psychotic symptoms, and patients with a history of neuroleptic malignant syndrome were excluded from the study.

Setting
The setting was secondary care, namely five medical schools covering 14 NHS Trusts in north western England, Nottingham, western London, south eastern London and Cambridge. The economic study was carried out in the UK.

Dates to which data relate
The patients were recruited between 12 July 1999 and 18 January 2002 and were followed up for up to 52 weeks. The dates of the cost data were not reported. The price year was also not reported.

Source of effectiveness data
The effectiveness data were derived from a single study.

Link between effectiveness and cost data
It would appear that costing was carried out prospectively on the same sample of patients as that used in the
effectiveness study.

**Study sample**

Power calculations demonstrated that a sample of at least 110 participants per treatment arm was required to find a difference in the Quality of Life Scale score (QLS) of 5 points, assuming a statistical power of 80%, 95% confidence, 2-tailed assumptions and a follow-up rate of 75%. Initially, 275 patients were referred from the five centres. Of these, 9 (3%) were ineligible, 1 (0.4%) was unable to give consent and 36 (13%) refused consent, while 2 psychiatrists withdrew one referral each (1%). Overall, 227 patients (referred by 73 psychiatrists) were randomly assigned to the FGA group (n=118) and to the SGA group (109).

**Study design**

The analysis was based on a multi-centre, rater-blinded, randomised controlled trial. The patients were followed up at baseline, and at 12, 26 and 52 weeks. They were assumed to have been lost to follow-up if they missed a minimum of four visits. At the end of the 52 weeks, 3 patients in each group had died, 11 (5%) were lost to follow-up and 22 (10%) were removed from the study.

Randomisation was achieved after baseline assessment through a distant telephone service. Stratification was conducted per treatment centre and the patients were randomised using commuted blocks within strata. Clinicians blinded to the intervention conducted assessments at baseline, 12, 26 and 52 weeks. Blinding was achieved by isolating assessors and obstructing their contact with team members, by applying passwords for electronic data, by encrypting e-mails for randomisation, by avoiding discussions about patients with research teams, and by keeping case report forms inaccessible.

**Analysis of effectiveness**

The analysis was conducted on an intention to treat basis. Those lost to follow-up were accounted for using multiple imputations. Data were analysed using SPSS for Windows 10 (SPSS Inc., Chicago) and Stata Version 7 (StataCorp, College Station). The statistical analysis demonstrated that the patient groups were comparable in terms of their demographic and clinical characteristics. The secondary outcomes included:

- patient syndromes, as assessed using the Positive and Negative Syndrome Scale score;
- the Calgary Depression Scale score;
- participant attitudes and adherence ratings;
- the Global Assessment of Functioning Scale score;
- the Adverse Effects Rating Scale scores; and
- cases of polypharmacy.

In addition, the participants' satisfaction with the new antipsychotic medication was assessed at 12 and 52 weeks.

**Effectiveness results**

The analysis demonstrated that the intervention groups had no statistical differences in health outcomes. Differences in patient satisfaction between the two groups were assessed using the Mann-Whitney test, which demonstrated that the patients were indifferent to drug treatment.

Similarly, in relation to polypharmacy, differences between the two groups before randomisation and at 52 weeks were not statistically significant. In addition, even though more patients in the SGA group continued with the assigned treatment than those in the FGA group, the difference was not statistically significant (65% versus 54%; p=0.1).
Clinical conclusions
The use of SGAs or FGAs as options for the treatment of patients with schizophrenia, whose drug treatment was altered for clinical reasons, resulted in similar efficacy for adverse effects, symptoms and patient satisfaction.

Measure of benefits used in the economic analysis
The authors did not derive a summary benefit in the economic analysis. As the analysis demonstrated equal effectiveness of the two treatment options, a cost-minimisation analysis was performed. A benefit that was not combined with the costs was quality of life. This was assessed at baseline, and at 12, 26 and 52 weeks using QLS. The analysis was carried out on available quality of life data using a longitudinal analysis of covariance.

Direct costs
The health service costs included in the analysis were for hospital inpatient and outpatient services, primary and community care services, and prescribed drugs. The cost categories, quantities of resources used and unit costs were not reported. The resource use data were derived from the effectiveness study. However, the sources of the cost data and the price year were not reported. Discounting was not relevant as the costs were incurred during less than 2 years.

