Updating and Confirming an Industry-Sponsored Pharmacoeconomic Model: Comparing Two Antipsychotics in the Treatment of Schizophrenia

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\textbf{ABSTRACT}

\textbf{Objective:} This study updated a 2001 decision economic model that used indirect data and confirmed its findings by developing a new cost-effectiveness model by using now available head-to-head data. The models compared olanzapine with ziprasidone in the treatment of schizophrenia in the United States. \textbf{Methods:} A decision analytic modeling approach was used to estimate annual health-care costs and health outcomes, incorporating events such as response, relapse, and suicide. Patients without response to first-line treatment switched to the other comparator. Decision tree probabilities were extracted from head-to-head studies and other published clinical literature. Direct health-care costs and quality-adjusted life-years (QALYs) were estimated on the basis of resource use and utility weights for initial and relapse episodes, maintenance therapy, and extended episodes of illness. Disutilities associated with treatment-emergent adverse events were included. \textbf{Results:} Consistent with the 2001 model, this model found that first-line treatment with olanzapine is associated with fewer hospital days, fewer days with extrapyramidal symptoms, and higher QALYs than is first-line treatment with ziprasidone. Total costs were lower for the olanzapine pathway ($70,232–$72,776 vs. $73,086–$73,310 in the Positive and Negative Syndrome Scale analysis) due to the cost savings associated with reduced health-care resource use. The incremental cost per QALY gained indicated that the olanzapine pathway dominated the ziprasidone pathway. \textbf{Conclusions:} Decision analytic models should be continuously assessed against new data. This case study shows that incorporating new data confirmed results of a previously published model in which olanzapine was associated with better expected health outcomes and lower total health-care costs than was ziprasidone.

\textbf{Keywords:} cost-effectiveness, economic model, olanzapine, schizophrenia.

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\section*{Introduction}

At the point of launch of new pharmaceutical products, decision makers are forced to evaluate each product’s efficacy, safety, and tolerability profile to determine approval status for the submitted indication as well as its economic profile for reimbursement. Decision analytic models are often used to help inform various health-care policy makers on better ways to allocate limited resources. Skepticism about potentially biased industry-sponsored economic models, however, prevails [1]. Ideally, decision makers would like to compare the new treatment against current standards of care and other treatments entering the market around the same time; however, limited head-to-head data make direct comparisons difficult in both the clinical and economic settings.

From the mid-1990s to early 2000s, many second-generation (atypical) antipsychotics were introduced in the market for the treatment of schizophrenia, an often severe and chronic neuropsychiatric disorder that is very costly in terms of total direct health-care costs per patient [2,3] due primarily to the relapsing nature of the illness and the need for costly psychiatric hospitalizations [4].

Olanzapine and ziprasidone are among the atypical antipsychotics. While olanzapine was launched in the United States in 1996, ziprasidone was approved by the US Food and Drug Administration in 2001. The individual phase 3 registration trials and other clinical trials for olanzapine and ziprasidone—in 2001, when ziprasidone was approved—were primarily against placebo or a first-generation (typical) antipsychotic, haloperidol, making head-to-head comparisons of these two drugs difficult. Having no head-to-head information on the efficacy of these products, an economic model was created to assist formulary decision makers in the United States determine which product produced the most benefit for the money spent when making formulary adoption decisions [5]. In the 2001 analysis, indirect comparisons were made by combining the clinical data from the individual drug trials, some limited head-to-head safety data on one safety parameter, and cost information from other published literature into a single economic model by careful use of the data and modeling assumptions.

The original 2001 decision model presented its findings as preliminary in nature and concluded that clinical head-to-head trials...
measuring important outcomes are needed to assess the true comparative clinical effectiveness, tolerability, and cost-effectiveness of olanzapine in relation to ziprasidone” that “would provide decision-makers with more precise information that could be easily incorporated into the existing or more elaborate models to update the results” [5]. Since 2001 several randomized head-to-head trials have been conducted that included both olanzapine and ziprasidone as treatment comparators in the treatment of schizophrenia. These comparative trials were sponsored by Eli Lilly and Company, the manufacturer of olanzapine, by Pfizer, the manufacturer of ziprasidone, and by independent researchers. We set out to update the previous model to confirm the model conclusions and test the robustness of the indirect comparisons by using data from head-to-head randomized trials. We additionally conducted a literature search to determine whether newer information was available regarding other model inputs and whether clinical guidelines had changed since the previous analysis. This article describes a case study of the update and confirmation process and the results of the updated economic comparison.

