Cost-Effectiveness of Sertindole among Atypical Antipsychotics in the Treatment of Schizophrenia in South Korea

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ABSTRACT

Objectives: This study assessed the cost-effectiveness of sertindole compared with existing atypical antipsychotics in the treatment of patients with schizophrenia in the South Korean setting. Methods: A Markov model was developed to estimate the cost-effectiveness of sertindole compared with risperidone, olanzapine, and quetiapine with a cycle of 6 months on a 5-year time horizon. Effectiveness was defined as the length of time without relapse and quality-adjusted life-years. Parameter estimates including drug-induced adverse events, compliance rate, and relapse rate were based on published literature and clinical trial data. Resource utilization data were obtained from the 2010 National Health Insurance reimbursement data, and costs were estimated from the health care system’s perspective. A discount rate of 5% was applied to both cost and effectiveness. One-way sensitivity analyses and probabilistic sensitivity analysis were carried out to check the robustness of the base-case analysis. Results: The length of time without relapse was 1.90 years for all study drugs. The estimated quality-adjusted life-years were 1.27 for sertindole, followed by quetiapine, risperidone, and olanzapine. Total costs were 10.51 million Korean won (KRW) for sertindole, 12.86 million KRW for olanzapine, 8.38 million KRW for risperidone, and 8.91 million KRW for quetiapine. The incremental cost-effectiveness ratios showed that sertindole was dominant only over olanzapine and was not cost-effective compared with risperidone and quetiapine. Various sensitivity analyses confirmed the results from the base-case analysis. Conclusions: Sertindole may be considered a valuable treatment option for South Korean patients who have failed the therapy with other atypical antipsychotic agents. Keywords: antipsychotics, atypical, cost-effectiveness, schizophrenia, sertindole.

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tients should be started on sertindole at 4 mg/d. The dose should be increased by increments of 4 mg after 4 to 5 days on each dose until the optimal daily maintenance dose, usually within the range of 12 to 20 mg, is reached [7]. Electrocardiogram (ECG) monitoring is required before and during treatment.

Two head-to-head comparisons of sertindole and risperidone showed equivalent efficacy on positive symptoms such as delusion, hallucination, hyperactivity, conceptual disorganization, and so on measured by the Positive and Negative Syndrome Scale. For negative symptoms such as emotional withdrawal, difficulty in abstract thinking, and poor rapport, one study obtained equiv-alent effects [9], while the other study obtained superior effects of sertindole to risperidone [10]. Sertindole should not be used as a first-line treatment for first-episode patients with schizophrenia because of QT prolongation. However, it has a side-effect profile that makes it a favorable alternative for many patients who do not respond well to the initial choice of antipsychotic drugs [11].

According to IMS health data in 2009, the market size of antipsychotics was almost 140 billion Korean won (KRW) in Korea. Among the antipsychotics, risperidone accounted for 26.24% of the market share, olanzapine 25.53%, and quetiapine 14.45%. Sertindole is not launched yet in Korea because of delayed approval of US FDA. But once it is approved by the Korean FDA, it is expected to compete with the other antipsychotic drugs in this market.

Using a decision analysis model, therefore, this study aimed to examine the cost-effectiveness of sertindole compared with risperidone, olanzapine, and quetiapine in the treatment of schizophrenia in the Korean health care setting.

Methods

Study design

This study is a cost-effectiveness analysis of atypical antipsychotic drugs for the management of schizophrenia. Sertindole was compared with three atypical antipsychotic medications that had the highest average market share for 5 years in Korea according to IMS health data: risperidone, olanzapine, and quetiapine [12] (Table 2).

Markov model for cost-effectiveness analysis is particularly suitable for the evaluation of chronic diseases such as schizophrenia. The study population consisted of treatment-resistant patients with schizophrenia requiring hospitalization. It was assumed that patients entered into the model on experiencing intolerance to their antipsychotic treatment during an episode of acute psychopathology after already having received a previous antipsychotic treatment.

