Thirty-five months experience of risperidone long-acting injection in a UK psychiatric service including a mirror-image analysis of in-patient care

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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 use of risperidone long-acting injection (RLAI), compared with conventional oral antipsychotics, for patients with schizophrenia. RLAI (50 mg) was administered once every 2 weeks.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients with mental illness (mainly schizophrenia). Patients with bipolar disorder were excluded.

Setting
The setting was the hospital and the community. The economic study was carried out in the UK.

Dates to which data relate
The effectiveness and resource use data were gathered from October 2002 to September 2005. The price year was not explicitly stated, although 2005 prices appear to have been applied.

Link between effectiveness and cost data
The costing was performed retrospectively on the same sample of patients as that included in the analysis of effectiveness.

Study sample
Power calculations, if performed, were not reported. All patients who commenced RLAI from October 2002 until September 2005 were retrospectively identified from the hospital pharmacy records. Over the study period, 92 patients commenced RLAI, but case notes could not be traced for 2 patients. Thus, the whole sample of RLAI patients comprised 90 individuals, of which 64.4% were male. The mean age was 39.7 years (95% confidence interval, CI: 37.2 to 42.2). Sixteen patients were not eligible for the mirror-image analysis, thus the mirror-image group comprised 74 patients, of which 60.8% were male. The mean age was 39.9 years (95% CI: 37.2 to 42.6). An external control group of 46 individuals (67.4% male) was defined by selecting the patient with the next alphabetical surname, with a psychotic disorder (excluding bipolar affective disorder), treated with oral antipsychotic medication and registered at the same community clinic as each patient prescribed RLAI at the time of the evaluation. The mean age of this group was 41.2 years (95% CI: 37.6 to 44.7).
To take into account the possible impact of confounding factors, separate analyses were carried out that excluded patients who were treatment resistant (TR) at baseline or who commenced input from the Assertive Outreach Team (AOT) during either the previous-treatment period or the RLAI-treatment period.

**Study design**
The design of the primary analysis was a mirror-image study, that is, a retrospective within-group comparison study. A retrospective cohort study was also performed using an external control group. The study was carried out within the General Adult Psychiatry Service in Salford, UK. The study lasted 35 months, but the average length of follow-up was not reported. No patient was lost to the follow-up assessment as only patients with complete case records were considered. No blinding was performed.

**Analysis of effectiveness**
In the mirror-image analysis, the primary clinical end point was the total number of days of psychiatric inpatient care during the period that the patient was prescribed RLAI versus the total number of days of psychiatric inpatient care during an equal length of time immediately prior to starting RLAI. For patients who started or stopped RLAI in the community, the start and end of treatment were defined as the date of the first and last injection of RLAI, respectively. For those who commenced RLAI as inpatients, the primary mirror-image analysis defined the start of the RLAI-treatment period as the date they were discharged from inpatient care on RLAI with the previous-treatment period being taken backwards from this discharge date. This methodology considered the admission during which RLAI was started (the .index admission/) as inpatient care associated with failure of the previous treatment. A secondary mirror-image analysis was conducted in which the index admission was ignored for those who started RLAI as inpatients. Other clinical end points were adverse effects, treatment duration, and rates or reasons for the discontinuation of RLAI.

All patients included in the initial study sample were taken into account in the analysis of effectiveness. At baseline, both RLAI groups differed significantly from the control group in terms of their higher baseline rates of drug misuse, alcohol misuse, and histories complicated by physical aggression, convictions and forensic psychiatry involvement.

**Effectiveness results**
In the RLAI group, 36 patients started treatment in the community and 54 as inpatients (including 37 who commenced treatment during a compulsory admission). The most common reason for starting RLAI was non-compliance with oral antipsychotic medication. The antipsychotic that preceded RLAI was atypical oral (57% of patients), conventional depot (39% of patients), clozapine (3% of patients) and no medication (1% of patients).

The total number of admissions fell from:

65 in the pre-RLAI phase to 33 in the RLAI phase in the total mirror-image group, (n=74);

53 to 21 when TR patients were excluded;

45 to 28 when AOT patients were excluded; and

38 to 18 when TR and/or AOT patients were excluded.

The reduction in all groups was statistically significant, (p<0.005 or p<0.05 when TR cases where excluded).

The total number of compulsory admissions fell from:

43 in the pre-RLAI phase to 12 in the RLAI phase in the total mirror-image group;

38 to 8 when TR patients were excluded;

28 to 11 when AOT patients were excluded; and
26 to 8 when TR and/or AOT patients were excluded; (p<0.005 for all cases).

The total days of inpatient stay fell from:

4,550 in the pre-RLAI phase to 2,188 in the RLAI phase in the total mirror-image group;
4,065 to 1,491 when TR patients were excluded;
3,254 to 2,042 when AOT patients were excluded; and
3,026 to 1,415 when TR and/or AOT patients were excluded.

All these differences where statistically significant, except for the case where only TR cases were excluded, (p=0.069).

In the RLAI group, no adverse effects were present in one third of patients, one third had no record of the presence or absence of adverse effects, and one third recorded an adverse effect attributed to RLAI (the most common being a movement disorder).

Almost 50% of RLAI patients discontinued therapy by the evaluation point, with 24 discontinuations occurring on an inpatient basis. The main reason for discontinuation was lack of efficacy, which accounted for approximately twice as many discontinuations as intolerability. Of the discontinued patients, 20.5% subsequently started clozapine.

