Cost-effectiveness analysis of schizophrenia relapse prevention: an economic evaluation of the ZEUS (Ziprasidone-Extended-Use-in-Schizophrenia) study in Spain

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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 study examined the atypical antipsychotic ziprasidone (ZIP), in differing doses, for the treatment of schizophrenia.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The target population comprised Spanish adult patients with stable chronic schizophrenia.

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

Dates to which data relate
The effectiveness and resource use evidence was drawn from the 52-week ZEUS trial, published in 2005. The price year was 2005.

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

Link between effectiveness and cost data
The costing was carried out prospectively on the same sample of patients as that used in the effectiveness analysis.

Study sample
The ZEUS study was reported in greater detail elsewhere (Bagnall et al. 2005, see 'Other Publications of Related Interest' below for bibliographic details). The study reported the results of a comparison between ZIP in daily doses of 40 mg (n=75), 80 mg (n=72) or 160 mg (n=71), versus placebo (n=75).

Study design
The ZEUS study was a randomised, double-blind, placebo-controlled clinical trial of 52 weeks in duration. It assessed the efficacy of ZIP at three doses. The method of randomisation, blinded assessment and loss to follow-up were not reported in the present study.
Analysis of effectiveness
The primary end points were the rate of relapse and relapse-free time, calculated using survival analysis from the number of relapses observed with each intervention. The rate of relapse was used to calculate the probability and risk of relapse in a given period, using an actuarial analysis. Adverse events (AEs) were reported as rates of serious AEs and severe AEs. It was not stated whether the analysis of the clinical study was conducted on an intention to treat basis or for treatment completers only. The authors did not report the comparability of the patient groups at baseline.

Effectiveness results
The probability of relapse requiring hospitalisation was 0.43 for ZIP 40 mg, 0.35 for 80 mg, 0.36 for 160 mg and 0.38 for the average dose (base-case), (p<0.001 in all cases, except for 40 mg with p<0.003), versus a probability of 0.77 with placebo.

The proportion of patients with serious AEs was 3.95% for ZIP 40 mg, 0% for 80 mg, 0% for 160 mg and 1.36% for the average dose, versus 0% with placebo.

The proportion with severe AEs was 13.16% for ZIP 40 mg, 6.94% for 80 mg, 2.82% for 160 mg and 7.74% for the average dose, versus 9.33% with placebo.

Clinical conclusions
Given that there were statistically significant differences in efficacy between ZIP and placebo, a cost-effectiveness analysis was then performed. AEs were considered for their effects on costs only.

Modelling
A deterministic model was constructed in Microsoft Excel as a theoretical framework allowing simulations to be made of complex health care processes related to drugs. It was designed according to pre-established protocols, using estimations obtained from available data on the efficacy, toxicity and costs of the alternatives compared. The time horizon was one year.

Measure of benefits used in the economic analysis
The outcome measure used in the economic analysis was the schizophrenia relapses avoided.

Direct costs
Discounting was not carried out since a one-year analysis was performed. The quantities and costs were analysed in terms of the proportions of patients requiring various resources and were presented in a disaggregated fashion. The costs included in the analysis were the acquisition costs of drugs and concomitant medications for treatment of symptoms associated with underlying disease, the cost of treating AEs related to study medication, and the cost of relapses requiring hospitalisation. The quantities were estimated on the basis of data collected in the ZEUS study. The drug costs were obtained from the database of proprietary medicinal products of the Spanish Board of Pharmacy, while other unit costs were obtained from a national database. Costs not included were those for resources scheduled in the clinical trial (assumed to be equivalent for all treatments), rescue medication (antipsychotic administered to patients assigned to placebo and who withdrew from the study), and direct non-health care costs (e.g. childcare or transport). The price year was 2005.

Statistical analysis of costs
The costs were treated deterministically.

Indirect Costs
The indirect costs were not included in the base-case analysis. In the sensitivity analysis, the authors estimated the indirect costs resulting from absenteeism from work that would be avoided with the intervention (by reducing hospitalisations).

**Currency**
Euros (EUR).

**Sensitivity analysis**
In the base-case, average values for ZIP doses, resource use and probabilities of relapse were used. A simple univariate sensitivity analysis was carried out in which the following scenarios were evaluated:

- different doses of ZIP (40, 80, 160 and 240 mg/day);
- minimum and maximum (+/- 20%) unit costs for health care resources;
- estimated threshold level of the probability of relapse with ZIP at which the annual cost of preventing a relapse was equal to the minimum cost reported in the Psychosp study (Peiro et al. 2004, see 'Other Publications of Related Interest' below for bibliographic details);
- estimated threshold of number of hospital days at which the cost of preventing a relapse would be zero; and
- estimated indirect costs that would be avoided with ZIP.

The ranges were derived from ranges and confidence intervals (CIs) given in the literature.

