# Changes in Perceived Health and Functioning as a Cost-Effectiveness Measure for Olanzapine Versus Haloperidol Treatment of Schizophrenia

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We utilize data from a large, double-blind, randomized clinical trial of treatment for schizophrenia to compare the effect of therapy with the second generation antipsychotic olanzapine versus therapy with the conventional agent haloperidol on the perceived functioning and well-being of patients over 1 year as measured by the Medical Outcome Study Short Form (SF-36). We also compare the total cost of care between the treatment groups over 1 year and combine cost and functional outcomes information to estimate the incremental cost-effectiveness of both therapies in this sample. Over 1 year of therapy, patients receiving olanzapine experienced a mean of 5.75 units greater improvement than did haloperidol-treated patients on the physical health and functioning factor of the SF-36 and 1.66 units greater improvement on the mental health and functioning factor. The mean annual total cost of care, including the cost of medication therapies, was $9386.87 less for olanzapine-treated patients than for haloperidol-treated patients. The incremental cost-effectiveness ratio for olanzapine versus haloperidol treatment indicated a savings of $1632.50 per unit of improvement in the SF-36 physical health and functioning score and a savings of $5654.74 per unit of improvement in the mental health and functioning composite. Improvements in perceived health and functioning were also associated with reduction in hospital costs in the full sample. These findings suggest that patient-centered measures of functioning such as the SF-36 are an important component of the evaluation of the cost-effectiveness of novel treatments for schizophrenia. *(J Clin Psychiatry 1999;60[suppl 19]:38–45)*

The purpose of the present study was to (1) quantify the changes in perceived functioning and well-being over 52 weeks associated with 2 pharmacologic interventions (the second generation antipsychotic olanzapine versus the typical agent haloperidol), (2) contrast changes in functioning with associated changes in hospitalization costs, and (3) demonstrate the use of functional status in assessing the cost-effectiveness of antipsychotic medications.

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## HEALTH AND FUNCTIONING OF PERSONS WITH SCHIZOPHRENIA

Individuals with schizophrenia or a related mental illness are at risk for a myriad of psychological, physical, and social problems (B. M. Johnstone, Ph.D.; T. W. Croghan, M.D.; R. C. Kessler, Ph.D.; et al., unpublished data, 1999; and references 1–8). Compared with the general population, they are more likely to report that their health and social functioning have been substantially compromised.[9–11] The direct and indirect costs of these impairments present a serious burden to the patient, the patient's family, private insurers, and increasingly, public health care systems.[12–14]

A major breakthrough in the treatment of persons with serious and persistent psychiatric disorders has been the development of new antipsychotic medications. These second generation antipsychotic agents represent a critical advance in that they provide equal or superior efficacy for the treatment of psychotic disorders with fewer debilitating side effects then did the older agents.[15–17] Such medications may have significant impacts on quality of life. Awad et al.[18] found that for stable schizophrenic patients, 50% of the variance in quality-of-life ratings was explained by symptom severity and degree of akathisia and neuroleptic dysphoria.

Second generation medications display particular efficacy in comparison with first generation agents in the treatment of the problematic negative symptoms of schizophrenia, such as affective flattening, avolition, and apathy.[19–21] These agents also show promise for alleviating the severe cognitive impairments and mood disruption that frequently accompany schizophrenia.[22–25] Improvement in these areas can have a direct and positive impact on patients' health status and need for health care services,[26] social integration, and ability to live independently and work or attend school in the community.[27,28]

Work functioning has been examined in a few studies of antipsychotic medication effectiveness, with improvements in work status and/or functioning over several years related to treatment with newer rather than first generation antipsychotics.[29,30] Olanzapine is a thienobenzodiazepine that has displayed an efficacy and adverse effects profile consistent with novel antipsychotic agents in large clinical studies.[15,31,32] A recent clinical trial comparing this second generation antipsychotic with haloperidol found that although the percentage of olanzapine patients who reported working full- or part-time was similar to that of haloperidol patients during the first 6 weeks of treatment (11.2% vs. 9.4%), the proportions diverged significantly in favor of olanzapine during the next 46 weeks (19.4% vs. 8.4%, $p < .001$) among those responding to treatment.[30,33]

The specific relationship of negative symptoms to work outcomes is receiving increased attention. Negative symptoms represent a major barrier to employment for persons with schizophrenia.[34] Second generation agents may allow these individuals to take increased advantage of rehabilitation efforts (reference 35 and data on file, Eli Lilly and Co., 1998).