Methods

Alexeyeva et al. [5] describe the original model, which was programmed in Microsoft Excel, in detail. Briefly, the pharmacoeconomic analysis follows schizophrenia patients for 1 year after treatment initiation by using a decision tree structure (Fig. 1). During the year, patients may experience response to the initial drug treatment (olanzapine or ziprasidone). If patients do not respond, they may switch to a second-line treatment (olanzapine, ziprasidone, or risperidone) and have another chance of treatment response. In addition, patients who do not respond to either first-line treatment or second-line treatment are switched to a third-line treatment that is assumed to be clozapine. Finally, patients who respond to either the first-line treatment or the second-line treatment have a chance of relapse during the year and may attempt and/or complete suicide. Using this structure, the direct medical costs attributable to schizophrenia and the drug treatments considered by the model are estimated from the perspective of a US third-party payer.

To update the economic model, the following steps were taken:
1. Identify new modeling techniques that are relevant to the analysis;
2. Identify head-to-head data for inclusion;
3. Analyze and synthesize data; and
4. Update model programming and data input parameters and perform a quality check.

These steps are described in detail in the following subsections.

Identify new modeling techniques

Quality-adjusted life-years (QALYs) and the incremental cost per QALY gained are expected to be a part of model outcomes and are required by some health technology assessment agencies for reimbursement approval. Therefore, relevant utility weights were included in the model health states and disutilities attributed to treatment-related adverse events.

Probabilistic sensitivity analyses (PSAs) are often requested and/or required by health technology assessment agencies for drug submissions. A PSA was programmed into the Excel model using Visual Basic for Applications to run the Monte Carlo simulation.

Finally, meta-analysis is a statistical technique that can combine point estimates of efficacy from several trials into a single measure using a series of weights and calculations. A random effects meta-analysis using the methods of Einarson [6] to incor-
porate the measures of response from different trials into a single input for the model was conducted.

**Identify up-to-date data**

A series of targeted Medline literature searches were conducted to identify published randomized, head-to-head trials that included both olanzapine and ziprasidone. All searches included the MeSH main heading term “schizophrenia” combined with free text terms and Medline limits targeting the major components of inputs for the model. The targeted literature searches were compiled and abstracts were reviewed to identify articles for full-text review (see Appendix Table 1 in Supplemental Materials at doi:10.1016/j.jval.2011.08.1741 for full search strategy and results).

**Analyze and synthesize data**

Clinical inputs

Ten primary studies were identified for further review and potential inclusion into the meta-analysis [7–16].

As described in the model description section, the efficacy measure of interest to the model was patient response to the drug treatment. In schizophrenia trials, response is often measured by using the Brief Psychiatric Rating Scale (BPRS), the Positive and Negative Syndrome Scale (PANSS), or both. As such, it was determined that these two measures were the most appropriate outcomes to assess response, as costs and utility weights identified were based on response to treatment.

From the 10 potential studies identified, only 3 [7,11,14] reported PANSS response, BPRS response, or both in their publication or included requested data from the manufacturer. The other trials had response estimates that were either not reported or not consistent with what was needed for the model. Table 1 provides a summary of the three included trials.

It can be seen that the three studies are all slightly different in length (6, 24, and 28 weeks), patient population, and response outcomes reported. We assumed that a trial length greater than 6 weeks does not affect the probability of response. This rationale is based on figures from Breier et al. [7] and Simpson et al. [14] that show little change in total score in PANSS and BPRS levels after weeks 5 to 6 of treatment. Therefore, it is assumed that response would occur at the same point regardless of trial length, and the estimates of timing of the three trials were comparable. In regard to the patient populations in the trials, Breier et al. [7] were the most inclusive as both inpatients and outpatients were randomized. The populations in Kinon et al. [11] (outpatients) and Simpson et al. [14] (inpatients) could be considered subsets of the population included in Breier et al. [7]. Therefore, to measure response over a broad population, we included all three studies in the meta-analysis. Sensitivity analyses were performed that examined the effect of including/excluding each of the studies in the meta-analysis as well as using the results of each individually in the model.