After starting treatment on the recommended daily dose of a given drug, patients can either die or remain alive at the first chance node of the decision tree. Patients then enter either of two possible paths: drop out or remain on treatment. Dropout patients are assumed to disrupt the antipsychotic treatment for a cycle of 6 months, after which they can either return to treatment because of relapse or remain as dropouts. Patients who remain on treatment are then at risk of experiencing different adverse events: EPS, weight gain (and associated diabetes), sexual dysfunction, somnolence, and other adverse events. The degree to which patients comply is assumed to be the same across medication regimens administered but to differ according to the side effects experienced. The patients may therefore be compliant or noncompliant. At the end of the 6-month period covered by the model, patients can be in one of two health states: relapse and nonrelapse. The risk of relapse increases with decreasing compliance to treatment. The patients with relapse are assumed to receive inpatient care in hospitals while the patients with no relapse are assumed to continue outpatient care (Fig. 1).

The length of a cycle was 6 months, which was based on clinical practice patterns and expert opinion. The decision to use a 6-month cycle was clinically justified, because it is currently accepted that any deterioration in schizophrenia that occurs within 6 months following a relapse should be considered as being part of that relapse [13]. As is commonly required in pharmacoeconomic analyses, a 5-year time horizon was employed [14] and a discount rate of 5% was applied to both cost and effectiveness.

Data

Clinical inputs

Clinical inputs of the treatment are based on the results of random double-blind comparative clinical trials. We performed systematic reviews by searching electronic databases: PubMed, EMBASE, Cochrane Library (Central register of controlled trial; CENTRAL), MEDLINE (OVID), Korea medicine database (KMBASE), and RISS database (produced by Korea Education and Research Information Service) from 1990 to March 2011. The keywords were “schizo*,” “relapse,” “hospitalization,” “sertindole,” “risperidone,” “olanzapine,” and “quetiapine” (Fig. 2). The inclusion criteria were to only accept schizophrenia or schizoaffective patients, flexible dose, and head-to-head trials between comparator and risperidone as common reference. Consequently, we selected seven randomized controlled clinical trials [10,15–20] (Table 1).

Drug-specific input data on adverse events for each drug were obtained through indirect comparison. Using meta-analysis, relative risks between drugs were derived on the basis of percentage of patients experiencing adverse events from selected articles (Table 2).

Non–drug-specific input data used in this study were based on published articles (Table 2). These included premature dropout rate, compliance rates, relapse rates by compliance, and mortality rate. Dropout rates were derived from data on flexible doses for patients with schizophrenia [21]. Compliance rates depended on different adverse events (EPS, weight gain, somnolence, and sex-
ual dysfunction). And noncompliance to antipsychotic treatment is clearly associated with an increased risk of schizophrenic relapse [22]. Relapse rates were independent of the antipsychotic medication taken, but indirectly dependent on the adverse events experienced because they impact compliance rates. Different relapse rates were applied depending on compliance [15]. The mortality rate of schizophrenia was estimated by using the prevalence rate of schizophrenia from Korea national statistical database [24] and the mortality rates of the whole mental disorder from a Korean epidemiological study [1].

Economic input

Costs were estimated from the health care system’s perspective. Indirect costs such as productivity loss were not included because of limited availability of Korean data. Direct costs consist of health care costs and non–health care costs. Commonly, health care costs include the costs for physician visits, medication, hospitalization, laboratory tests, mental therapy, mental health day-care center, and adverse events. Health care costs were estimated by gross costing by using 2010 Health Insurance Review and Assessment Service (HIRA) data in Korea [3]. HIRA data are a claims data of NH that include frequency of patient visit and total cost of health care utilization by disease classification. Annual costs of in-/outpatient care for schizophrenia were obtained from HIRA data and were divided by 2 to get 6-month costs for model input. The same costs of adverse events were applied for each comparator in the model, except for ECG monitoring cost added on sertindole. It was assumed that there was no difference in health care resource utilization among adverse events (EPS, weight gain, somnolence, and sexual dysfunction) except for medication costs. The drug costs of benzotropine for EPS, metformin for diabetes, and modafinil for somnolence were included while weight gain and sexual dysfunction were assumed to have no prescription. The drug costs included in the model were obtained from the weighted average annual drug price in HIRA [25] (Table 3). Prices were presented according to the mean daily dose for each drug by inpatients/outpatients. The mean daily doses for sertindole and comparators were based on a previous study in Korea [27]. All the health care costs were adjusted for inflation in 2010 by health care inflation rate of national statistics [28].