In a cross-sectional observational study in a large psychiatric rehabilitation agency, clinical and effectiveness outcomes for clients taking second generation antipsychotics versus those for a group receiving first generation agents were examined (data on file, Eli Lilly and Co., 1998). When scores on the Positive and Negative Syndrome Scale[36,37] were examined separately for 5-factor analytic subscales,[38] the clients taking second generation medications were rated as having significantly fewer cognitive symptoms (14.0 vs. 16.9, $p < .05$) and significantly less hostility (5.1 vs. 6.3, $p < .05$) than those taking the older drugs. Hostility was, in turn, significantly correlated with level of employment as measured by an 8-point continuum ($p < .05$). Also, fewer cognitive symptoms were significantly related to placement in an integrated work setting ($p < .01$).

Findings of this nature are being reported by others as well. Sharma and Mockler[39] suggest a paradigm shift in the conceptualization of schizophrenia treatment success, namely that success can be measured by improved cognitive function rather than merely by clinical symptom improvement.

## HEALTH AND FUNCTIONING AS OUTCOME MEASURES

Until quite recently, outcome information related to antipsychotic pharmacotherapies has been almost exclusively focused on disease-specific symptom severity (efficacy) and adverse events (safety). As the work cited above illustrates, there is now growing recognition that successful treatment of schizophrenia involves the ability to affect the more distal patient-centered outcomes such as patient functioning and well-being.[40–45]

Quantifying the effects of antipsychotic treatment on patient functioning (mental, physical, and social) is important from a variety of perspectives. It is important for patients, families, and treatment providers when faced with different long-term treatment options.[45] It is also important for administrators in institutions and state or local planning groups who must weigh the acquisition costs of medications against their probable impact on effectiveness and subsequent cost outcomes.[30] For example, 2 pharmacotherapies may demonstrate equal efficacy in relieving disease-specific symptoms, but may have very different effects on other outcomes such as social or community functioning or long-term physical health.[4,43] Functioning and long-term health differences may have substantial implications for future service use and expenditures. Nevertheless, there have been very few studies that empirically examine these important aspects of effectiveness.

An accurate and comprehensive assessment of medication cost-effectiveness is particularly vital for the new generation of antipsychotics, which have higher acquisition costs but greater potential to have a positive impact on the lives of schizophrenic patients.[46] Although an analysis of a medication's true value must include functional effects, these types of outcomes are often less immediate and less easy to measure than are clinical symptoms.[47,48] Moreover, many functional outcomes will necessarily be influenced by a variety of factors other than medication. For example, the ability to have successful social interactions will be influenced by clinical factors such as improved negative symptomatology as well as by environmental and health services factors such as supportive social networks or nonmedication treatment interventions.[49]

Given the complexity and the multiple determinants of functioning outcomes, demonstrating even modest medication effects on functioning could represent an important advance.[30] The ability to tie a medication's "main" effects on patient functioning and well-being to subsequent medical service utilization and cost would be of even greater value.[10,50] The routine inclusion of functioning outcomes in calculations of medication cost-effectiveness would inform and assist consumers, service providers, and those faced with pharmacy acquisition decisions.

### Cost-Effectiveness Analysis

Determination of the value of a novel health care intervention must include a combined assessment of the cost and the effectiveness of the treatment in comparison with existing therapies.[51] Cost and effectiveness can be summarized in a single value by calculating the cost-effectiveness ratio.

***Incremental cost-effectiveness ratio.*** Cost-effectiveness ratios are used to compare alternative health care interventions such as pharmacotherapies and to estimate the marginal cost per unit of improved outcome.[47,52] The incremental cost-effectiveness ratio (ICER) is the difference in average per-patient charges associated with 2 alternative treatments (Cn – Cs) divided by the difference in average effectiveness units (En – Es), where Cn = novel treatment cost, Cs = standard treatment cost, En = novel treatment effectiveness, and Es = standard treatment effectiveness. Although both the cost and effectiveness distributions may be significantly skewed, the averages, as well as the resulting numerator and denominator differences, are approximately normally distributed.[53] The ICER is a reliable method for estimating cost-effectiveness.[54]

***Bootstrap analysis of ICER.*** Bootstrapping is a nonparametric statistical technique that allows one to construct a confidence region around an ICER by literally reanalyzing the data through many resampling iterations.[54] This method was used by Johnstone et al.[55] in an analysis of total direct health care expenditures incurred over 52 weeks by U.S. patients randomly assigned to treatment with olanzapine or haloperidol. In that study, costs were defined as the total direct health care expenditures incurred by patients in the United States (1995 values) over the 52-week therapeutic interval. Effectiveness was defined as the total number of psychiatric symptom-free days as measured by the Brief Psychiatric Rating Scale (a BPRS total score of ≤ 18, normalized scoring system, over the 52-week interval). On average, the olanzapine-treated patients displayed over 18 more symptom-free days compared with haloperidol-treated patients. The calculated ICER revealed a saving of $563 per symptom-free day with olanzapine treatment. This result was highly stable, i.e., in resampling the result 25,000 times using a 2-sample bootstrap analysis, the observed percentage of negative estimates (indicating that olanzapine therapy was more effective at lower costs than haloperidol) was 96.4%.[55]

