PHARMACOECONOMIC EVALUATIONS OF CLOZAPINE IN TREATMENT-RESISTANT SCHIZOPHRENIA AND RISPERIDONE IN CHRONIC SCHIZOPHRENIA

prepared by Dr. Judith L. Glennie, FCSHP
Pharmaceutical Consultant to CCOHTA
The Canadian Coordinating Office for Health Technology Assessment (CCOHTA) is a non-profit organization, funded by the federal, provincial and territorial governments. It was established to encourage the appropriate use of health technology by influencing decision-makers through the scientific evaluation of medical procedures, devices and drugs. The effectiveness and cost of technology and its impact on health are examined.

This overview has been prepared by staff at CCOHTA and is based in part on a study commissioned by CCOHTA: *Pharmacoeconomic Evaluation of Risperidone and Clozapine in Chronic and Treatment-Resistant Schizophrenia* conducted by Oh P^1,3^, Einarson TR^2^, Iskedjian M^2^, Addis A^4,5^, Lanctôt K^3^.

This overview does not necessarily reflect the opinions of the original investigators.

1. General Internal Medicine and Clinical Epidemiology, Sunnybrook Health Sciences Centre (Toronto, Ontario); 2. Faculty of Pharmacy, University of Toronto (Toronto, Ontario); 3. Program in Clinical Pharmacology, Sunnybrook Health Sciences Centre and University of Toronto (Toronto, Ontario); 4. MotherRisk Program, Hospital for Sick Children and Clinical Pharmacology, University of Toronto (Toronto, Ontario); 5. Mario Negri Institute (Milan, Italy).

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SUMMARY REMARKS

BACKGROUND

Schizophrenia is a prevalent psychiatric disorder with extremely high direct, indirect, and intangible costs to patients, their families, and society. Traditional approaches to therapy do not adequately treat all symptoms of schizophrenia, and fail in up to 30% of patients through lack of response or intolerable adverse events. Risperidone and clozapine are recently introduced therapeutic alternatives which offer lower rates of adverse effects and improved symptom control. Unit costs for these agents are higher than traditional therapies. This factor, coupled with the absence of long-term outcome information (risperidone) and the presence of potentially severe adverse effects (clozapine), makes it difficult to define the most appropriate role(s) for these medications.

To address these issues, a study commissioned by CCOHTA entitled *Pharmacoeconomic Evaluation of Risperidone and Clozapine in Chronic and Treatment-Resistant Schizophrenia* evaluated the use of these agents in schizophrenia. Specifically, the study’s objectives were to carry out a comparative therapeutic and economic evaluation of: a) clozapine in treatment-resistant schizophrenic patients or those suffering from debilitating adverse effects from conventional phenothiazines; and of, b) risperidone as first line therapy for patients with schizophrenia, and in patients suffering adverse effects from phenothiazines.

CONCLUSIONS

1) The cost-utility analysis demonstrated that **clozapine** was the dominant strategy compared to chlorpromazine or haloperidol in hospitalized patients with treatment-resistant schizophrenia with moderate symptoms. The estimated cost savings was approximately $39,000 per patient per year while producing 0.04 more quality-adjusted life years (QALYs) per year.

2) In this situation, the use of clozapine may be associated with $389 million in annual cost savings in direct health care expenditures, mainly due to reduced hospitalization. The associated incremental increase in drug expenditure would be $63 million (approximately $6,300 per patient per year).

3) The cost-utility analysis demonstrated that **risperidone** was the dominant strategy compared to haloperidol, haloperidol decanoate or fluphenazine decanoate in hospitalized patients with chronic schizophrenia with moderate symptoms. The estimated cost savings (versus haloperidol) was approximately $6,500 per patient per year while producing 0.04 more QALYs per year.

4) In the above situation, the use of risperidone may be associated with $662 million in annual cost savings in direct health care expenditures (overall, approximately $9,500 savings per patient per year) mainly due to reduced hospitalization. The associated incremental increase in drug expenditure would be $113 million (approximately $1,600 per patient per year).
5) The savings in direct health care expenditures for both of these medications were conditional upon the presence of adequate services to support the care of these patients in the community. These savings were based on a reduction in hospitalization, and no savings accrue if patients remain institutionalized due to inadequate community-based care.