The measure of response selected for the meta-analysis was at least 30% improvement from baseline to end point (trial completion) in PANSS, BPRS, or both by using the last observation carried forward as this was the most consistently reported outcome. Simpson et al. [14] did not report PANSS; therefore, we were unable to include this study in the meta-analysis for PANSS response. However, it was included in the BPRS meta-analysis. Table 2 summarizes the response outcomes from each individual trial and the random effects meta-analyses conducted. Overall, heterogeneity was detected between trials in all analysis. Forest plots for all analyses are available in the appendix (Appendix Fig. 1A–D in Supplemental Materials at doi:10.1016/j.jval.2011.08.1741). These outcomes serve as the model inputs for the probability of response.

Another clinical data component that was shown to be a major driver of costs and outcomes in the original model was relapse rate. Only one of the three identified head-to-head studies reported relapse-related information. Breier et al. [7] report that 14.6% of olanzapine-treated patients and 25.3% of ziprasidone-treated patients experience an exacerbation of symptoms (defined as 20% or more decline in PANSS total score and decrease of 1 or more points on the Clinical Global Impression-Serious Illness Scale after week 8 of the trial). Exacerbation of symptoms has previously been used as a proxy for relapse and was used as such in the updated model as well.

Cost inputs

Our search of the cost literature found that current cost-effectiveness studies were continuing to use the same sources of schizophrenia-related costs from the original model [5,19–23]. Therefore, with the exception of drug costs, cost sources were unchanged; however, costs were inflated to 2009 US dollars by using the medical component of the Consumer Price Index [22].

The amount and probability of medical resources used (e.g., hospital days, outpatient visits, group therapy, and residential treatment) were kept constant from the original Alexeyeva et al. model [5] and are shown in Table 3. Table 4 summarizes the updated unit cost inputs and data sources used in the current analysis. Drug costs were updated to the most recent Wholesale Acquisition Costs from the Red Book [25]. Assumptions were made by using the data reported in clinical publications for average dose per day, which is used in combination with drug acquisition costs to calculate an average cost per day. The mean modal doses for

<table>
<thead>
<tr>
<th>Study</th>
<th>Trial design</th>
<th>Comparators</th>
<th>Patient population</th>
<th>Response outcomes reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breier et al. [7]</td>
<td>28-week, multicenter, randomized, double-blind, parallel design</td>
<td>Olanzapine (n = 277); ziprasidone (n = 271)</td>
<td>Inpatients and outpatients</td>
<td>LOCF 30% improvement from baseline to end point in total scores of PANSS (Breier et al., [7]) and BPRS (Eli Lilly and Company, unpublished data, 2009)</td>
</tr>
<tr>
<td>Kinon et al. [11]</td>
<td>24-week, multicenter randomized, double-blind, parallel design, fixed dose</td>
<td>Olanzapine (n = 202); ziprasidone (n = 192)</td>
<td>Outpatients with prominent depressive symptoms</td>
<td>LOCF 30% improvement from baseline to end point in total scores of PANSS and BPRS (Eli Lilly and Company, unpublished data, 2009)</td>
</tr>
<tr>
<td>Simpson et al. [14]</td>
<td>6-week, multicenter, randomized, double-blind, parallel design, flexible dose</td>
<td>Olanzapine (n = 133); ziprasidone (n = 136)</td>
<td>Acutely ill inpatients</td>
<td>LOCF 20%, 30%, and 40% improvements from baseline to end point in BPRS total score</td>
</tr>
</tbody>
</table>

BPRS, Brief Psychiatric Rating Scale; LOCF, last observation carried forward; PANSS, Positive and Negative Syndrome Scale.
olanzapine and ziprasidone in the Breier et al. [7] trial were reported to be 15.27 and 115.96 mg/d, respectively. For simplification, a 15-mg/d dose is assumed for olanzapine and a 120-mg/d dose is assumed for ziprasidone. An average dose for risperidone is assumed to be 4 mg/d as a 4-mg dose has been shown to be compared with 15 mg of olanzapine in clinical trials such as Conley and Mahmoud [27]. Finally, Mauskopf et al. [19] report the average dose for clozapine to be 304 mg/d. For simplification, a 300-mg/d dose for clozapine is assumed.