Non–health care costs included time and travel costs of the patients in the treatment of schizophrenia. Estimation of time and travel costs was based on the data from 2005 Korea National...
Table 2 – Model input: Effectiveness data.

<table>
<thead>
<tr>
<th>Sales market share of atypical antipsychotics in Korea&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risperidone</td>
<td>26.24%</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>25.53%</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>14.45%</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug-specific input&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Value</th>
<th>Non–drug-specific input</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse event RR-EPS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sertindol vs. risperidone</td>
<td>0.41 (0.13-1.28)</td>
<td>Dropout rate&lt;sup&gt;3&lt;/sup&gt;</td>
<td>EPS</td>
</tr>
<tr>
<td>Olanzapine vs. risperidone</td>
<td>0.68 (0.51-0.91)</td>
<td>Weight gain</td>
<td>3.97%</td>
</tr>
<tr>
<td>Quetiapine vs. risperidone</td>
<td>0.57 (0.42-0.77)</td>
<td>Somnolence</td>
<td>1.78%</td>
</tr>
<tr>
<td>Adverse event RR-Weight gain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sertindol vs. risperidone</td>
<td>1.31 (0.71-2.44)</td>
<td>Sexual dysfunction</td>
<td>4.86%</td>
</tr>
<tr>
<td>Olanzapine vs. risperidone</td>
<td>2.16 (1.57-2.98)</td>
<td>Total</td>
<td>14.59%</td>
</tr>
<tr>
<td>Quetiapine vs. risperidone</td>
<td>1.08 (0.81-1.44)</td>
<td></td>
<td></td>
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<tr>
<td>Adverse event RR-Somnolence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sertindol vs. risperidone</td>
<td>1.05 (0.40-2.77)</td>
<td>Weight gain</td>
<td>96.03%</td>
</tr>
<tr>
<td>Olanzapine vs. risperidone</td>
<td>1.02 (0.86-1.20)</td>
<td>Somnolence</td>
<td>98.22%</td>
</tr>
<tr>
<td>Quetiapine vs. risperidone</td>
<td>1.25 (1.05-1.49)</td>
<td>Sexual dysfunction</td>
<td>95.14%</td>
</tr>
<tr>
<td>Adverse event RR-Sexual dysfunction</td>
<td></td>
<td>Total</td>
<td>85.41%</td>
</tr>
<tr>
<td>Sertindol vs. risperidone</td>
<td>4.59 (1.03-20.37)</td>
<td>Conditional probability&lt;sup&gt;4&lt;/sup&gt;&lt;sup&gt;*&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Olanzapine vs. risperidone</td>
<td>1.30 (0.99-1.71)</td>
<td>P(relapse</td>
<td>comp&lt;sup&gt;+&lt;/sup&gt;)</td>
</tr>
<tr>
<td>Quetiapine vs. risperidone</td>
<td>1.30 (0.99-1.71)</td>
<td>P(relapse</td>
<td>comp&lt;sup&gt;−&lt;/sup&gt;)</td>
</tr>
<tr>
<td>HRQOL&lt;sup&gt;5&lt;/sup&gt;</td>
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<td>Healthy: 0.88 (±0.20), illness: 0.73 (±0.31)</td>
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<tr>
<td>Mortality rate of schizophrenia&lt;sup&gt;6&lt;/sup&gt; 2.82 per 10,000 person</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Sources. 1IMS Health Data [12]; 2Azorin et al. [10] and meta analysis; 3Martin et al. [21]; 4Hansen et al. [22]; 5Lieberman et al. [15]; 6Seong et al. [23]; and 7Korea Statistical Information Service [24].