6) The clinical outcome, cost, and utility results of these analyses do not apply to the more general schizophrenic population, or those in the early stages of their disease. The role of clozapine and risperidone in these groups remains to be studied.

7) The limitations of these analyses include: the absence of long-term outcome data, thus mandating a modeling approach; the absence of a Monte Carlo sensitivity analysis to evaluate the impact of concurrent changes in multiple parameters in the model; the absence of information regarding costs or savings accrued via avoiding tardive dyskinesia; the very small number of subjects available for utility assessment; and interprovincial analyses which focused only on drug price variation and did not take into account variation in the non-drug component (primarily hospitalization and community care costs).
INTRODUCTION

Schizophrenia

Schizophrenia is a chronic and disabling psychiatric condition, with symptoms which include the “positive” or psychotic symptoms: disorganized thinking, hallucinations, delusions, hostility, and bizarre behaviour; and the “negative” symptoms: loss of self-esteem, apathy/lack of motivation, blunted feelings/affect, depression, and social withdrawal. The disease affects approximately 1% of the population, with no predilection towards any socioeconomic or cultural subgroups. The typical onset is during early adulthood and this is a life-long condition for most patients, normally accompanied by incomplete treatment response and frequent relapses throughout their lives.²

Schizophrenia is biochemical in origin and research has implicated the role of two neuro-transmitters in separate, but interconnected, parts of the brain. On the one hand, excessive dopamine activity appears to be the central mechanism responsible for the positive symptoms of the disease. More recent work has suggested that the negative symptoms of schizophrenia appear to be caused by excessive levels of serotonin in a related portion of the brain.²

In addition to the impact on the patient’s quality of life and ability to function, families and society are also affected by this disease. Many schizophrenics are in prison, one-third of the homeless have this disorder, and 40% of patients attempt suicide (one-quarter with success). The overall economic costs of this disease are formidable: over $CAN2.3 billion are spent in direct health care costs and $CAN2 billion in indirect support services each year.³ Institutionalization for acute and treatment-resistant schizophrenic episodes is a major cause of hospital bed utilization in today’s health care system. It is estimated that 1 in 12 beds is occupied by a patient with schizophrenia.³

Treatment³

There is no cure for schizophrenia. In addition to medication, community support and long-term medical follow-up are cornerstones in treatment. Phenothiazines and butyrophenones (e.g. chlorpromazine and haloperidol, respectively) have been the mainstay of drug therapy for most patients with this disorder. Both groups of drugs block dopamine activity in the brain, and are more effective in the treatment of the positive as opposed to the negative schizophrenic symptoms.

Aside from their limitations in efficacy, long-term use of these agents is associated with bothersome adverse effects in 50-70% of patients including: sedation; significant drops in blood pressure (postural hypotension); extrapyramidal effects (involuntary muscle movement, restlessness, inability to move); tardive dyskinesia (difficulty performing voluntary movements, often irreversible, 4-5% annual incidence which increases with age); and various other effects involving most organ systems of the body. Up to 30% of patients receiving traditional therapy require a change in medication due to inadequate therapeutic effect or adverse events.

The most recent developments in drug treatment for schizophrenia have focused on providing relief for both positive and negative symptoms through simultaneous effects on dopamine and serotonin levels in the central nervous system. Both clozapine and risperidone have activity at various serotonin and dopamine receptor subtypes, thus dealing with the complete spectrum of schizophrenic symptoms.
PHARMACOECONOMIC EVALUATIONS OF CLOZAPINE IN TREATMENT-RESISTANT SCHIZOPHRENIA AND RISPERIDONE IN CHRONIC SCHIZOPHRENIA

Clozapine is approved for use in treatment-resistant\textsuperscript{a} patients, including those with incomplete response or severe adverse reactions to standard antipsychotic drug therapy. Risperidone is most widely used in chronic\textsuperscript{b} schizophrenia.