Utility weight inputs
The model was updated to include utility weights as a measure of societal health state preferences. The updated model contains utility weight estimates for the time period patients are treated during an initial episode (cycle) or a relapse episode (cycle) and treated during a maintenance cycle. Utility weights for initial and relapse episodes are further subdivided into whether treatment is provided in an inpatient hospitalization setting or is nonhospital based. In addition to these utility weights, the updated model contains disutilities for common adverse events associated with the model comparators.

We derived utility weights to match the treatment settings described above and the disutilities by using the data reported in Lenert et al. [28]. The incidence of common adverse events attributable to the model comparators is displayed in Table 5, while

Table 2 – Observed response from individual studies and combined meta-analysis results.

<table>
<thead>
<tr>
<th>Analysis study</th>
<th>Response measure (30% improvement from baseline to trial end point)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PANSS, mean (SE)</td>
</tr>
<tr>
<td></td>
<td>Olanzapine</td>
</tr>
<tr>
<td>Original model (Alexeyeva et al., [5])</td>
<td>—</td>
</tr>
<tr>
<td>Beasley et al. [17], Keck et al. [18]</td>
<td>58.6% (0.0301)</td>
</tr>
<tr>
<td>Breier et al. [7]</td>
<td>28.8% (0.0328)</td>
</tr>
<tr>
<td>Kinon et al. [11]</td>
<td>NR</td>
</tr>
<tr>
<td>Simpson et al. [14]</td>
<td>43.7% (0.1489)</td>
</tr>
<tr>
<td>Breier et al. [7] and Kinon et al. [11]</td>
<td>UE</td>
</tr>
<tr>
<td>Breier et al. [7] and Simpson et al. [14]</td>
<td>UE</td>
</tr>
<tr>
<td>Kinon et al. [11] and Simpson et al. [14]</td>
<td>UE</td>
</tr>
</tbody>
</table>

BPRS, Brief Psychiatric Rating Scale; NR, not reported; PANSS, Positive and Negative Syndrome Scale; SE, standard error; UE, unevaluable.
utility weights, their derivation and assumptions, and disutilities are summarized in Table 6.

The key model inputs for both the current model and the previous model are provided in Appendix Table 2 in order to clearly identify what has been updated.

Probabilistic sensitivity analysis inputs
A PSA was undertaken to evaluate the impact of simultaneous variation in clinical outcome and resource utilization parameters on the model results by using second-order Monte Carlo methods. Beta distributions were used for model probabilities and utility weights. Gamma distributions were used for health state costs. Standard errors were set to those calculated in the meta-analysis for response or reported in the clinical publications for other model input parameters where available. Where unavailable, standard errors were assumed to be 10% of the mean reported value.

Update model programming and perform a quality check
The original model was updated to include a new input system that allowed the selection of trials to be included in the meta-analysis and the outcome on which to base the meta-analysis (PANSS or BPRS). In addition to updating other model inputs, a PSA was added and utility weights were incorporated into the Excel programming.

In order to ensure that the updated model was producing accurate results and that errors were not introduced during the update process, two types of quality checks were performed. The first quality check was conducted by entering the input parameters from the original model into the updated model and checking to make sure that the results of the two models matched. This provided validation that no errors were introduced into the components that were shared between the two model versions.

The second type of quality check involved a thorough review of the updated model inputs to ensure they were extracted properly from their respective source publications, a check of all model calculations, and a check of the Visual Basic for Applications code that runs the PSA.

Results
The base-case analyses conducted were based on the meta-analyses of the PANSS scale (PANSS analysis) and the BPRS scale (BPRS analysis). For reference, the PANSS meta-analysis included data

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### Table 4 – Cost inputs and data sources.