Statistical analysis of costs
No statistical analysis of the costs was reported.

Indirect Costs
The indirect costs were not included in the analysis.

Currency
UK pounds sterling () and US dollars ($). A conversion rate was not reported.

Sensitivity analysis
The authors conducted sensitivity analyses to investigate the impact of interchanging between treatment options during the first 12 weeks. Applying a 12-week horizon, the analysis was first performed on all patients. A second protocol analysis was conducted in which all patients who changed treatment arms before the end of 12 weeks were excluded from the analysis. To account for missing values on the QLS, the authors conducted multiple imputations.

Estimated benefits used in the economic analysis
Although FGAs seem to have shown better results for QLS scores, differences between the two treatment arms were not statistically significant, (p=0.24).

Cost results
At 52 weeks, the mean total costs were lower in the FGA group ($34,750, standard deviation, SD=48,100; 18,800, 26,000) than in the SGA group ($37,185, SD=46,250; 20,100, SD=25,000).

Synthesis of costs and benefits
The costs and benefits were not combined. As equal effectiveness was demonstrated in the clinical study, a cost-minimisation analysis was performed.

Authors' conclusions
"In people with schizophrenia whose medication is changed for clinical reasons, there is no disadvantage across 1 year
in terms of quality of life, symptoms, or associated costs of care in using FGAs (first-generation antipsychotics) rather than nonclozapine SGAs (second-generation antipsychotics).”

CRD COMMENTARY - Selection of comparators
The selection of the comparators was explicitly justified. The authors, in accordance with clinical guidelines in their setting, compared two broad drug categories (i.e. first- versus second-generation antipsychotic drugs) and not individual drugs. You should decide if the comparators used comprise a widely used technology in your own setting.

Validity of estimate of measure of effectiveness
The analysis was based on a multi-centre, rater-blinded, randomised controlled trial. This seems to have been appropriate given the study question. The study sample was representative of the study population and the patient groups were comparable at analysis. The methods of randomisation, blinding, length of study and loss to follow-up were all reported, suggesting that the internal validity of the study is likely to be good. In addition, an extensive statistical analysis was undertaken to deal with potential biases and confounding factors. Power calculations were conducted, but the power of the study was lower than anticipated (75% versus 80%) in the planning phase for the detection of expected differences in QLS score. However, this smaller sample size is unlikely to have affected the results.

Validity of estimate of measure of benefit
The authors did not use a summary measure of benefit in the economic analysis. As equal effectiveness was demonstrated, a cost-minimisation analysis was performed.

Validity of estimate of costs
The cost analysis was subject to a number of deficiencies. The cost and resource categories included were unclear and were not reported separately. In addition, the sources of the cost data, the conversion rates and the price year were not reported and no statistical or sensitivity analysis of the costs was carried out. These factors will have introduced uncertainty into the results, will make the analysis difficult to rework for other settings, and will limit the interpretation of study findings.

Other issues
The authors compared their findings with those from other studies and showed them generally to be in agreement. The issue of generalisability of the results was not directly addressed. The authors did not present their results selectively and the results from the statistical tests were well reported. However, the cost analysis was not well documented. The study considered adult patients with schizophrenia, whose medical treatment was changed because of adverse events or low efficacy, and this was reflected in the authors’ conclusions. One of the limitations of the study was the lack of a more robust valuation tool for the quality of life of patients with schizophrenia. In addition, the design of the study did not allow for within-group comparisons of different drugs within the same drug category. Finally, a sub-group analysis of patients with different characteristics (e.g. specified clinical symptoms, different duration of illness) was not performed.

Implications of the study
The authors made no explicit recommendations for changes in policy or practice. The analysis indicates areas where more research-based information is needed (e.g. comparisons within drug categories, sub-group analysis of patient groups, analysis on a greater sample size).

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Other publications of related interest
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Adolescent; Adult; Antipsychotic Agents /adverse effects /classification /therapeutic use; Cost-Benefit Analysis; England; Female; Follow-Up Studies; Health Care Costs; Humans; Male; Middle Aged; Patient Satisfaction; Practice Patterns, Physicians' /statistics & numerical data; Psychiatric Status Rating Scales; Quality of Life; Schizophrenia /drug therapy; Treatment Outcome

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