The frequency of adverse events, particularly extrapyramidal effects and tardive dyskinesia, is significantly reduced with both these agents. However, the risk of clozapine-induced agranulocytosis (i.e. decrease in white blood cell counts; estimated frequency of 0.8% per year of treatment) requires careful selection and close monitoring of patients treated with this medication. Risperidone has not demonstrated any rare, serious, side effects to date.

PARAMETERS OF THE EVALUATION

The methods used to evaluate risperidone and clozapine were similar in most respects. The following summarizes the methods which were common to both, and points out the areas of difference between the two analyses.

**Therapy Evaluated**

**Clozapine** was compared to haloperidol (HAL) and chlorpromazine (CPZ) in the treatment of hospitalized, treatment-resistant schizophrenic patients with moderate symptoms. These are the least expensive alternatives to clozapine, and were used in the published comparative clinical trials used in the analysis.

**Risperidone** was compared to haloperidol (HAL), haloperidol decanoate (HAL-DEC) and fluphenazine decanoate (FLU) in previously treated, hospitalized, chronic schizophrenic patients with moderate symptoms. This population reflects the patient group involved in the clinical trials used in the analysis, and these agents represent the most commonly used “classical” neuroleptics, based on Canadian market share information.

**Perspective/Target Audience**

Both analyses were carried out using a government payer perspective. The base case analysis was developed for Ontario, repeated for Quebec, and then subjected to a sensitivity analysis to address potential scenarios for remaining jurisdictions. A full societal perspective was not adopted due to the absence of information regarding indirect costs for this disorder, especially in relation to competing therapies.

\begin{itemize}
  \item[a] Treatment-resistance is defined as an inadequate response to therapeutic doses (>1000mg/day chlorpromazine-equivalents) of at least two antipsychotics from at least two drug classes, for an adequate treatment duration (> 6 weeks per trial).
  \item[b] Defined by DSM-IV (the diagnostic manual of the American Psychiatric Association) as at least two years of more or less continuous disturbance, including prodromal, active and residual phases (i.e. exacerbations despite maintenance therapy).
\end{itemize}
**Type of Analysis**

i) **Analysis**

Cost-utility analysis was the overall approach used to compare costs and quality-adjusted outcomes in both the risperidone and clozapine evaluations.

ii) **Decision Model**

Decision analysis models were constructed based on literature data and expert panel input to evaluate treatment sequences for both drugs and their respective comparators. The basic scheme for each tree was as follows: after choosing an initial drug, possible downstream events included tolerability, “success” versus “failure”, discharge from hospital, and relapse. The **risperidone** decision tree also incorporated the development of extrapyramidal symptoms (EPS) into its design.

Standard meta-analysis methods were used to determine point estimates and 95% confidence intervals (CI) for pertinent clinical outcomes (as defined below). For those outcomes not reported in the literature, event probabilities were derived with the assistance of an expert panel.

iii) **Time Horizon**

Cost and outcomes were evaluated over the first year of drug use in order to capture important clinical events, and then projected over a lifetime (see below). Future costs and outcomes were discounted at a rate of 5%.

iv) **Assumptions**

For purposes of analysis, the following assumptions were made:

a) all patients began therapy with risperidone or clozapine in the hospital
b) all clozapine patients were enrolled in an agranulocytosis prevention monitoring program
c) clozapine patients had 39 complete blood counts (CBCs) in their first year of therapy
d) drug doses and frequencies were based on typical regimens used in clinical efficacy trials
e) daily doses of 500mg of clozapine and 6mg of risperidone were used in their respective base case analyses
f) after successful discharge, patients lived in a supervised “residential care” environment
g) a case manager (nurse or social worker) and psychiatrist saw the patient at regular, predetermined intervals
h) relapse, if it occurred, transpired at the 48 week point of the 1-year evaluation period, resulting in hospitalization of average cost and duration (see Table 3 below for rate of relapse)
i) the remaining lifetime for the typical schizophrenic patient was 37 years (based on the average life expectancy for a typical 29 year old schizophrenic patient[6]
Outcomes of Interest

i) Clinical Outcomes

The main clinical outcome evaluated for both analyses was the proportion of patients with a clinically significant response to therapy. This incorporated the following measures: the efficacy rate, the drop-out rate due to side effects, and the drop-out rate due to lack of efficacy. The risperidone analysis incorporated an additional measure into the model in terms of the emergence of EPS requiring treatment. The use of concomitant anti-parkinsonian medication precluded the assessment of this outcome in the clozapine trials reviewed.