Utility
To get quality-adjusted life-years (QALYs), utility values for each state experienced in the treatment pathways were employed. The utility weights were obtained from the published data of health-related quality of life from the Korean population, which was measured by using EuroQol five-dimensional questionnaire validated in Korean language [23]. The utility weight was multiplied by the time spent in that state for each branch of the model and summed across all branches to get QALYs.

Analysis
The main outcome measure was time without relapse (TwR). In addition, QALYs were calculated on the basis of utility values of each health state in the model. The costs of treatment were assessed on the basis of typical resource use in Korea associated with each different treatment path. The cost per outcome, that is, either TwR or QALY, was expressed by using incremental cost-effectiveness ratio of sertindole versus comparators.

To check uncertainties for economic modeling for schizophrenia, we conducted one-way sensitivity analysis and probability sensitivity analysis (PSA). The sensitivity analyses were carried out on parameters such as compliance rate, relapse rate, drug cost of sertindole, and discount rate. PSA was conducted on the assumption of the beta distribution for effectiveness parameters and the normal distribution for all the costs according to the guideline of pharmacoeconomic evaluation in HIRA [29].

All analyses were performed by using Tree-Age Pro 2009 (Tree-Age Software, Williamstown, MA).

Results
Based on the model, sertindole showed nearly equivalent outcomes compared with its comparators. The length of TwR was 1.90 years for all study drugs during 5 years on model projection. The estimated QALYs were 1.27 for sertindole, followed by quetiapine, risperidone, and olanzapine. Total costs including in- and outpatient care were 10.51 million KRW for sertindole, 12.86 million KRW for olanzapine, and 8.91 million KRW for quetiapine. The incremental cost-effectiveness ratios showed that sertindole was dominant only over olanzapine and was not cost-effective compared with risperidone and quetiapine (Table 4).

Various one-way sensitivity analyses showed that sertindole was still a dominant alternative to olanzapine while it had very high incremental cost-effectiveness ratios compared with risperidone and quetiapine. The compliance rate connected to EPS had to be increased to 50% to make sertindole a cost-neutral alternative to comparators. The main driver in the difference in total costs between sertindole and comparators was inpatient care. When the resource utilization of inpatient care was reduced by 50%, sertindole was still the dominant treatment strategy compared with olanzapine. Changes in the time frame of the analysis from 5 years to 3 years and 10 years did not affect the results from the base-case analysis. Neither did the changes in the discount rate from 5% to 3% and 7%. On the other hand, the results of PSA,
presented in cost-effectiveness scatter plots, showed that sertindole had nearly the equivalent effectiveness to its comparators and that it was cheaper than only olanzapine among other atypical antipsychotic medications (Fig. 3).

Discussion

In schizophrenia, failure in therapy is particularly expensive and is due to several factors such as lack of efficacy, side effects, nonresponsiveness to treatment, and repetitive hospitalizations.

When compared with typical antipsychotic medication, atypical antipsychotic medications have improved the treatment of schizophrenia because they are associated with significantly fewer extrapyramidal side effects. This has, however, renewed attention toward other side effects such as weight gain, diabetes, sexual dysfunction, and somnolence. Because of the individual patients’ response and tolerance of specific compounds, many patients need to switch from one compound to another. Consequently, important unmet needs exist for treatments that can fulfill individual patients’ needs in terms of response and tolerability.

The purpose of this pharmacoeconomic analysis was to examine whether sertindole still fulfills the criteria for general reimbursement in the Korean NHI. The model was adapted to fit clinical practice, current reimbursement criteria, and treatment costs in Korea. Because of cardiovascular safety concerns, sertindole should be used only for those patients who are intolerant to at least one other antipsychotic agent.

By performing the cost-effectiveness analysis, it was possible to compare the different atypical antipsychotic agents in the treatment of patients with schizophrenia. The results showed that sertindole was able to slightly increase the length of TwR and QALY compared with other atypical antipsychotics for patients with chronic schizophrenia. With regard to total treatment costs, sertindole was cost-saving compared with olanzapine, but it was involved in higher costs compared with risperidone and quetiapine. In other words, sertindole was dominant over olanzapine (greater effect at lower cost), but it was not a cost-effective alternative to risperidone and quetiapine.

