The Costs of Drugs for Schizophrenia

The article in this issue of the *Journal* by Rosenheck et al. ("Cost-Effectiveness of Second-Generation Antipsychotics and Perphenazine in a Randomized Trial of Treatment for Chronic Schizophrenia") summarizes the costs of treatment of patients during the NIMH-sponsored Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study. Patients with chronic schizophrenia were assigned to treatment with perphenazine, olanzapine, risperidone, quetiapine, or ziprasidone for up to 18 months. During the 18 months, they could be switched to another drug (including clozapine but generally not to a first-generation drug) whenever a doctor or patient decided that there was insufficient benefit or problematic side effects with the current treatment. The initial report found that patients were treated longer with olanzapine (median 9.2 months) before a doctor or patient felt the need to switch medications; all other drugs had median treatment durations of under 6 months (1). The first-generation drug perphenazine was no different from risperidone, quetiapine, or ziprasidone. A further clinical analysis of switching medications is reported in this issue by Essock et al. ("Effectiveness of Switching Antipsychotic Medications") with an accompanying Editorial by Carol Tamminga.

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Rosenheck et al. reassessed the outcome data to assign each patient a quality-adjusted life year (QALY) rating, which takes both symptoms and side effects into account. A year of high quality life is rated 1. Patients improved modestly from a mean baseline rating of 0.686 to a range of 0.698 to 0.721 over the 18 months. There was no significant difference in final rating regardless of which drug the patient took initially. The investigators then estimated the costs for each patient, both drug costs and inpatient and outpatient treatment costs. The treatment costs for the group assigned to perphenazine were significantly lower than for any other group. The difference was accounted for entirely by the lower cost of perphenazine, which is no longer protected by a patent. During treatment with perphenazine, the average monthly cost was $960, for which the perphenazine accounted for $50. By comparison, olanzapine treatment cost $1,404 per month, with the olanzapine accounting for $545. Most patients were eventually switched from perphenazine, but their months of low-cost treatment still made a significant difference when all costs over the 18-month period were considered. Although drug switches were made for clinical reasons, there were no significant associated costs, such as higher inpatient or outpatient costs. Rosenheck et al. carefully avoid clinical recommendations, but the results suggest significant economic benefits of cheaper first-generation medications without any significant decrement in the overall clinical effect. Because fewer than one-third of persons with schizophrenia are now prescribed first-generation drugs and because health costs are always under constraint, this article is likely to be controversial and subject to much scrutiny.

The study has limitations that became apparent during its peer review at the *Journal*. First, the 18-month time period, although extensive for a study, is short for the lifetime of care for schizophrenia. In particular, it does not allow for the development of either tardive dyskinesia or the metabolic syndrome that can lead to diabetes mellitus and cardiovascular disease—side effects for which the drugs differ. Second, although there are random elements in the assignment of patients to treatment group, the restriction of perphenazine to patients who did not have tardive dyskinesia limits randomness, even though perphenazine patients were compared only to other patients who also did not have tardive dyskinesia. Third, the comparison of costs by initial treatment assign-

ment when patients did not continue on the same treatment for the entire study has an uncertain value. Fourth and most troubling to the reviewers was that there was no difference in QALY outcome between treatments. Failure to find difference does not mean that there is no difference. It could also mean that methods are too crude to demonstrate differences that may nonetheless be important for patients. The fact that patients and doctors decided to stay with olanzapine longer in the initial phase and that clozapine was helpful for patients in later stages may indicate differences in the effects of some drugs that are clinically relevant, even if they are not captured in the QALY analysis. Finally, this is not a first-episode study, and the results say nothing about what initial treatment for schizophrenia works best. The clinical setting was the outpatient treatment of chronic, not acutely ill, patients who had either stopped taking medicine or had decided to switch medications. Because of these limitations, there is a reasonable likelihood that this study did not fully capture the differences in longer-term benefit and cost between drugs. Therefore, its analyses should not be used to limit treatment of patients to first-generation antipsychotics.

We decided to publish the paper, despite these serious reservations, because there are important lessons to be learned from it. Most important, the calculation of lower costs for perphenazine has already been suggested in several commentaries, including an editorial in *The New England Journal of Medicine* (2) and a letter to the editor in *The American Journal of Psychiatry* (3). Rosenheck et al. performed the calculation rigorously, taking into account available discounts for publicly funded patients and adding important data on other treatment costs. If there is to be a debate about the use of lower cost medications, then the most complete data should be available. To that end, the CATIE investigators have agreed to make the full database available to other researchers by September 2007.

A second important lesson is that we can now see how much the costs of treatment of chronic schizophrenia are driven by the costs of drugs. Nearly one-third of the cost of treatment is ascribable just to the antipsychotic drug for patients receiving second-generation drugs during their patent period. There are other drug costs as well that are substantial. The Rosenheck et al. study gives us a unique view into how the costs of pharmaceutical industry drug development and marketing impact the cost of treatment of chronically mentally ill patients.

The Rosenheck et al. paper further illuminates the debate over the relationship between industry profit and new drug discovery by its finding, at the level of QALY analysis, that there is little if any clinical difference between the first- and second-generation antipsychotics. This disappointing result is consistent with the drugs' common pharmacological mechanism, dopamine receptor blockade, which until now has been the predominant target of industry's antipsychotic drug development effort. The hundreds of millions of dollars in profit that come from successful marketing of a new drug are the financial incentive to companies to assume the risks of drug development. The enormous costs of development and marketing of a new generation of drugs have primarily changed side effect profiles, not clinical efficacy. Over the last decade, the decline in tardive dyskinesia and other movement disorders has been heartening for patients and doctors, but with the growing seriousness of metabolic side effects, it is apparent that the side effect burden has shifted, not disappeared. From this perspective, it is hoped that the Rosenheck et al. study will increase discussion of what drug discovery model, both scientific and financial, could better improve treatment of schizophrenia.

References

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