Impact of side-effects of atypical antipsychotics on non-compliance, relapse and cost

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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 use of atypical antipsychotics in schizophrenia. Olanzapine, risperidone and ziprasidone were compared with quetiapine.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised outpatients with schizophrenia who were taking oral conventional antipsychotics.

Setting
The setting was secondary care. The study was carried out in the UK.

Dates to which data relate
The effectiveness data were derived from a review of published studies conducted in the past 20 years. Literature data were supplemented by expert opinion, the dates of which were not provided. The cost data for the US were obtained from two studies published in 1996 and 2001, while the cost data for the UK were obtained from another study published in 2000. The price year was not reported.

Source of effectiveness data
The evidence for the final outcomes was derived from a review of published studies and reviews. It was supplemented by a two-round Delphi study, in which a panel of 25 experts on schizophrenia assessed the impact of different side effect profiles on non-compliance.

Modelling
A state-transition model was used to represent the relationship between compliance and relapse over a 1-year period following recovery from an episode of schizophrenia. This technique involved identifying clinically important events and defining them as health states. The model incorporated three such states, "well, compliant" (starting state), "well, not compliant" and "relapsed". A theoretical cohort of patients then moved cyclically from one health state to another, in cycles set at the end of the month, for one year. To allow for the possibility that the probabilities of becoming not compliant and/or relapsing vary over time, Weibull survival distributions were fitted to the relevant data for each of the transition probabilities.
Outcomes assessed in the review
The outcomes assessed in the review were:

- the non-compliance and relapse rates observed when there was an abrupt withdrawal of antipsychotic medication,
- the rate of recovered patients continuing treatment with atypical antipsychotics, and
- the relapse rates linked to a particular treatment period.

Study designs and other criteria for inclusion in the review
Longitudinal observational studies, carried out in North America, Europe and Australasia, of outpatients with schizophrenia who were taking oral conventional antipsychotics, and which reported time-specific non-compliance rates, were included in the review.

Sources searched to identify primary studies
MEDLINE, EMBASE and PsycINFO were searched for primary studies.

Criteria used to ensure the validity of primary studies
Not stated.

Methods used to judge relevance and validity, and for extracting data
Only those studies reporting a time-specific non-compliance rate were judged to be relevant.

Number of primary studies included
A total of 32 publications were included in the analysis.

Methods of combining primary studies
Survival analysis methods were used to summarise the data and estimate non-compliance rates after 3, 6 and 12 months' treatment with conventional antipsychotics.

Investigation of differences between primary studies
Not reported.

Results of the review
The estimated differential 1-year relapse rate of olanzapine compared to quetiapine was 6.1% (95% confidence interval, CI: 3.2 - 9.3; 99% CI: 2.3 - 11.1). This difference was highly significant as the 99% CI did not include zero.

The estimated differential 1-year relapse rate of risperidone compared to quetiapine was 5.6% (95% CI: 2.7 - 9.3; 99% CI: 1.5 - 11.4). Again, this difference was highly significant.

The estimated differential 1-year relapse rates of ziprasidone compared to quetiapine were small and statistically insignificant.

Methods used to derive estimates of effectiveness
A two-round Delphi study involving 25 leading European and North American experts on schizophrenia was undertaken. These experts were asked to assess the impact of different side effect profiles on non-compliance.
Information on side-effect profiles for conventional and atypical antipsychotics, as derived from published studies and the Cochrane Collaboration Reviews, was given to each expert. The experts were blinded to the identities of the atypical antipsychotics (identified by fictitious names) and were presented in a balanced order. The experts were then asked to estimate, using the information supplied, an estimate of the "lowest likely", "most likely" and "highest likely" non-compliance rates after 3, 6 and 12 months' treatment for each atypical antipsychotic. Four weeks later, each expert was presented with all his estimates and those of the other experts (anonymously). Each expert was then asked to confirm or revise their initial estimates in the light of other experts' conclusions. This was done in order to bring the experts closer to a consensus.

**Estimates of effectiveness and key assumptions**

The experts concluded the following:

- the estimated non-compliance rates for all atypical antipsychotics profiles at 3, 6 and 12 months were better than those derived from the literature for conventional antipsychotics;
- the estimated non-compliance rates of quetiapine and ziprasidone were practically equal;
- the non-compliance rates based on the profiles of olanzapine and risperidone were greater than those based on the profiles of quetiapine and ziprasidone;
- the difference between the two pairs (olanzapine, risperidone and quetiapine, ziprasidone) increased with the duration of treatment.

**Measure of benefits used in the economic analysis**

No summary benefit measure was used in the economic analysis. A cost-consequences approach was therefore adopted.

**Direct costs**

The resources and the quantities were not reported separately. The direct costs of the hospital were included in the analysis. For the US-based costs, the authors derived their cost data from two studies (see Other Publications of Related Interest). One study (Glazer and Ereshefsky) built an economic model of outpatient antipsychotic therapy in schizophrenic patients who had been admitted to hospital numerous times in order to estimate the 1-year direct costs. The other study (Rosenheck et al.) estimated the average cost of hospitalising a veteran administration patient on atypical antipsychotics. For the UK-based costs the authors derived their cost data from a study by Almond and O'Donnell (see Other Publications of Related Interest), who used a Markov model to compare the 5-year costs of olanzapine, risperidone and haloperidol in the treatment of schizophrenia in the UK. Discounting was unnecessary, as all the costs were incurred during one year, and was not conducted. The study reported the incremental costs of olanzapine, risperidone and ziprasidone over quetiapine. The price year was not reported.