**Estimated benefits used in the economic analysis**
The benefits over a one-year analysis were reported as the numbers-needed-to-treat (NNTs) to prevent a relapse and the NNTs to observe a relapse:

- for ZIP 40 mg, these were 2.9 (95% CI: 1.8 to 3.1) and 2.3 (95% CI: 2.0 to 2.8), respectively;
- for ZIP 80 mg, these were 2.3 (95% CI: 2.2 to 4.2) and 2.9 (95% CI: 2.4 to 3.7), respectively;
- for ZIP 160 mg, these were 2.4 (95% CI: 2.1 to 4.0) and 2.8 (95% CI: 2.3 to 3.5), respectively;
- for ZIP average dose, these were 2.6 (95% CI: 2.0 to 3.7) and 2.6 (95% CI: 2.2 to 3.3), respectively; and
- for placebo, the NNT to observe a relapse was 1.3 (95% CI: 1.2 to 1.4).

The side effects of treatment were considered in the economic analysis.

**Cost results**
The approximate annual cost per patient treated was EUR 2,724 with ZIP 40 mg, EUR 2,446 with 80 mg, EUR 3,100 with 160 mg and EUR 2,754 with the average dose, versus EUR 2,682 in the placebo group.

Therefore, the incremental costs produced by ZIP were EUR 42 with the 40-mg dose, -EUR 236 (savings) with the 80-mg dose, EUR 418 with the 160-mg dose and EUR 72 with the average dose.

**Synthesis of costs and benefits**
The estimated benefits and costs were combined in an incremental cost-effectiveness ratio (ICER).
The average annual incremental cost per relapse avoided was EUR 186 for the average dose of ZIP, ranging from approximately -EUR 557 (savings) for the 80-mg dose to EUR 1,015 for the 160-mg dose. These values were all lower than the minimum cost of a relapse (EUR 2,830).

The daily dose of ZIP did not determine the annual cost per relapse avoided in a uniform manner because no relationship between the dose administered and the efficacy of ZIP in preventing a relapse was found.

ZIP 240 mg/day resulted in an ICER of EUR 3,221 per relapse avoided.

Minimum and maximum costs of health care resulted in large variation, changing the ICER to -EUR 234 (savings) and EUR 606, respectively.

For the cost of preventing a relapse to be equal to the minimum in the Psychosp study (i.e. EUR 2,830), the probability of a relapse with ZIP would have to increase to 0.54. This is 11 to 19% higher than the rates seen in the ZEUS study (0.35 to 0.43).

The duration of hospital stay only had to increase from a base-case value of 21.78 days to 22.96 days for the additional cost of ZIP to be zero in comparison with placebo.

The estimated indirect cost-savings with ZIP were EUR 71 per patient.

Authors' conclusions
From the perspective of the Spanish National Health Service, the prevention of schizophrenia relapse with ziprasidone (ZIP) was cost-effective in comparison with no treatment. However, the base-case showed large quantitative variations in relation to most of the parameters examined in the sensitivity analysis.

CRD COMMENTARY - Selection of comparators
The authors did not provide an explicit justification for the choice of the comparator (placebo) but this may have been discussed in the publication of the clinical trial (Bagnall et al. 2005). Treatment guidelines in schizophrenia usually recommend active therapy with typical or atypical antipsychotics, therefore it is important to decide whether this comparator does represent current practice in your own setting.

Validity of estimate of measure of effectiveness
The analysis was based on a single, randomised controlled trial, which was appropriate for the study question. The study sample, patient groups and loss to follow-up were not described in this paper, nor was the basis of the effectiveness analysis (intention to treat or treatment completers only). In a study of 52 weeks’ duration, which is relatively lengthy in schizophrenia trials, the loss to follow-up may have been significant. Consequently, the handling of the analysis could have had a substantial impact on the results.

Validity of estimate of measure of benefit
The estimate of benefits (relapses avoided) was obtained directly from the effectiveness analysis. It was justified by being a major clinical objective as well as one of the determining factors in the greater costs of treating schizophrenia.

Validity of estimate of costs
All the categories of cost relevant to the perspective adopted were included in the analysis. Some relevant costs were omitted because they arose from the trial protocol and were common to all comparators. This is unlikely to have affected the authors’ conclusions. The costs and the quantities were reported separately, which will enhance the generalisability of the results. No statistical analysis of the quantities was performed. However, medication dosage and duration of hospital stay during relapse were varied in the sensitivity analysis. The unit costs were taken from national published sources. A sensitivity analysis of the prices was conducted. Discounting was unnecessary since all costs were incurred during one year. The price year was reported, which will aid any possible inflation exercises.
Other issues
The authors noted the results of other studies, but acknowledged that they were not comparable because most analyses compared ZIP with active comparators rather than placebo. The issue of generalisability to other settings was not addressed. The authors did not present their results selectively and their conclusions reflected the scope of the analysis. They did not justify their choice of a single study for the analysis, even though other clinical trials of ZIP existed.

The authors acknowledged and reported further limitations to their study. In particular, they pointed out that a dose-dependent relationship was not established for the efficacy of ZIP in the ZEUS study, which makes interpretation of the results difficult since daily dose is an important factor in the final cost of the disease. Another limitation of the study was the use of a theoretical model (i.e. a simplified simulation of reality) based on a non-pragmatic clinical trial.

Implications of the study
The authors suggested that, based on data from a long (52-week) Spanish clinical trial, the treatment of patients with chronic schizophrenia with ZIP prevents a considerable number of relapses at a reasonable cost, thus producing cost-savings in Spain.

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Other publications of related interest


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MeSH
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