From an operational perspective, therapeutic “success” was defined in the model as a sufficient improvement in symptoms such that the patient was well enough to be discharged; while “failure” was defined as the persistence of symptoms over the treatment period of six weeks such that ongoing hospitalization was required. A “relapse” occurred if symptoms of schizophrenia developed with sufficient severity to warrant re-hospitalization for intensive therapy.

ii) Utilities

Health state utilities (i.e. patient preferences for various health scenarios) were obtained using the Standard Gamble technique and a rating scale. Interviews were carried out with seven schizophrenic patients who were felt by the schizophrenia clinic nurse to be capable of understanding the three scenarios presented in the interview process. An additional scenario related to the disutility of EPS was incorporated into the risperidone analysis. The utility ratings derived and incorporated into the decision models are summarized in Tables 1 and 2. These formed the basis of quality-adjusted life year determinations (i.e. QALYs) in the cost utility analysis.

<table>
<thead>
<tr>
<th>Table 1: Utility Ratings for Schizophrenia Health States: Clozapine Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scenario</td>
</tr>
<tr>
<td>Moderate delusional symptoms, hospitalized</td>
</tr>
<tr>
<td>Mild delusional symptoms, community-dwelling</td>
</tr>
<tr>
<td>clozapine</td>
</tr>
<tr>
<td>CPZ</td>
</tr>
<tr>
<td>risperidone</td>
</tr>
<tr>
<td>HAL, HAL-DEC, FLU</td>
</tr>
<tr>
<td>Mild delusional symptoms, hospitalized</td>
</tr>
<tr>
<td>clozapine</td>
</tr>
<tr>
<td>CPZ</td>
</tr>
<tr>
<td>Additional disutility for EPS</td>
</tr>
</tbody>
</table>

c Disutility refers to an outcome which has a negative impact on preference rankings.

d A composite of the quantity of life improvement as well as the health-related quality of life improvement associated with a given intervention
Table 2: Utility Ratings for Schizophrenia Health States: Risperidone Model

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Average Utility Rating</th>
<th>95% Confidence Interval (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate delusional symptoms</td>
<td>0.82</td>
<td>0.76, 0.88</td>
</tr>
<tr>
<td>Mild delusional symptoms</td>
<td>0.89 (risperidone)</td>
<td>0.84, 0.94</td>
</tr>
<tr>
<td></td>
<td>0.86 (HAL, HAL-DEC, FLU)</td>
<td>0.77, 0.95</td>
</tr>
<tr>
<td>Additional disutility for hospitalized patient</td>
<td>0.07</td>
<td>0, 0.17</td>
</tr>
<tr>
<td>Additional disutility for EPS</td>
<td>0.07</td>
<td>0, 0.17</td>
</tr>
</tbody>
</table>

EFFICACY

Three randomized controlled trials (RCTs; n = 157), primarily involving inpatients, were used in the meta-analysis of clozapine and its comparators in treatment-resistant schizophrenia. Eight RCTs (n = 645), involving primarily inpatients, were used to determine event rates for risperidone in chronic schizophrenia. Data for the comparator agents were derived from various sources. Data for HAL were derived from six of the eight risperidone trials used in the risperidone meta-analysis to ensure comparability of patient populations. Six separate and additional trials of HAL-DEC or FLU (versus various other comparator agents, no comparative trials with risperidone) were used to determine the event rates for use in the risperidone model to represent HAL-DEC and FLU. Tables 3 and 4 outline the event rates derived from these meta-analyses, as well as the values derived via the deliberations of the expert panel.