<table>
<thead>
<tr>
<th>Resource</th>
<th>Unit cost ($)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital day</td>
<td>898*</td>
<td>Palmer et al. [20]; The Essential RBRVS [21]</td>
</tr>
<tr>
<td>Residential treatment day</td>
<td>520*</td>
<td>Palmer et al. [20]; NAPHS [23]</td>
</tr>
<tr>
<td>Outpatient psychiatrist visit</td>
<td>91</td>
<td>The Essential RBRVS [21]</td>
</tr>
<tr>
<td>Non-MD group therapy</td>
<td>73*</td>
<td>Palmer et al. [20]; RFI [24]</td>
</tr>
<tr>
<td>Partial treatment day</td>
<td>371*</td>
<td>Palmer et al. [20]; NAPHS [23]</td>
</tr>
<tr>
<td>Outpatient treatment day</td>
<td>116*</td>
<td>Palmer et al. [20]; NAPHS [23]</td>
</tr>
<tr>
<td>Suicide attempts/completion</td>
<td>7829*</td>
<td>Mauskopf et al. [19]</td>
</tr>
<tr>
<td>Suicide legal costs</td>
<td>1755*</td>
<td>Mauskopf et al. [19]</td>
</tr>
<tr>
<td>State psychiatric hospital day</td>
<td>567*</td>
<td>Mauskopf et al. [19]</td>
</tr>
<tr>
<td>Residential home care day</td>
<td>567*</td>
<td>Mauskopf et al. [19]</td>
</tr>
<tr>
<td>Drug cost per day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olanzapine</td>
<td>19.50</td>
<td>Breier et al. [7]; Red Book for Windows [25]</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>15.09</td>
<td>Breier et al. [7]; Red Book for Windows [25]</td>
</tr>
<tr>
<td>Risperidone (generic)</td>
<td>2.38</td>
<td>Assumed 4-mg dose; Red Book for Windows [25]</td>
</tr>
<tr>
<td>Clozapine (generic)</td>
<td>3.67</td>
<td>Mauskopf et al. [19]; Red Book for Windows [25]</td>
</tr>
<tr>
<td>Compliance</td>
<td>85%</td>
<td>Mauskopf et al. [19]; Tran et al. [26]</td>
</tr>
<tr>
<td>Anticholinergic drug cost per day</td>
<td>0.99</td>
<td>Alexeyeva et al. [5]; Red Book for Windows [25]</td>
</tr>
</tbody>
</table>

* Inflated to 2009 US dollars using the medical component of the Consumer Price Index (US Department of Labor [22]). Standard error for use in the probabilistic sensitivity analyses estimated as 10% of the mean cost.

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### Table 5 – Adverse event incidence.

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Incidence (%)</th>
<th>SE</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPS symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olanzapine</td>
<td>17.0</td>
<td>0.017*</td>
<td>Mauskopf et al. [19]</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>19.0</td>
<td>0.019*</td>
<td>Alexeyeva et al. [5]; FDA [39]</td>
</tr>
<tr>
<td>Risperidone</td>
<td>29.0</td>
<td>0.029*</td>
<td>Mauskopf et al. [19]</td>
</tr>
<tr>
<td>Clozapine</td>
<td>10.0</td>
<td>0.010*</td>
<td>Mauskopf et al. [19]</td>
</tr>
<tr>
<td>Weight gain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olanzapine</td>
<td>12.6</td>
<td>0.20</td>
<td>Breier et al. [7]</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>1.9</td>
<td>0.008</td>
<td>Breier et al. [7]</td>
</tr>
<tr>
<td>Risperidone</td>
<td>5.9</td>
<td>0.02</td>
<td>Lieberman et al. [12]; Breier et al. [7]</td>
</tr>
<tr>
<td>Clozapine</td>
<td>12.6</td>
<td>0.02</td>
<td>Bitter et al. [29]</td>
</tr>
<tr>
<td>Hypotension (all)</td>
<td>1.0</td>
<td>0.001*</td>
<td></td>
</tr>
</tbody>
</table>

EPS, extrapyramidal symptoms; SE, standard error.
* Standard error for use in the probabilistic sensitivity analyses estimated as 10% of the mean cost.
from Breier et al. [7] and Kinon et al. [11] while the BPRS included data from these two studies and from Simpson et al. [15] as well.

### Deterministic results

In both the PANSS and BPRS analyses, the olanzapine pathways resulted in fewer hospital days, fewer days with extrapyramidal symptoms, and greater QALYs than did the ziprasidone pathways. These results and also a breakdown of costs by cost category are displayed in Table 7. Overall, among the cost categories, inpatient costs contributed the most to costs being between 77% and 80% of total costs. Outpatient costs were the next largest cost component followed by antipsychotic drug costs, suicide costs, and anticholinergic drug costs.