**Statistical analysis of costs**

The costs were treated in a stochastic manner. The authors reported the mean incremental costs with their respective 95% and 99% CIs.

**Indirect Costs**

The indirect costs were not included in the analysis.

**Currency**

US dollars ($) when the US data sets were used. UK pounds sterling (£) when the UK data sets were used.
Sensitivity analysis
No sensitivity analyses were performed.

Estimated benefits used in the economic analysis
See the 'Effectiveness Results' section.

Cost results
The modelled estimates of difference of olanzapine from quetiapine in incremental 1-year per patient costs of differing side effect profiles were $530 (95% CI: 275 - 800; 99% CI: 200 - 960) for US costs and 630 (95% CI: 330 - 960; 99% CI: 235 - 1,140) for UK costs.

The modelled estimates of difference of risperidone from quetiapine in incremental 1-year per patient costs of differing side effect profiles were $485 (95% CI: 235 - 800; 99% CI: 130 - 985) for US costs and 575 (95% CI: 280 - 960; 99% CI: 155 - 1,170) for UK costs.

The modelled estimates of difference of ziprasidone from quetiapine in incremental 1-year per patient costs of differing side effect profiles were $45 (95% CI: -145 - 235; 99% CI: -240 - 320) for US costs and 50 (95% CI: -175 - 275; 99% CI: -285 - 370) for UK costs. These differences were not statistically significant since both sets of CIs contained 0.

Synthesis of costs and benefits
The costs and benefits were not combined since a cost-consequences approach was taken.

Authors' conclusions
Differing side effect profiles of the newer antipsychotic agents were likely to lead to different compliance rates and, consequently, variation in the relapse rates. The authors also concluded that the cost implications of the heterogeneous clinical outcomes were considerable.

CRD COMMENTARY - Selection of comparators
The choice of quetiapine as the comparator was not explicitly justified, although it would appear to be one of the four atypical antipsychotics currently being prescribed. Thus, it represented common practice in the authors' setting. You should decide if the comparator represents current practice in your own setting.

Validity of estimate of measure of effectiveness
The authors did not state that a systematic review of the literature had been undertaken, reporting only that a review using three search engines had found 32 publications. However, even if a systematic review was not performed to identify relevant research and minimise biases, the review undertaken was quite thorough. Three search engines were used to identify relevant studies carried out in North America, Europe and Australasia within the past 20 years. Data from these 32 studies were then supplemented with data from 2 systematic reviews. Survival analysis methods were used to summarise the data and estimate non-compliance rates. However, this method was not reported clearly, and it would appear that no weighting scheme was applied to reflect differences in sample sizes. Even though an investigation of differences between the primary studies was not reported, the inclusion criteria for entry into the review were fairly narrow (longitudinal observational studies of outpatients with schizophrenia who were taking oral conventional antipsychotics, which reported a time-specific non-compliance rate). Thus, any differences between the primary studies should not have greatly affected the estimate of effectiveness.

The data derived from the literature review were supplemented by expert opinion. A Delphi panel of 25 leading European and North American experts in the field was assembled to derive the impact of different side effect profiles on non-compliance. The authors took steps to avoid attrition between the two rounds and, at the end of the study, all 25
experts had participated. To minimise biases, all materials given to the experts were standardised and the experts were blinded to the identities of the four antipsychotic treatments. To bring experts closer to consensus, feedback comprised both the individual and group responses. Sampling variation and intra-individual uncertainty were taken into account by bootstrapping. Despite these strengths, the authors noted that the Delphi experts were not randomly selected, thus raising the possibility of being a biased sample of experts on the treatment of schizophrenia. However, the authors also pointed out, that there was no a priori reason to assume that any bias would be related to the views of the experts on the relationship between drug side effects and compliance.

**Validity of estimate of measure of benefit**
The authors did not derive a summary measure of health benefit. The analysis was therefore categorised as a cost-consequences analysis.

**Validity of estimate of costs**
Since the cost data were derived and combined from several studies, and the authors gave very few details of which costs had been included, it is not possible to say whether all the categories of cost and all relevant costs were included in the analysis. However, the authors did point out that the per patient cost of managing treatment-induced side effects was ignored in the model, as it was assumed to be the same for each of the four atypical antipsychotics studied. Therefore, it is unlikely that such an omission will have affected the authors' conclusions. The costs and the quantities were not reported separately and the price year was not reported. These two limitations weaken the generalisability of the results and hinder refutation exercises to other settings. The incremental costs were presented with their respective 95% CIs and 99% CIs, thus acknowledging uncertainty in the costs. Discounting was unnecessary, as all the costs were incurred in one year, and was not performed.

**Other issues**
The authors did not compare their findings with those from other studies. The issue of generalisability to other settings was not addressed, further hampering the generalisability of the authors' results. The authors do not seem to have presented their results selectively. The authors' conclusions reflect the scope of the analysis. The authors reported no further limitations to their study.

**Implications of the study**
The authors seem to suggest that the results should be confirmed in patient-based studies. If these confirm the authors' results it would imply that, for 1.5% of UK patients with schizophrenia, changing the medication to an atypical antipsychotic with a better side effect profile could realise savings of up to 1 million per annum in direct treatment costs.

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**Other publications of related interest**


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