Table 3: Outcome Probability/Event Rates (95% CI) for Clozapine Model

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Clozapine</th>
<th>Comparators Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Success” rate</td>
<td>0.65 (0.04-1.00)</td>
<td>0.04 (0.01-0.08)</td>
</tr>
<tr>
<td>Drop-out rate - adverse effects</td>
<td>0.05 (0.02-0.09)</td>
<td>0.05 (0.02-0.09)</td>
</tr>
<tr>
<td>Discharge rate - if symptoms improve</td>
<td>0.81 (0-1)#</td>
<td>0.81 (0-1)#</td>
</tr>
<tr>
<td>Relapse within 1 year (after initial response to therapy)</td>
<td>0.16 (0-1)#</td>
<td>0.16 (0-1)#</td>
</tr>
</tbody>
</table>

* Event rates were derived from the meta-analysis, the expert panel and Gilbert et al., 1993.
# Range, established by expert panel
Table 4: Outcome Probability/Event Rates (95% CI) for Risperidone Model

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Risperidone</th>
<th>HAL</th>
<th>HAL-DEC</th>
<th>FLU</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;Success&quot; rate</td>
<td>0.67 (0.60-0.75)</td>
<td>0.50 (0.32-0.68)</td>
<td>0.46 (0.28-0.65)</td>
<td>0.39 (0.29-0.50)</td>
</tr>
<tr>
<td>Drop-out rate - adverse effects</td>
<td>0.07 (0.05-0.08)</td>
<td>0.48 (0.31-0.65)</td>
<td>0.48 (assumed same as HAL; data lacking)</td>
<td>0.29 (0.07-0.51)</td>
</tr>
<tr>
<td>Discharge rate - if symptoms improve</td>
<td>0.81 (0-1)#</td>
<td>0.81 (0-1)#</td>
<td>0.81 (0-1)#</td>
<td>0.81 (0-1)#</td>
</tr>
<tr>
<td>Relapse within 1 year (after initial response to therapy)</td>
<td>0.16 (0-1)#</td>
<td>0.16 (0-1)#</td>
<td>0.16 (0-1)#</td>
<td>0.16 (0-1)#</td>
</tr>
</tbody>
</table>

* Event rates were derived from the meta-analysis, the expert panel and Gilbert et al., 1993.
# Ranges, established by expert panel.

EFFECTIVENESS

There was no evaluation of the effectiveness of clozapine or risperidone in the “real world” setting. The model focused on data from clinical trials, and did not take into account factors such as compliance rates, that might modify the impact of these drugs.

COSTS

Given the perspective chosen for analysis, the costs to be included in the analysis were limited to include all direct costs. Indirect costs for schizophrenia (and, therefore, the societal perspective) were excluded due to the absence of such data in the literature, especially in relation to the competing therapies assessed.

Standard costs for both analyses were derived from the following sources: the 1995 Ontario Drug Benefit Formulary and the 1996 RAMQ (Québec) Drug Benefit Formulary (medication costs); the 1992 Ontario Ministry of Health (OHIP) Schedule of Benefits (physician visit and laboratory test costs); the Alberta Standard Cost List (community care costs, including nursing, social work, case manager and residential care); the Sunnybrook Health Sciences Centre case costing system (hospitalization costs); and 1992-93 Statistics Canada Hospital Statistics (long-term hospitalization costs). The “Clozaril Guarantee Program” (rebate of drug acquisition cost for discontinuation within the first six months due to adverse reactions) was factored into the clozapine analysis.