Also, in the PANSS analysis, the 1-year direct medical costs for starting treatment with olanzapine were $72,776 when patients were switched to ziprasidone if no response and $70,232 when switched to risperidone. Starting treatment with ziprasidone resulted in costs of $73,682 with a switch to olanzapine and $73,459 with a switch to risperidone. Thus, starting treatment with olanzapine resulted in cost savings of $906 compared with starting treatment with ziprasidone if no response and $70,232 when both are switched to the other and cost savings of $3,227 when both are switched to risperidone.

In the BPRS analysis, the 1-year direct medical costs for starting treatment with olanzapine were $68,840 when patients were switched to ziprasidone if no response and $68,176 when switched to risperidone. Starting treatment with ziprasidone resulted in costs of $70,075 with a switch to olanzapine and $71,505 with a switch to risperidone. Thus, starting treatment with olanzapine resulted in cost savings of $1,235 compared with starting treatment with ziprasidone when both are switched to the other and cost savings of $3,329 when both are switched to risperidone.

Overall, antipsychotic drug costs for the olanzapine pathways were higher than for the ziprasidone pathways in all analyses owing to the higher drug acquisition cost for olanzapine. These price differences, however, were overcome by other direct medical costs being higher for ziprasidone pathways than for olanzapine pathways because of the higher efficacy in both the PANSS and BPRS analyses for olanzapine.

Given the cost savings of the olanzapine pathways and the better patient outcomes (hospital days, extrapyramidal symptom days, and QALYs), all incremental cost-effectiveness ratios (ICERs) calculated (incremental cost per hospital day avoided, extrapyramidal symptom day avoided, and QALY gained) resulted in the olanzapine pathways dominating (less costly and more effective) the ziprasidone pathways.

### Sensitivity analyses

#### One-way sensitivity analysis

A one-way sensitivity analysis was conducted and indicated that the model was robust to alternate sources of input parameters (generally ranging from ±20% of the baseline value). The most sensitive parameter was the source of response selected for the model. We conducted a series of scenario analyses specifically examining how response was estimated. This included varying the studies included in the meta-analysis and looking at how results fared by using results from each study independently. In each of these scenarios, the olanzapine pathways remained cost saving to the ziprasidone pathways and in all but one scenario the ICER dominated the ziprasidone pathway. Incremental costs and QALYs from each of these scenarios are summarized in Figures 2 and 3.

#### Probabilistic sensitivity analysis

Results of 10,000 second-order Monte Carlo simulations of the PSA are summarized in the form of cost-effectiveness scatter plots. In the PANSS analysis, olanzapine, compared with ziprasidone, had an incremental cost per QALY gained less than or equal to the generally accepted cost-effectiveness threshold of $50,000 per QALY gained, when both are switched to the other, in 87.6% of the simulations performed (Fig. 4). When switching to risperidone, the results were similar, showing that the olanzapine pathway had an
incremental cost per QALY gained less than or equal to $50,000 in 81.7% of the simulations compared with the ziprasidone pathway (see Appendix Fig. 2A in Supplemental Materials at doi:10.1016/j.jval.2011.08.1741). In addition, the olanzapine pathways dominated the ziprasidone pathways in 83.1% of the simulations when switching to each other and 54.7% of the simulations when switching to risperidone.

The BPRS analysis showed similar results to the PANSS analysis. Olanzapine had an incremental cost per QALY gained less than or equal to $50,000 compared with ziprasidone, when both are switched to the other, in 95.5% of the simulations performed (see Appendix Fig. 2B in Supplemental Materials at doi:10.1016/j.jval.2011.08.1741). When switching to risperidone, the olanzapine pathway had an incremental cost per QALY gained less than or equal to $50,000 in 86.9% of the simulations compared with the ziprasidone pathway (see Appendix Fig. 2C in Supplemental Materials at doi:10.1016/j.jval.2011.08.1741). Finally, the olanzapine pathways dominated the ziprasidone pathways in 90.6% of the simulations when switching to each other and 59.3% of the simulations when switching to risperidone.

Exploratory sensitivity analysis
Changes in metabolic parameters, including new-onset diabetes, have been reported during treatment with atypical antipsychotics, including olanzapine and ziprasidone [30]. Because of this increased class risk, it is important to understand how the management of diabetes in this population impacts the cost-effectiveness of olanzapine. To further understand the impact of this medical condition, we conducted an exploratory sensitivity analysis around this risk.