This model was built on the hypothesis that the side effects from antipsychotic therapy would influence the compliance rate of the antipsychotic medication in question. It is a well-known fact that noncompliance to antipsychotic treatment is associated with...
an increased risk of schizophrenic relapse [30]. The effectiveness of antipsychotic drug treatment in terms of TwR was therefore estimated in the model on the basis of drug-specific data (percentages of patients experiencing certain adverse events) derived from clinical trial data. Only five adverse events (EPS, weight gain, diabetes, somnolence, and sexual dysfunction) were included because those were the major concomitant diseases and had great effects on the compliance of schizophrenia patients.

Treatment with sertindole is associated with an increased risk of QT prolongation. However, patients are closely monitored during treatment and have their ECG taken every third month. QT prolongation was not handled as a separate adverse event in the model, only with the inclusion of the ECG costs in the sertindole branch. Adverse events defined as “other adverse events” included all events except EPS, weight gain, diabetes, somnolence, and sexual dysfunction. Because of the broad spectrum of other adverse events, they were not associated with a cost in the model. Because sertindole had the lowest rate of “other” events among atypical antipsychotic agents in the model, the strategy of not including the costs for these events was considered to be conservative.

There are some limitations in this study. One of the limitations was the absence of direct comparative clinical trial data between sertindole and its comparators, quetiapine and olanzapine, respectively. This lack of direct comparison was resolved by employing indirect comparisons of sertindole versus those two comparators with risperidone as common reference. Another limitation was lack of the detailed empirical data of resource utilization of Korean patients with schizophrenia. For example, such information as the number of hospital/clinic visits of individual patients, the type and amount of health services after relapse, and the type and cost of treatment for adverse events was not available because of protection of personal information. Instead of the microcosting method, therefore, this study used the gross-costing method based on aggregated number of patients and hospital/clinic visits for 1 year and annual total reimbursement cost in schizophrenia. Besides, indirect costs were not considered because of the lack of data on productivity loss of the patients with schizophrenia in Korea.

Despite the limitations mentioned above, this study has some implications in a few aspects. First, in terms of decisions on the reimbursement in the Korean NHI, the study results suggest the possibility that sertindole could be used as another option of atypical antipsychotic medication for the treatment of patients with schizophrenia who do not respond to initial medication. Second, it is anticipated that, though not yet launched, sertindole will be able to have a room for the market share and competition among atypical antipsychotic drugs in Korea if its price is set at an appropriate level. Third, because there have not been many studies conducted on schizophrenia in Korea, this study is meaningful in that it is a pharmacoeconomic evaluation using the Markov model and the PSA.

Conclusions

Sertindole should not be used as first-line treatment for first-episode patients with schizophrenia because of the QT prolongation. However, it has a side-effect profile that makes it a useful alternative for many patients who do not respond well to the initial choice of antipsychotic drug. Sertindole demonstrated nearly equivalent outcomes to other atypical antipsychotics and proved to be a cost-saving alternative to olanzapine. Therefore, it is concluded that sertindole may be considered as a treatment option for Korean patients who have failed the therapy with other atypical antipsychotic agents.

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[10] Azorin J, Strub N, Loft H. A double-blind, controlled study of sertindole and its comparators, quetiapine and olanzapine, respectively with risperidone as common reference. Another limitation was lack of direct comparative clinical trial data between sertindole and its comparators, quetiapine and olanzapine, respectively. This lack of direct comparison was resolved by employing indirect comparisons of sertindole versus those two comparators with risperidone as common reference. Another limitation was lack of the detailed empirical data of resource utilization of Korean patients with schizophrenia. For example, such information as the number of hospital/clinic visits of individual patients, the type and amount of health services after relapse, and the type and cost of treatment for adverse events was not available because of protection of personal information. Instead of the microcosting method, therefore, this study used the gross-costing method based on aggregated number of patients and hospital/clinic visits for 1 year and annual total reimbursement cost in schizophrenia. Besides, indirect costs were not considered because of the lack of data on productivity loss of the patients with schizophrenia in Korea.

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