Cost-effectiveness analysis of ziprasidone versus haloperidol in sequential intramuscular/oral treatment of exacerbation of schizophrenia: economic subanalysis of the ZIMO trial
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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 present study compared ziprasidone treatment with haloperidol in sequential intramuscular/oral treatment for patients with exacerbation of schizophrenia. The study was based on the Ziprasidone Versus Haloperidol in Sequential IM/Oral Treatment (ZIMO) trial. The mean intramuscular doses were 32.1 mg/day for ziprasidone and 14.8 mg/day for haloperidol. Initial and final mean oral doses were, respectively, 113.9 and 137.2 mg/day for ziprasidone and 19 and 17 mg/day for haloperidol. Further details of the intervention strategies were described elsewhere (Perez et al. 2006, see 'Other Publications of Related Interest' below for bibliographic details).

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The population comprised patients with a schizophrenia exacerbation under conditions of standard medical practice. The patients included in this study were those who were assigned to treatment with haloperidol or ziprasidone and who took at least one dose of these drugs, and for whom information was available on both treatment effectiveness and consumption of resources whilst in hospital.

Setting
The practice setting was inpatient care. The economic study was carried out in Spain.

Dates to which data relate
The effectiveness data came from the ZIMO study published in 2006. The resource use and cost data were derived from sources published between 2004 and 2005. The price year was 2005.

Link between effectiveness and cost data
The same patients represented the prospective source for both clinical and resource use data.

Study sample
A total of 325 patients who met the criteria (see 'Study Population') were included. Of these, 255 were treated sequentially with ziprasidone and 70 with haloperidol. The authors reported the baseline characteristics of the patients and stated that there were no statistically significant differences between the groups. The only difference in baseline score that was very close to statistical significance was the positive symptoms sub-scale. No other details of sample
selection and power calculations were reported in this paper.

**Study design**
The analysis was based on the ZIMO study, a naturalistic, prospective multi-centre trial comparing the effectiveness and tolerability of oral and parenteral formulations of ziprasidone and haloperidol in patients with acute schizophrenia exacerbation under routine conditions of care (Perez et al. 2006). Though not reported explicitly in the paper, its naturalistic design implies that the intervention was individually decided by each provider, in a non-randomised way.

**Analysis of effectiveness**
Effectiveness was defined as the percentage of responders at the end of the study to each of the sequential treatments analysed. A responder was defined as a patient showing a >= 30% reduction from baseline score on the Brief Psychiatric Rating Scale (BPRS) negative symptoms sub-scale. A secondary analysis was performed in which responders were defined as those patients with a >= 50% reduction. No blinding of the outcome assessment was reported. The time horizon of the evaluation was adjusted to the duration of treatment for acute schizophrenia exacerbation in the hospital psychiatric ward until discharge. Further details were explained elsewhere (Perez et al. 2006). The statistical analysis included a descriptive study with central tendency and dispersion parameters. The continuous variables were evaluated by an analysis of covariance, which adjusted for potential confounders.

**Effectiveness results**
According to the effectiveness values obtained with the two treatments, a difference in effectiveness in favour of ziprasidone was observed in terms of the proportion of patients showing both >= 30% (15.3%; p=0.023) and >= 50% (15.4%; p=0.031) reductions in negative symptoms of the BPRS.

**Clinical conclusions**
The results showed that ziprasidone had a greater effectiveness in treating negative symptoms of schizophrenia regardless of whether the effectiveness criterion was a BPRS negative symptoms sub-scale reduction of >= 30% or >= 50%.

**Measure of benefits used in the economic analysis**
The measure of benefit used was that of patient responders (see 'Analysis of Effectiveness' section for definition).

**Direct costs**
The direct health care costs were based on the number of days of hospital stay, and the study medications and concomitant medications required for the treatment of acute schizophrenia exacerbations. The costs of hospital stay covered medical, nursing and other staff costs, room and catering, allocated common service costs and the costs of drug administration. The costs per day in hospital were taken from the published literature. Study drug and concomitant medications prices were from the Drug Product Catalogue, which equated to the hospital acquisition prices. For concomitant medication, the defined daily dose established by the World Health Organization was assigned to patients when information on administration route and dosage was lacking. The costs were adjusted for inflation using the Consumer Price Index. Discounting was not carried out because of the short-term time horizon. The price year was 2005.

**Statistical analysis of costs**
The data were treated stochastically and a similar statistical approach to that described in the 'Analysis of Effectiveness' section was used. Measures of central tendency and variability were reported. The mean total cost and cost per responder with each treatment option were reported, along with their 95% confidence intervals (CIs).
Indirect Costs
Productivity costs were not included in the analysis, which was appropriate given the study perspective.

Currency
Euro (EUR).

Sensitivity analysis
To estimate uncertainty around the incremental cost-effectiveness ratio, the quasi-95% intervals were calculated. In addition, bootstrapping techniques were used to calculate 95% CIs for effectiveness and costs, with a total of 2,000 additional items obtained via re-sampling. Cost-effectiveness planes, willingness-to-pay acceptability curves, and a threshold analysis to observe how variations affected the duration of hospital stay, were also reported.