Currently, there is no consensus around the incidence of diabetes risk potentially associated with schizophrenia treatments. A meta-analysis has shown that second-generation antipsychotics have a slightly higher increased risk of diabetes than do first-generation antipsychotics [31]. Within the second-generation antipsychotics, Lambert et al. [30] found diabetes incidence to be similar between olanzapine and other antipsychotics (risperidone, quetiapine, clozapine, and haloperidol) in a large study of US Veterans. However, other analyses have found olanzapine to have an increased risk of diabetes than other atypicals [12,32,33]. To investigate the potential effect of incident diabetes on model results, we conducted two exploratory sensitivity analyses. In both analyses, the development of diabetes was associated with a disutility of $100.2 [34].

In the first exploratory analysis, we attributed an annual diabetes incidence of 5.5% to all atypical antipsychotics included in the model based on the number of diabetes cases reported for patients treated with olanzapine (1,098) and the total number of olanzapine-treated patients (19,780) in the Lambert analysis.

In the second exploratory analysis, we assumed that olanzapine had an increased risk of diabetes over that of the other atypical antipsychotics modeled. We estimated this risk by estimating the risk of diabetes for risperidone in the Lambert et al. [30] analysis to be 5.2% (also assumed 5.2% for clozapine and ziprasidone) and applied an estimated hazard ratio of 1.71 [32] for olanzapine, resulting in an estimated incidence of diabetes of 8.9%.

In both exploratory analyses, the olanzapine pathways remained dominant by incurring less total costs and accruing more QALYs than the ziprasidone pathways.

Discussion
This article describes a case study of the process and results of updating and confirming an economic model when better data (i.e., head-to-head) become available. Based on the updated input param-
eters, first-line treatment with olanzapine is cost saving compared with starting treatment with ziprasidone. This was shown to be the case across a wide variety of methods to examine the efficacy of both products and switching scenarios to second-line treatments if response was not experienced. The olanzapine pathways dominated the ziprasidone pathways in all but one of a multitude of base-case and scenario analyses. In addition, the vast majority of the simulations performed in the PSA indicated that the olanzapine pathways were cost-effective compared with the ziprasidone pathways.

The original model [5] also showed the olanzapine pathway to be cost saving in comparison with the ziprasidone pathway. The savings were approximately $200 in 2001 US dollars. Our analysis calculated savings between $890 and $3500 depending on the treatment pathway and analysis (PANSS vs. BPRS) examined in 2009 US dollars. The majority of the savings differences are attributable to the increase in incremental efficacy between olanzapine and ziprasidone seen in the head-to-head trials versus those trials used in the original model.

This article discusses cost-effectiveness practices that have evolved since the original analysis. Completed today, the original analysis would likely have taken a different form as well. Current standard practices such as network meta-analyses could be used to strengthen indirect analysis of clinical data. Furthermore, when the direct head-to-head trials were completed their clinical data could have been added to the network analysis so that all available clinical data could be used in the analysis. Value of information analysis also could have been completed to determine the benefit of conducting the head-to-head comparisons between olanzapine and ziprasidone before trial initiation.

Fig. 2 – Scenario analysis of response input derivation with switch to olanzapine/ziprasidone. BPRS, Brief Psychiatric Rating Scale; PANSS, Positive and Negative Syndrome Scale; QALY, quality-adjusted life-year; Scenario 1, PANSS analysis using data from Breier et al. [7]; Scenario 2, BPRS analysis using data from Breier et al. [7]; Scenario 3, PANSS analysis using data from Kinon et al. [11]; Scenario 4, BPRS analysis using data from Kinon et al. [11]; Scenario 5, BPRS analysis using data from Simpson et al. [14]; Scenario 6, BPRS meta-analysis with data from Breier et al. [7] and Kinon et al. [11]; Scenario 7, BPRS meta-analysis with data from Breier et al. [7] and Simpson et al. [14]; Scenario 8, BPRS meta-analysis with data from Kinon et al. [11] and Simpson et al. [14].

