Effectiveness and cost of olanzapine and haloperidol in the treatment of schizophrenia: a randomized controlled trial


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 antipsychotic drugs. The patients were assigned to receive oral olanzapine (5 - 20 mg/day) or haloperidol (5 - 20 mg/day). Dose adjustments were made as clinically indicated, using four fixed dosage levels at 5-mg intervals. The patients assigned to haloperidol also received prophylactic benztropine mesylate (1 - 4 mg/day) for extrapyramidal symptoms (EPS). The olanzapine group received matching placebo benztropine, and both groups could increase the dose with active benztropine. A predefined programme of psychosocial treatment was offered to both drug treatment groups through a structured planning process.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population initially comprised patients who had been hospitalised for schizophrenia for less than 365 days. However, the criteria were expanded after 9 months to include patients with schizoaffective disorder and outpatients with any history of psychiatric hospitalisation during a 2-year period. Patients were eligible if they had a Diagnostic and Statistical Manual of Mental Disorders (4th ed., DSM IV) diagnosis of schizophrenia or schizoaffective disorder on the Structured Clinical Interview for DSM-IV Disorders. Other criteria were serious symptoms (score of >36 on the Brief Psychiatric Rating Scale), and serious dysfunction for the prior 2 years with inability to work or social constriction. Patients were excluded if they or their clinicians were unable or unwilling to cooperate. They were also excluded if they had a serious medical illness, unexplained seizures, or severe medication allergies, or if they had participated in olanzapine research.

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

Dates to which data relate
The effectiveness data and resource use data related to June 1998 to June 2000. The price year was 1998.

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

Link between effectiveness and cost data
The costing was undertaken prospectively on the same patient sample as that used in the effectiveness study.

**Study sample**

Power calculations were performed in the planning phase of the study. These indicated that randomising 600 patients would be necessary to yield an 80% chance of detecting a difference of $8,700 in VA inpatient costs. However, only 309 patients were recruited. This yielded an 80% chance of detecting a 5-point (6%) difference in symptoms on the Positive and Negative Syndrome Scale (PANSS), or a 5-point (11%) difference in the Heinrichs-Carpenter Quality of Life Scale (QOLS).

From the 4,386 patients initially assessed for eligibility, 4,077 were excluded. Reasons for exclusion were patients refusal (969), clinician refusal (561), hospitalisation not according to the study protocol (262) or for more than 365 days (421), diagnostic criteria not met (485), patient unable to cooperate (423) or unsuitable for the study (286), medical contraindications (365) and non-specified reasons (302). Of the remaining 309 patients, 159 were randomised to olanzapine and 150 to haloperidol. The olanzapine group comprised 154 (96.9%) males and the mean age at randomisation was 46.8 (+/- 9.5) years. The haloperidol group comprised 144 (96.0%) males and the mean age at randomisation was 46.2 (+/- 7.7) years.

**Study design**

The study was a randomised controlled trial that was carried out in 17 VA medical centres. Data from an 18th site were excluded because of problems with a local institutional review board unrelated to the study. Medication kits were prepared in sets of 4 (2 olanzapine and 2 haloperidol) and each was labelled with a random sequence number. The patients were assigned a kit at the end of a telephone conversation with the coordinating centre. Both groups were then followed for 12 months. In the group receiving olanzapine, 95 (59.7%) patients completed the follow-up and a further 56 (35.2%) completed some follow-up visits. In the group receiving haloperidol, 87 (58%) patients completed the follow-up and a further 56 (37.3%) completed some follow-up visits. Both the clinicians and patients were blinded to the type of treatment given to the patient.

**Analysis of effectiveness**

The analysis of the clinical study was conducted on an intention to treat basis. The primary health outcomes used were symptom outcomes, social functioning and severe behavioural deficits, adverse events, neurocognitive status, and premorbid intellectual functioning.

Symptom outcomes were assessed at baseline, 6 weeks and at 3, 6, 9 and 12 months using the PANSS. High scores reflected worse symptoms (range of scores: 30 - 210), while a 20% reduction represented a clinically important improvement.

Social functioning and severe behavioural deficits were measured using the clinician-rated Heinrichs-Carpenter QOLS. Higher scores indicated an improvement.

Adverse events were assessed using the Barnes scale for akathisia (i.e. restlessness and agitation) (range: 0 none - 5 severe), the Abnormal Involuntary Movement Scale (AMIS) for tardive dyskinesia (range: 0 - 42), the Simpson Angus scale for EPS (range: 0 - 4) and a checklist of adverse reactions. Clinical status was further assessed using the Clinical Global Impression scale, and QOL using the Short Form 36-Item Health Survey (SF-36).

Neurocognitive status was assessed at baseline and at 3, 6 and 12 months using the list learning, recall, recognition, and coding sub-sets from the Repeatable Battery for the Assessment of Neuropsychological Status, along with the Grooved Pegboard, Wisconsin Card Sorting Test-64 Card Version, Trail-Making Test Part B, and the Controlled Oral Word Association test.