The intensity/quantity of resource use was based on the clinical algorithms developed by the expert panel (described above). The unit costs used in the analysis are summarized in Table 5.
<table>
<thead>
<tr>
<th>Item</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine 500 mg/day</td>
<td>$18.89</td>
</tr>
<tr>
<td>Haloperidol 20 mg/day</td>
<td>$0.69</td>
</tr>
<tr>
<td>Chlorpromazine 1000 mg/day</td>
<td>$0.53</td>
</tr>
<tr>
<td>Risperidone 6 mg/day</td>
<td>$6.10</td>
</tr>
<tr>
<td>Fluphenazine decanoate 25 mg q3weeks (used full 100 mg ampule per dose)</td>
<td>$39.70</td>
</tr>
<tr>
<td>Haloperidol decanoate 100 mg q3weeks</td>
<td>$16.66</td>
</tr>
<tr>
<td>Psychiatry Visit (14 visits over 46 weeks)</td>
<td>$323.40</td>
</tr>
<tr>
<td>Nursing Visit (14 10-minute visits over 46 weeks)</td>
<td>$81.62</td>
</tr>
<tr>
<td>Social Work Visit (14 10-minute visits over 46 weeks)</td>
<td>$81.62</td>
</tr>
<tr>
<td>Community Care Manager*</td>
<td>$1,610</td>
</tr>
<tr>
<td>- 46 weekly 1-hour visits for clozapine</td>
<td></td>
</tr>
<tr>
<td>- 44 weekly 1-hour visits for risperidone</td>
<td>$1,540</td>
</tr>
<tr>
<td>Residential Care*</td>
<td>$15,600</td>
</tr>
<tr>
<td>- 323 days for clozapine</td>
<td></td>
</tr>
<tr>
<td>- 309 days for risperidone</td>
<td>$14,925</td>
</tr>
<tr>
<td>Hospital day for acute admission</td>
<td>$363</td>
</tr>
<tr>
<td>Hospital day for prolonged admission beyond 8 weeks</td>
<td>$261</td>
</tr>
<tr>
<td>Relapse hospitalization</td>
<td>$11,009</td>
</tr>
</tbody>
</table>

* Different time frames and costs for Community Care Manager and Residential Care are due to differences in patient populations and outcomes.

**COST-UTILITY ANALYSIS**

**Results of the Cost Utility Analysis**

Based on the clinical outcome, utility, and cost information outlined above, expected costs and utilities (QALYs) were calculated from the decision model using the DATA 2.6.6 software program (TreeAge, Boston).

In the clozapine analysis (Table 6), clozapine was the dominant therapy since it was associated with the lowest overall cost and the highest number of QALYs. Compared to CPZ, clozapine may save approximately $39,000 per year while producing 0.04 more QALYs. Over the remaining lifetime of
### Table 6: Clozapine: Expected Annual Costs and Outcomes

<table>
<thead>
<tr>
<th>Drug</th>
<th>Drug Acquisition Costs (no fee)</th>
<th>Non-Drug Costs</th>
<th>Total Expected Costs Over 1 Year</th>
<th>Expected QALYs Over 1 Year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Dispensing</td>
<td>Hospital</td>
<td>Community</td>
</tr>
<tr>
<td>Clozapine</td>
<td>$6,541</td>
<td>$73</td>
<td>$74,751</td>
<td>$8,681</td>
</tr>
<tr>
<td>CPZ/HAL</td>
<td>$194</td>
<td>$73</td>
<td>$128,767</td>
<td>$573</td>
</tr>
</tbody>
</table>

- Complete blood count

### Table 7: Risperidone: Expected Annual Costs and Outcomes

<table>
<thead>
<tr>
<th>Drug</th>
<th>Drug Acquisition Costs (no fee)</th>
<th>Non-Drug Costs</th>
<th>Total Expected Costs Over 1 Year</th>
<th>Expected QALYs Over 1 Year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Dispensing</td>
<td>Hospital</td>
<td>Community</td>
</tr>
<tr>
<td>Risperidone</td>
<td>$2,116</td>
<td>$83</td>
<td>$58,492</td>
<td>$9,164</td>
</tr>
<tr>
<td>HAL</td>
<td>$295</td>
<td>$91</td>
<td>$69,114</td>
<td>$6,865</td>
</tr>
<tr>
<td>HAL-DEC</td>
<td>$306</td>
<td>$113</td>
<td>$71,652</td>
<td>$6,316</td>
</tr>
<tr>
<td>FLU</td>
<td>$701</td>
<td>$115</td>
<td>$76,094</td>
<td>$5,355</td>
</tr>
</tbody>
</table>
the typical schizophrenic patient (i.e. 37 years), this represents a savings of approximately $682,000 and a gain of 0.70 QALYs per patient treated with clozapine (discounted at 5%). Cost savings have been a consistent finding in similar evaluations from the US\(^8\) and the UK\(^5\). The magnitude of those savings have varied due to differences in the models.

