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

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A B S T R A C T

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.

Introduction

Schizophrenia is a mental illness with substantial short-term and long-term consequences for individuals, their families, the health care system, and society. Schizophrenia is a relatively common illness and the most common form of psychotic disorder. The 12-month prevalence of schizophrenia reported in a South Korean epidemiological study was 0.3% in 2006 [1]. The economic burden of schizophrenia is high [2]. According to National Health Insurance (NHI) claims data in South Korea (hereafter, Korea), the expenditure on schizophrenia accounted for 0.7% of total health insurance expenditures in 2008 [3]. In schizophrenia, early onset, persistent psychotic symptoms even with antipsychotic treatment, adverse events, frequent failure of treatments, and prolonged functional impairment all contribute to making schizophrenia a particularly costly illness [4].

In the late 1990s, progress was made in the management of schizophrenia following the introduction of atypical antipsychotic medications that demonstrated marked improvements in tolerability profiles when compared with typical antipsychotic medications. But current pharmacological options still carry some limitations. Atypical antipsychotic medications are associated with various adverse events such as extrapyramidal symptoms (EPS), weight gain, metabolic disorders including diabetes mellitus, somnolence, and sexual dysfunction. The tolerability profiles differ between atypical antipsychotic medications, and drug-induced side effects have been suggested to be one of the main factors contributing to treatment nonadherence [5].

Sertindole (Serdolect) is an antipsychotic drug with affinity for dopamine D2, serotonin 5-HT2A and 5-HT2C, and alpha1-adrenoreceptors. In Europe, sertindole was approved and marketed in 19 countries from 1996. In the United States, it first applied for Food and Drug Administration (FDA) approval. But this application was withdrawn in 1998 following concerns over adverse events, that is, the increased risk of sudden death from QT prolongation [6]. In 1999, however, it was revealed that the adverse event was not associated with increasing rates of cardiac arrhythmias and that patients on sertindole had the same overall mortality rate as those on risperidone using the results of the Sertindole Cohort Prospective study [7]. As of January 2012, the drug has not been approved by the FDA for use in the United States [8].

Despite concerns about safety issues, sertindole has a good tolerability profile, which is likely to favor long-term treatment adherence, reduce relapse, rehospitalization, and suicide, and improve overall functioning. Sertindole is prescribed to patients who are intolerant to at least one other antipsychotic agent. All pa-

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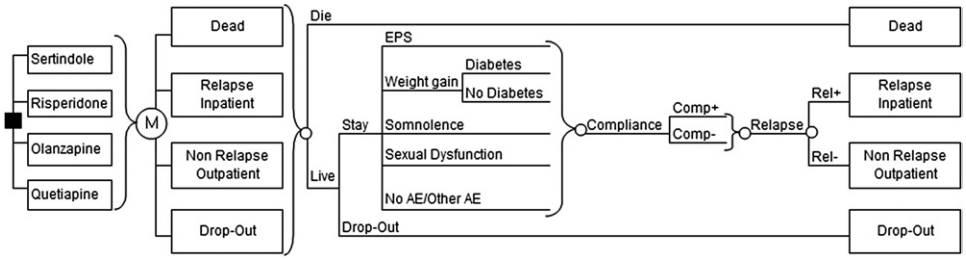

Fig. 1 – Markov model for cost-effectiveness analysis. Comp +, compliant; Comp –, noncompliant; EPS, extrapyramidal symptoms; M, Markov; Rel +, relapse; Rel –, nonrelapse.

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 equivalent 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-