Estimated benefits used in the economic analysis
In the >= 30% reduction group, the percentage of responders was 71.0% (95% CI: 65.4 to 76.6) for ziprasidone and 55.7% (95% CI: 44.1 to 67.4) for haloperidol, (p=0.023), significantly favouring ziprasidone.

In the >= 50% reduction group, the percentage of responders was 56.9% (95% CI: 50.8 to 62.9) for ziprasidone and 41.4% (95% CI: 29.8 to 53.8) for haloperidol, (p=0.031).

The percentage of patients taking one or more concomitant drugs was 38.6% for the ziprasidone group and 30.2% for the haloperidol group.

Cost results
The mean total cost per patient was EUR 3,582 (95% CI: 3,226 to 3,937) for ziprasidone and EUR 2,953 (95% CI: 2,471 to 3,436) for haloperidol, (p=0.039).

Synthesis of costs and benefits
The incremental cost for ziprasidone per additional responder was EUR 4,105 (95% CI: 113 to 51,864) for a reduction of >= 30% in BPRS negative symptoms and EUR 4,078 (95% CI: 376 to 51,213) for a reduction of >= 50%. The incremental cost-effectiveness ratios (ICERs) calculated using bootstrapping techniques were EUR 4,095 (95% CI: -130 to 22,231) and EUR 3,994 (95% CI: -305 to 21,583), respectively.

The cost-effectiveness plane of the re-samplings showed that most of the ICERs fell within the upper right quadrant, corresponding to greater effectiveness with higher cost. The acceptability curves showed ICER cut-off points for a 95% acceptance probability level of EUR 13,891 for a reduction of >= 30% in symptoms and EUR 13,884 for a reduction of >= 50%.

Authors' conclusions
The results of the analysis showed that the greater cost associated with the use of ziprasidone was offset by its greater effectiveness compared with haloperidol in treating the negative symptoms of schizophrenia, resulting in a lesser cost per responder. Therefore, the authors considered that the results, and the potential impact of relief of the negative symptoms of schizophrenia at both economic and social levels, showed that sequential intramuscular/oral treatment with ziprasidone is a cost-effective option in comparison with haloperidol.

CRD COMMENTARY - Selection of comparators
The comparator was justified and was intended to reflect routine practice in the authors' setting. However, readers should consider if this is an adequate comparator in their own settings.
Validity of estimate of measure of effectiveness
The analysis was based on the ZIMO study, a naturalistic, prospective multi-centre trial. However, no information about power and sample size calculations was reported; the reader may need to refer to the main clinical paper for these details. The authors stated some limitations to the generalisability arising from the unequal sample sizes. There was insufficient detail in this report about the parent trial to be able judge the adequacy of its internal validity, and the reader should refer to Perez et al. 2006 for further information. The statistical analysis and different analytical strategies were handled credibly, but limited details were reported. Given that this was a naturalistic non-randomised study, care should be taken in assessing whether the results were due solely to the intervention as other potential confounders could have been responsible. Although the two groups were comparable in most reported parameters, there was little detail of the adjustments method used.

Validity of estimate of measure of benefit
The measure of health benefit chosen (percentage of responders with >= 30% and >= 50% reductions in negative symptoms in the BPRS) is context specific and can only be compared with other psychiatric studies (and not with other economic evaluations). In addition, some other aspects such as positive symptoms were not evaluated. Uncertainty analyses over effectiveness estimates were conducted and reported.

Validity of estimate of costs
Relevant cost categories and their associated costs were taken into consideration. The resource quantities and the unit costs were not reported separately, which would make it difficult to rework the analysis for other settings. The price year, the sources of resource use and unit costs were adequately reported. In addition, sensitivity analyses were conducted to assess the robustness of the cost estimates used.

Other issues
The findings of the analysis were well reported, using both cost-effectiveness acceptability curves and cost-effectiveness planes. The authors compared their findings with those from other studies and their results were generally in agreement. They also addressed the issue of the generalisability of their results to other settings in the limitations reported. One such limitation was a possible overestimation of the costs of concomitant medication, although this was probably not significant in relation to the conclusions. Furthermore, the evaluation was based on a secondary objective, namely the reduction of negative symptoms, instead of the total BPRS score which would have identified haloperidol as the dominant option.

Implications of the study
As the authors reported, this study was aimed at evaluating only the negative symptoms of schizophrenia. It would probably have shown greater benefits if a societal perspective had been contemplated. This would have enabled a more accurate capture and costing of the true burden of negative symptoms of schizophrenia on the patient's and family's daily life.

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Other publications of related interest
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Indexing Status
Subject indexing assigned by NLM

MeSH
Administration, Oral; Adult; Antipsychotic Agents /administration & dosage /economics; Brief Psychiatric Rating Scale; Cost of Illness; Cost-Benefit Analysis; Drug Costs; Drug Therapy, Combination; Female; Haloperidol /administration & dosage /economics; Hospital Costs; Humans; Injections, Intramuscular; Length of Stay /economics; Male; Piperazines /administration & dosage /economics; Quality of Life; Research Design; Schizophrenia /drug therapy /economics; Spain; Thiazoles /administration & dosage /economics; Treatment Outcome

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