In the risperidone analysis (Table 7), risperidone was the dominant therapy in the base case analysis since it was associated with the lowest overall cost and the highest number of QALYs. Compared to HAL, risperidone may save approximately $6,500 per year while producing 0.04 more QALYs. Over the remaining lifetime of the typical schizophrenic patient (i.e. 37 years), this represents a savings of approximately $114,000 and a gain of 0.70 QALYs per patient treated with risperidone (discounted at 5%). Cost savings through a reduction in hospital days have been a consistent finding in various evaluations of risperidone in the US\(^10\), the UK\(^11\) and Canada\(^12\). The comparability of the patient populations involved in these studies and the current evaluation cannot be confirmed.

Sensitivity Analysis

A number of one-way sensitivity analyses were carried out as part of this study. The cost parameters were varied over the range of 50% to 150% of baseline, whereas the probability and utility values were varied from 0 to 1. Threshold values (i.e. the point at which the conclusions of the analysis shifted from one strategy to another) were determined for all key parameters used in the analysis. A summary of the results of the sensitivity analysis is outlined below, subdivided into cost, utility, and clinical outcome parameters.

Clozapine

i) Costs

In the clozapine analysis, none of the changes in the cost variables had an effect on therank ordering of the total expected costs.

ii) Utilities

The model was sensitive to changes in the utility values for the schizophrenic states used in the interview process. However, CPZ was the least expensive therapy only when utilities reached values that were well outside the 95% confidence intervals defined for the various scenarios. In other words, the utility values would have to be significantly different from those ratings given by patients for clozapine to be replaced by CPZ in this model.

iii) Clinical Outcomes

In terms of clinical parameters, the model was sensitive to the probability of treatment success for clozapine. As the success rate for clozapine decreased to the level of success which could be expected for CPZ (Table 1), the CPZ strategy became the less expensive treatment option based on total expected costs due to its lower acquisition price. Such a low clozapine success rate was not felt to be clinically likely to occur. There are two reasons for this rationale. First, the patients in the model were, by definition, resistant to standard therapy (i.e. CPZ). In addition, the absolute clozapine success rate demonstrated in clinical trials which compared these two drugs in this patient population ranged from 34...
to 96%, which was much higher than that demonstrated by CPZ.

**Risperidone**

i) **Costs**

In the risperidone analysis, none of the changes in the cost variables (including a lower dosing level, i.e. 4 mg per day) had an effect on the rank ordering of the total expected costs.

ii) **Utilities**

The model was sensitive to changes in certain utility values, such as the utility of mild symptoms on HAL and on risperidone. The threshold values for both of these utilities were at the bounds of their respective 95% CIs. Haloperidol would produce more QALYs if the rating of mild disease on this therapy were much higher than for the rating with risperidone. Observations from clinical trials suggest that this scenario is unlikely.

iii) **Clinical Outcomes**

In terms of clinical parameters, the model was sensitive to changes in the individual success rates for the comparator drugs. As the success rate for HAL approached or surpassed that for risperidone (Table 2), the HAL strategy became the least expensive approach to therapy through a direct impact on hospitalization costs. At this point the incremental cost utility ratio for risperidone compared with HAL would be approximately $61,000 per QALY gained. A similar situation was demonstrated with HAL-DEC, with an incremental cost utility ratio of approximately $58,000 per QALY gained. Given that clinical trials demonstrated a consistent and significant benefit of risperidone over HAL, it is unlikely that the situations described by the threshold analysis are realistic.

Haloperidol became less expensive as a therapy option over risperidone if the overall discharge rate estimated by the expert panel was significantly decreased (from 0.81 to 0.20). Again, the likelihood of this situation is low, as the majority of patients are discharged from hospital when their symptoms improve.

**Interprovincial Analysis**

Costs from Ontario were used in both baseline analyses, with secondary analyses carried out using drug prices from the Quebec provincial formulary. The results of the Quebec analyses did not differ significantly from the baseline analyses for either clozapine or risperidone.