Fig. 3 – Scenario analysis of response input derivation with switch to risperidone. BPRS, Brief Psychiatric Rating Scale; PANSS, Positive and Negative Syndrome Scale; QALY, quality-adjusted life-year; Scenario 1, PANSS analysis using data from Breier et al. [7]; Scenario 2, BPRS analysis using data from Breier et al. [7]; Scenario 3, PANSS analysis using data from Kinon et al. [11]; Scenario 4, BPRS analysis using data from Kinon et al. [11]; Scenario 5, BPRS analysis using data from Simpson et al. [14]; Scenario 6, BPRS meta-analysis with data from Breier et al. [7] and Kinon et al. [11]; Scenario 7, BPRS meta-analysis with data from Breier et al. [7] and Simpson et al. [14]; Scenario 8, BPRS meta-analysis with data from Kinon et al. [11] and Simpson et al. [14].
Although we updated the model with the best available data, several limitations to the updated process and the resultant model should be noted. First, while we consider our literature search to be thorough and inclusive of the major clinical trials including both olanzapine and zipraside in the last decade, it was not conducted by using a full systematic method. Despite this limitation, it is likely that systematic methods and inclusion of additional databases would not have resulted in additional data points for the meta-analyses.

Next, of the clinical studies that were identified for full-text review from our targeted literatures searches, the majority did not report outcomes in a manner that would lend them to inclusion in the meta-analysis. Thus, the meta-analysis was limited to three studies for the BPRS analysis and two for the PANSS analysis. Given that, the meta-analysis was not quite as robust and inclusive of head-to-head studies as we had initially hoped. However, results from the excluded studies indicate that their inclusion likely would not have changed the conclusions and results of the model. Overall, both olanzapine and zipraside were similar among the effects measured. It is important to note that Lieberman et al. [12] showed that compared with zipraside, the olanzapine treatment group had much lower annual risk of hospitalization for exacerbation of schizophrenia (risk ratio of 0.29 for olanzapine; 0.57 for zipraside). A lower rate of relapse, as measured by psychiatric inpatient hospitalization, was also found in The Ziprasidone Observational Study of Cardiac Outcomes (ZODIAC) [35], sponsored by Pfizer, the manufacturer of zipraside. These results are not unlike the differential risk of relapse used in the present cost-effectiveness model.

Another study limitation is the inclusion of a limited number of treatment-emergent adverse events and exclusion of treatment-emergent diabetes in the base-case analysis. We conducted two exploratory sensitivity analyses regarding the possibility of similar risk and increased risk of diabetes for olanzapine. Neither analysis changed the conclusions of the model. A limitation of the exploratory analyses is that we did not include the costs associated with diabetes. However, prior research on the cost of diabetes among patients with schizophrenia [36] and cost-effectiveness models in the antipsychotic treatment of schizophrenia [37,38] have found the cost of this potential adverse event to be relatively small compared with the total treatment cost of schizophrenia.

Finally, of the studies that were included in the meta-analyses, the patient populations varied widely. Because of differences in patient severity, the response estimates were also greatly variable. To control for these differences, we performed a wide variety of scenario analyses examining various possible combinations of studies in the meta-analysis and results of individual studies through the model. In all but one scenario, the results of the model were similar to those of the base-case analyses.

Strengths of the model include the use of data from randomized head-to-head clinical trials and the use of state-of-the-art modeling techniques that helped to confirm model robustness and conclusions. In addition, the wide variety of scenario analyses conducted help demonstrate that different assumptions surrounding clinical efficacy sources would produce similar results.

We believe that this publication serves as a good example of the process of updating an economic model when new data become available to confirm earlier findings. Results of the model were shown to be robust to numerous scenarios performed and also confirm the results of the original model that was based on indirect efficacy data. In both the original model and the updated model, olanzapine was shown to be a cost-saving option for first-line schizophrenia treatment compared with zipraside. This indicates that, while imperfect, economic models that are built on limited indirect data and reasonable assumptions can be used as a proxy for economic decisions until more direct data are available.

Source of financial support: Eli Lilly and Company.

### Supplemental Materials

Supplemental material accompanying this article can be found in the online version as a hyperlink at doi:10.1016/j.jval.2011.08.1741 or, if a hard copy of article, at www.valueinhealthjournal.com/issues (select volume, issue, and article).
REFERENCES