

Cost and Cost-Effectiveness in a Randomized Trial of Long-Acting Risperidone for Schizophrenia

To the Editor: Dialogue on the design, conduct, analysis, and reporting of comparative effectiveness research is important for formulating valid treatment guidance and ensuring effective and efficient health care resource utilization. The analysis by Barnett et al¹ assessed the cost-effectiveness of long-acting injectable (LAI) risperidone versus physician's choice of oral antipsychotics in Veterans Health Administration patients with unstable schizophrenia or schizoaffective disorder. The study on which this analysis was based (Rosenheck et al²) was partly funded by our company. We fully support research characterizing our products' efficacy, safety, appropriate use, and cost-effectiveness. However, aspects of this analysis and its interpretation warrant discussion.

The original study was designed to evaluate whether LAI risperidone was superior to oral alternatives. The nonsignificant test for superiority cannot support Barnett and colleagues' conclusion of no between-group difference in outcomes (ie, "adoption of long-acting risperidone would increase pharmaceutical costs without any improvement in outcomes"¹[p701]). Such a conclusion requires a different study design and a larger sample.

The conclusion that LAI risperidone is not cost-effective was based on higher medication costs versus oral agents; however, total between-group health care costs per quarter were not significantly different (\$14,916 vs \$13,980, respectively; $P = .732$). This lack of difference is despite the fact that higher proportions of the LAI risperidone group versus the oral antipsychotics group were hospitalized at randomization (45.5% vs 35.2%, $P < .01$) and had "problems with alcohol or drug use" (40.6% vs 33.5%; reported by Rosenheck et al²). Subjects in the LAI risperidone group also had a longer index hospitalization (mean = 1.0 vs 0.3 days, $P = .021$). Thus, LAI risperidone-treated subjects were more recently ill, were less stable, and had more comorbidity and therefore differed in risk for treatment nonadherence and rehospitalization. Further, the baseline hospitalization imbalance between groups resulted in cost differences that inflated costs in the LAI risperidone group and therefore limit interpretation of results.

The original study² reported that 45% (81/182) of patients in the oral treatment group and 39% (72/187) of patients in the LAI risperidone group were hospitalized. Some oral agent subjects switched to LAI risperidone during the trial (discrepant numbers: 21 of 182 [12%] in Rosenheck et al²; 41 of 182 [22.5%] in Barnett et al¹). Despite this, the odds ratio for hospitalization was 28% greater for oral treatment (OR = 1.28; 95% CI, 0.85–1.94). If switching from oral agents prevented hospitalizations (treatment failure) in ≤ 21 patients, the risk increases up to 103% greater for oral agents (if ≤ 41 hospitalizations were prevented, the risk is up to 224% greater).

Research evaluating comparative efficacy in narrowly defined subpopulations must be cautiously translated to broader populations. This is particularly true of LAIs, for which the key differentiator relates to adherence rather than pharmacology. The protocol-specified enhanced visit frequency and intensity of this trial may have eliminated or significantly attenuated the naturalistic environment necessary to demonstrate compliance advantages of biweekly LAI risperidone dosing by health care professionals.

In summary, results from this study, powered for superiority, do not support the conclusion that LAI risperidone is "not cost-effective" compared to oral agents. The possibility that in a naturalistic setting LAI risperidone would be cost-effective cannot be excluded given differences in treatment groups and the explanatory characteristics of this study design.

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Drs Barnett and Rosenheck Reply

To the Editor: We have reported the first economic evaluation of long-acting injectable (LAI) risperidone using data from a clinical trial.¹ We believe that trial fairly evaluated this medication for treatment of unstable schizophrenia and schizoaffective disorder.

The treatment groups were equivalent. They did not differ in any of 5 measures of severity of illness. Each group had a baseline measure of psychiatric hospital use that was significantly greater than that of the other group. At the time of randomization, the LAI risperidone group was more likely to be in the psychiatric hospital. In the year preceding randomization, the oral antipsychotic group spent more days in the psychiatric hospital (mean of 25.7 days vs 20.9 days for LAI risperidone, $P < .01$). This does not mean that randomization failed. Nevertheless, we compared the groups' costs while controlling for baseline differences, including psychiatric hospitalization at randomization. The results were unaffected: total costs incurred by the treatment groups were not significantly different. Results were also unaffected when we excluded the cost of psychiatric stays underway at randomization. Costs excluding this care were \$13,829 per quarter for LAI risperidone versus \$13,616 for oral antipsychotics ($P = .937$).

Some patients assigned to oral agents switched to LAI risperidone. The converse was also true. The majority of patients received their intended treatment, and the intent-to-treat analysis found no evidence that random assignment to LAI risperidone prevented hospitalization. Our 2 publications^{1,2} do report different amounts of crossover treatment. Our first article² reported information on medication use gathered by site staff on case-report forms. The economic study¹ supplemented this with comprehensive information from the US Department of Veterans Affairs pharmacy database. Although we describe these sources in the methods section of each article, we should have been more explicit in stating that the results were different and why this was so.

We conducted an "on treatment" analysis and found no significant association between the number of LAI risperidone injections received and the cost of subsequent psychiatric hospitalizations. A contamination-adjusted intent-to-treat analysis to control for selection bias, using randomization as the instrumental variable, yielded the same result.

The intensity of care received by trial participants was affected very little, if at all, by the monthly visits specified in the protocol. A minimum of 1 visit per month is not an unusual intensity of care for patients at risk for a psychiatric hospital stay. Study participants

entered the study as intense users of care, with 54 visits in the year prior to randomization. They had 66 visits per year during the trial. The acute instability that made them eligible for the trial may account for much of this increase in service use.

It has been hypothesized that the extra cost of injectable antipsychotic medications like LAI risperidone will be offset by reduced psychiatric hospitalization costs. We determined that patients randomly assigned to LAI risperidone had higher medication cost, but we found no significant offset.

This study was not designed to show the equivalence of LAI risperidone and oral antipsychotics. Its findings were consistent with 4 previous trials that found no significant superiority for LAI risperidone as compared to oral agents.³⁻⁶ A fifth trial that found an advantage to LAI risperidone may have used less-than-optimal doses of the oral comparator.⁷

Adoption of a more costly medication can be justified only if it increases value. We found that LAI risperidone increased pharmaceutical costs without offsetting other costs or generating any therapeutic benefit. Health care sponsors will be hard-pressed to include LAI risperidone in their formulary when it cannot show a significant benefit in repeated trials.

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