To address the effects of interprovincial variations in drug prices, more global analyses were conducted wherein prices were increased and then decreased by 10% versus the baseline analyses (i.e. versus Ontario drug prices). The total expected costs did not differ significantly from the baseline analyses for either clozapine or risperidone. The effect of interprovincial variation in drug prices on the rank ordering of therapies within each evaluation was not an important variable.
Overall Cost Impact

The cost implications to the Canadian health care system and to provincial drug plans were projected by considering the incremental differences in cost for each therapy, which was then adjusted based on projected national prevalence figures for schizophrenia (estimated range of 0.6 to 8.3 cases per 1000 population). Approximately 100,000 individuals (range 15,000 to 200,000) have a diagnosis of schizophrenia in a given year. The course of illness is such that approximately 30% of these individuals will have a single psychotic episode with a subsequent long-lasting remission. Overall, 70% of all schizophrenic patients (approximately 70,000) will have a chronic disease course. This is the patient population likely to require long-term pharmacotherapy. Within this group, 5 to 25% are considered “treatment-resistant” (approximately 10,000; range 3,500 to 17,500).

In the case of clozapine, the impact of its use in hospitalized, treatment-resistant patients with moderate symptoms (i.e. assuming 10,000 possible candidates) is as follows: $389 million in annual cost savings in direct health care expenditures (mainly institutional care); $63 million in annual incremental drug expenditures (approximately $6,300 per patient per year).

In the case of risperidone, the impact of its use in hospitalized, chronic schizophrenic patients with moderate symptoms (i.e. assuming 70,000 possible candidates) is as follows: $662 million in annual cost savings in direct health care expenditures (mainly due to reduced hospitalization); $113 million in annual incremental drug expenditures (approximately $1,600 per patient per year); and $180 million in annual incremental community care expenditures. Note that patients eligible for clozapine have not been excluded from this chronic disease group.

STUDY LIMITATIONS

There were limitations to these analyses, in terms of the data used to form the models, as well as the methods used in the primary and follow-up sensitivity analyses.

The number of trials eligible for inclusion in the meta-analyses was limited for both drugs. Outcomes for the clozapine study were based on only three studies involving 157 patients, while eight risperidone studies (n=645) provided outcome information. However, conclusions from those studies excluded from the meta-analyses for methodological reasons were consistent with those used in the evaluations.

The generalizability of both evaluations is limited to the types of patients used in the clinical trials (i.e. institutionalized, confirmed treatment-resistance for clozapine, chronic patients with exacerbations for risperidone). The impact of the use of either drug earlier in the course of the disease (e.g. as first line therapy) cannot be extrapolated from the literature or from these evaluations.

Both the clozapine and the risperidone studies were of moderately short duration (6-8 weeks) and did not report explicitly on parameters which were relevant from an economic perspective (i.e. resource utilization patterns); hence the need for modeling and the derivation of these estimates with the expert panel. In addition, the models used this short term data to estimate events over a one year time frame, the results of which were then projected over a 37 year period. There are insufficient data to confirm the consistency of the effect of either of these medications over an extended period of time. Thus, the lifetime economic
outcomes identified by the evaluation need to be interpreted with caution.

Health state utilities were not assessed in the clinical trials. The health state utilities used in the analyses were developed based on the responses of only seven schizophrenic patients (out of 50 patients screened for their ability to understand the interview process). The process for deriving utilities has been neither validated in the schizophrenic population, nor assessed for reliability. While patient-derived health state utility ratings are preferred, this disease state is an example of how difficult it is to be sure one is obtaining valid, reliable or even pertinent data from study participants (because of the impact of the disorder and the therapy on cognitive function).  

There were limitations to the various subanalyses carried out as part of the evaluations for clozapine and risperidone. The impact of variation in other prices (e.g. institutionalization, community care) was not evaluated in the interprovincial analysis portion of each analysis. In addition, there was no Monte Carlo analysis of the interaction amongst all the factors within the models which impact on total expected cost.
REFERENCES