For the sample of 90 RLAI patients, the median duration of treatment (measured from first injection to last injection) was 9.5 months (mean 12.2; range: 0.5 to 35.0).

**Clinical conclusions**
The effectiveness analysis showed that RLAI led to a significant reduction in total admissions and length of stay in comparison with conventional oral antipsychotics.

**Measure of benefits used in the economic analysis**
The health outcomes were left disaggregated and no summary benefit measure was used in the economic analysis. In effect, a cost-consequences analysis was carried out.

**Direct costs**
The viewpoint of the analysis was unclear, but it might have been that of a third-party payer. The cost categories included in the analysis were RLAI (acquisition and administration), home visits by a community psychiatric nurse (CPN), and inpatient care in a psychiatric ward. The unit costs were reported, whereas details of the quantities of resources used were not. The cost of drugs was derived from the British National Formulary. CPN time was based on the Personal Social Services Research Unit. The hospitalisation costs came from National Health Service reference costs. Resource use was derived from the sample of patients included in the effectiveness study. Discounting was not applied, but it was not clear whether it would have been relevant given that the time horizon of the analysis was unclear. The price year was not explicitly stated, but it is presumed that 2005 prices were used.

**Statistical analysis of costs**
Statistical analyses of the costs were not performed.

**Indirect Costs**
Productivity costs were not considered.

**Currency**
Sensitivity analysis
The issue of uncertainty was not addressed.

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

Cost results
The expected cost-savings due to the use of RLAI per patient per year of treatment were:

1,172 in the total mirror-image group;
3,972 when TR patients were excluded;
-828 (suggesting an additional cost) when AOT patients were excluded; and
2,172 when TR and/or AOT patients were excluded.

Synthesis of costs and benefits
A synthesis of the costs and benefits was not relevant as a cost-consequences analysis was carried out.

Authors' conclusions
The use of risperidone long-acting injection (RLAI) for the treatment of schizophrenia reduced hospital admissions and led to financial savings.

CRD COMMENTARY - Selection of comparators
The authors justified the choice of RLAI as the intervention under examination in that, at the time of the study, risperidone was the only atypical antipsychotic available as an LAI. The maximum licensed dose for risperidone was used in order to conduct a conservative analysis. You should decide whether this is a valid comparator in your own setting.

Validity of estimate of measure of effectiveness
The authors noted two strengths of the analysis. First, the analysis identified all patients who commenced RLAI irrespective of whether treatment was continuing at the evaluation point, considering the reasons for starting treatment and adverse events. Second, patients were identified in a large district service, thus ensuring that the sample of patients was representative of the patient population. The analysis of treatment effectiveness was mainly based on a within-group comparison study (mirror-image analysis), which is usually associated with some drawbacks, as the authors acknowledged. On the one hand, the use of each patient as their own control reflects real-world conditions, but on the other hand, the lack of an external control group means that the effect of confounders cannot be ruled out. Further, clinical outcomes were evaluated in two different time periods, but the impact of time-related factors was not extensively evaluated. The authors included an external control group to deal with this issue, but the results for this group were not clearly reported. Another critical issue was the retrospective nature of the study, in which the validity of the data depends strongly on the quality of the information recorded in the clinical notes. These issues tend to limit the internal validity of the study and cast some doubt on the cause-effect relationship tests in the analysis.

Validity of estimate of measure of benefit
No summary benefit measure was used because of the cost-consequences design. Please refer to the comments in the Validity of estimate of measure of effectiveness-field (above).

**Validity of estimate of costs**
The viewpoint adopted in the cost analysis was not explicitly stated, but the categories of costs included and the sources used to derive these costs suggest that the perspective of the National Health Service may have been chosen. Although extensive data on the unit costs were provided, there was little information on resource consumption and this limits the possibility of replicating the analysis in other settings. The authors noted that the economic analysis was explicitly biased against RLAI. In effect, the assumption of zero drug costs in the previous-treatment period and the fact that the maximum dose was assumed make the results conservative, thus underestimating the cost-savings of RLAI. The costs were treated deterministically and the impact of using alternative cost estimates was not investigated. Further, the price year was not explicitly stated, although costs were mainly derived using 2005 prices.

**Other issues**
The authors stated that a number of studies on LAIs had been conducted several decades previously and many changes in treatment patterns had been introduced in the health care system since then. However, some comparisons with recent studies suggested discrepant results, probably arising from methodological differences. The issue of the generalisability of the study results to other settings was not explicitly addressed and no sensitivity analyses were performed. This reduces the external validity of the analysis. The conservative nature of the analysis applies not only to the financial side but also to the benefit side of the study. As the authors noted, a reduction in informal and compulsory admissions has intangible psychological and social benefits for both patients and their families.

**Implications of the study**
The study results support the use of RLAI in patients with schizophrenia. However, the authors stated that the decision to use RLAI should be made on an individual basis in collaboration with the patient and should consider a range of factors, such as previous antipsychotic response, tolerability concerns, previous compliance and future risk of relapse. They authors also suggested that a prospective, randomised study should be carried out to corroborate the results of the current economic evaluation.

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**Indexing Status**
Subject indexing assigned by NLM

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