Premorbid intellectual functioning was assessed using the Wide Range Achievement Test-Revised reading sub-set.

The two groups were shown to be comparable in terms of their age, gender, and prognostic features. The groups, however, were not shown to be comparable at baseline in relation to the PANSS, (p=0.02).
Effectiveness results
The intention to treat analysis showed no significant overall differences during the 12 months of treatment on the PANSS total symptom score (average difference -1.1 points; -1.3% favouring olanzapine; p=0.35), or on either the positive, (p=0.64), or negative, (p=0.31), sub-scales. There were also no significant differences at any time point in the proportion of patients showing a 20% improvement in PANSS scores.

No significant difference was found between the groups on the QOLS (average difference 0.1; 0.2% favouring olanzapine; p=0.71).

Olanzapine was associated with significantly lower scores overall on the Barnes scale for akathisia, (p<0.01), but not on the AIMS measure of tardive dyskinesia, (p=0.17), or on the Simpson-Angus scale for EPS, (p=0.34). Although a smaller proportion of olanzapine patients had moderate or marked akathisia (5.8% versus 9.6% across all assessments), this difference was modest in magnitude.

Neurocognitive test results showed significantly greater improvement among patients assigned to olanzapine on tests of motor functioning, (p=0.02), and memory, (p=0.03). In observations following discontinuation of the study drug, these effects were more robust for motor functioning, (p=0.005), and memory, (p=0.003). However, these differences small in magnitude, reaching a maximum of 0.16 standard deviations on motor function and 0.22 standard deviations on memory at 9 months. These were not of sufficient magnitude to improve overall QOL, interpersonal relationships, or instrumental role functioning.

Among patients assigned to olanzapine, there were more frequent reports of weight gain attributed by the patient as possibly or probably related to study drug at 3 months (27.6% versus 16.8%; p=0.07), 6 months (32.5% versus 12.5%; p=0.002) and 12 months (24.7% versus 8.3%; p=0.01).

Among patients assigned to olanzapine, there were fewer reports of restlessness than with haloperidol at 3 months (17.6% versus 30.0%; p=0.047) and 6 months (15.1% versus 28.0%; p=0.04).

A secondary analysis, which excluded observations after the first discontinuation of the study drug, also showed no differences on either the PANSS symptom scores or the QOLS. However, it indicated statistically significant differences on the Barnes scale for akathisia, (p<0.01), and significant differences on the AIMS, (p=0.48).

Clinical conclusions
The study found no statistically or clinically significant advantages of olanzapine for schizophrenia on measures of compliance, symptoms, or overall QOL.

Modelling
The primary clinical outcomes were analysed using random-effects repeated measures models, conducted with PROC MIXED software (SAS version 8). The models accommodated correlations among the repeated observations and allowed the inclusion of available data from individuals with missing observations. Missing data in these models were assumed to be missing at random. All the models included an adjustment for baseline values of the dependent measures and side effects.

Measure of benefits used in the economic analysis
No summary benefit measure was used in the economic analysis. Thus, this study has been classified as a cost-consequences analysis.

Direct costs
The resource quantities and the costs were reported separately. The direct costs to the health service (in this case the VA department) were included in the analysis. The health care costs were calculated by multiplying the number of units
of service for each patient by the estimated unit costs. Such costs were for inpatient and residential care, medical and mental health outpatient visits, group therapy, and intensive case management. The unit costs for VA inpatient and residential care were estimated from the VA's Health Economic Resource Centre using data from the VA's Cost Distribution Report (CDR). The VA medical and mental health outpatient unit costs were also derived from the CDR. The group therapy unit costs were weighted at 20% of the cost of an individual visit, psychosocial rehabilitation at one third, and day treatment at half. The costs of intensive case management were derived using cost data from each facility.

The study also included non-VA costs, such as those related to schizophrenia patients for all payers in society. These were derived from an analysis of costs in a 1998 compilation of all insurance claims from more than 500,000 private sector mental health service users (MarketScan data set), VA contract payments for private nursing home care available in the CDR, and VA payments for contract residential treatment. Also, from published literature presenting unit costs from large non-VA health care systems.

Discounting was not relevant since all of the costs were incurred during one year and, appropriately, was not performed. The study the reported average costs. The price year was 1998.

**Statistical analysis of costs**

The authors presented both mean and median values of aggregated cost data since the cost data were skewed. Statistical significance was assessed by an analysis of covariance of log-transformed measures and of ranks, controlling for baseline symptoms and service use (significance established at p<0.05).

**Indirect Costs**

The indirect costs were not included in the analysis.

**Currency**

US dollars ($).

**Sensitivity analysis**

The costs of medication were the only parameters varied in the sensitivity analysis. These were estimated in the sensitivity analysis using both the 1999 discounted VA pharmacy cost levels and wholesale community costs.

**Estimated benefits used in the economic analysis**

See the 'Effectiveness Results' section.

**Cost results**

There were no significant differences between the treatment groups on any measure of service use or VA costs, exclusive of medication. Non-VA health costs and non-health costs showed no significant differences.

Using VA medication prices, the total medication costs were greater for the olanzapine group ($2,224 +/- 1,347) than for the haloperidol group ($394 +/- 579), (p<0.001).

With the cost of medication included, both the total VA mental health costs and total VA health costs were significantly greater for patients assigned to olanzapine.

The total societal costs (with medications at VA prices) were $45,8111 (+/- 48,079) for patients in the olanzapine group (median $30,693) and $38,439 (+/- 35,502) for those in the haloperidol group (median $26,383). However, these differences in total societal costs were not statistically significant, (p=0.24 when comparing mean costs; p=0.4 when comparing median costs).
Synthesis of costs and benefits

The costs and benefits were not combined. The sensitivity analysis showed that, when using medications at wholesale prices, the total costs incurred were higher than when using VA prices. However, differences between the two groups in total societal costs remained statistically insignificant (p=0.07 when comparing mean costs; p=0.2 when comparing median costs).

Authors' conclusions

The authors concluded that their study found no statistically or clinically significant advantages of olanzapine for schizophrenia on measures of compliance, symptoms, or overall quality of life (QOL). In addition, the authors did not find evidence of reduced inpatient use or total cost.

CRD COMMENTARY - Selection of comparators

The use of haloperidol was justified as the comparator because it was a widely used conventional antipsychotic agent. You should decide if this is a widely used health technology in your own setting.

Validity of estimate of measure of effectiveness

The basis of the analysis was a randomised controlled trial, which was appropriate for the study question. The study sample was representative of the study population, although halfway through the study the authors extended the entry criteria and patients with any hospitalisation for schizophrenia during the last 2 years were eligible to participate. This appears to have been done because the study was insufficiently powered, as a large number of the potential sample had either refused to take part or had been excluded. Thus, there was the need to increase the study sample. The patient groups were shown to be comparable at analysis, except in one measure at baseline (the PANSS negative sub-scale).

The analysis of effectiveness was handled in a very credible way. The outcomes were analysed on an intention to treat basis, the randomisation process was undertaken in a concealed manner, and the study was double-blinded. All these factors minimise the potential for confounding or bias affecting the authors' results. Further, appropriate statistical techniques were undertaken, controlling for service use and baseline symptoms. Unfortunately, as the authors pointed out, the study did not meet the power target of 600 patients. However, the authors still had an 80% power to detect a 6% difference between the groups on the PANSS and an 11% difference on the QOLS.

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 study.

Validity of estimate of costs

Although the authors reported that the costs were estimated from a societal perspective, the indirect costs were not included in the analysis. Such costs would have included any productivity losses, which the authors did not consider. However, for all other categories of cost, all the relevant costs appear to have been included in the analysis. The costs and the quantities were reported separately, which will enhance the generalisability of the authors' results. Resource use was derived from the study and appropriate statistical analyses of the quantities were performed. The unit costs were derived from the authors' settings and from published sources. Appropriate statistical analysis of the costs was performed. The authors considered two possible prices for medications, those of the VA and the wholesale prices. These two values were used to calculate the cost of medication, thus enhancing the generalisability of the authors' results. Discounting was unnecessary since all the costs were incurred during one year. The dates to which the prices related were reported, which will aid any possible reflation exercises.

Other issues

The authors made appropriate comparisons of their findings with those from other studies and found their results to be substantially less favourable for olanzapine. The issue of generalisability to other settings was partly addressed through
the sensitivity analysis and by reporting the costs and the quantities separately. However, the authors pointed out that because the study sample was overwhelmingly male, all treatment was provided in VA facilities and less than 10% of patients considered for recruitment were enrolled, the generalisability of their results to other populations and health care systems was unknown. The authors do not appear to have presented their results selectively and their conclusion reflected the scope of the analysis.

The authors reported a number of further limitations to their study. First, the loss of follow-up data and, second, the use of concomitant non-study atypical antipsychotic agents. However, the authors pointed out that there were no significant differences between the groups in the duration of adherence to the study protocol, reasons for discontinuation of the study drug, or use of any concomitant medication. Further, the results based on all data did not differ from those in the first 3 months of the trial when protocol adherence was high. A third possible limitation was the placing of a 20 mg/day upper limit on both haloperidol and olanzapine, although the average doses of these drugs were similar to the average national dosages in the VA. A final limitation was that the study did not determine whether the benefits of olanzapine were worth the additional costs and adverse consequences.

**Implications of the study**

Even though an incremental cost-effectiveness or cost-utility analysis was not performed to assess whether the benefits of olanzapine are worth the additional costs, the authors pointed out that it would seem unlikely that olanzapine would have proven to be cost-effective. This is because of the very small average difference between the two groups in QOL, and the significantly higher QOL scores in the haloperidol group at 6 weeks when adherence to the research protocol was best.

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