## THE MEDICAL OUTCOME STUDY SHORT FORM HEALTH SURVEY

The Medical Outcome Study Short Form (SF-36) is a widely used self-report instrument that assesses an individual's perceived functioning and well being.[56,57] The instrument's 36 questions assess 8 domains: physical functioning (limit in physical activities because of health problems), role limitations due to physical health problems, bodily pain, general health perceptions, vitality (energy versus fatigue), social functioning (limitations in social activities because of physical and/or emotional problems), role limitations due to emotional problems, and mental health (psychological distress versus well-being).[58–60] The instrument was constructed to represent 2 major dimensions of health and functioning, physical and mental.[56,61]

The SF-36 has been validated in schizophrenia patient populations.[9,11,62] It has been used to measure the impact of this illness on individuals and to quantify the nature and degree of the effects of pharmacotherapy.[41,63,64] Compared with the general population,[9,60] schizophrenia patients report marked deficits in vitality, role limitations with work or other daily activities as a result of emotional problems, and poorer general mental health. The level of social functioning reported denoted extreme and frequent interference with normal social activities due to physical and emotional problems.[11,59]

The SF-36 is sensitive to differences in treatment effects. In a study comparing schizophrenia treatment with olanzapine or haloperidol, after 6 weeks, those randomly assigned to olanzapine treatment improved in 5 of the 8 functioning and well-being domains to a statistically significantly greater degree than did those randomly assigned to haloperidol treatment. The most dramatic 6-week improvement was in role limitations due to emotional problems. In this respect, the olanzapine patients improved by 14.23 points on a scale in which a 5-point change is considered clinically significant.[11]

The SF-36 has been shown to be a useful measure for differentiating the short-term effects of treatment with a second generation medication (olanzapine) versus a first generation agent (haloperidol). In this article, we assess longer term medication cost-effectiveness based on changes in perceived functioning and well-being.

## METHOD

### Subjects

Data for the analyses of perceived functioning and hospital costs were obtained from a prospective, randomized, double-blind clinical trial.[15] That study's purpose was to evaluate the safety, efficacy, and cost-effectiveness of olanzapine (5–20 mg/day) compared with haloperidol (5–20 mg/day) for treating schizophrenia and related psychotic disorders.[15] Patients were randomly assigned at a 2:1 ratio to receive olanzapine or haloperidol.

The 17-country trial included 1996 male and female adult patients, in either inpatient or outpatient settings, who met DSM-III-R[65] diagnostic criteria for schizophrenia, schizophreniform disorder, or schizoaffective disorder. To enter the trial, patients had to be experiencing a clinically significant psychosis and either receiving no neuroleptic treatment or demonstrating less than a clinically optimal response to their current treatment. They

could also enter as a result of being intolerant of their current antipsychotic medication (excluding haloperidol). Additional information regarding entry criteria is provided by Tollefson et al.[15]

A subsample of 1155 patients from English-speaking countries (United States, United Kingdom, and Canada) completed the standard version of the SF-36.[59,60] The sample was 70% male and 73% white. The mean age at study admission was 39 years. Among subjects completing the SF-36 at baseline, there were no differences between the olanzapine (N = 772) and haloperidol (N = 383) treatment groups with respect to baseline characteristics and perceptions, including demographics, psychiatric diagnosis and history, symptom severity variables, and perceived health and functioning as defined by each of the 8 SF-36 subscales.[11]

## Procedures

The "acute" portion[15] of the trial lasted for 6 weeks, with patients eligible to enter a 46-week "responder extension" phase if they demonstrated medication tolerability and experienced medication efficacy, according to predefined standardized clinical criteria. Thus, a maximum follow-up period of 52 weeks was possible.[55] Institutional Review Board approvals were obtained and appropriate consent procedures followed.[15]

In addition to the baseline assessment, the SF-36 was administered at the end of the 6-week acute phase and, for those in the extension phase, every 8 weeks for an additional 46 weeks. During these visits, information on resource utilization was collected through self-report and corroborative written records. SF-36 data were collected via interviews, following published guidelines for administration.

## Data Analyses

***Treatment of missing observations.*** Per the design of the 52-week clinical trial, patients not demonstrating a clinically significant treatment response were discontinued from the study after the initial 6 weeks of double-blind therapy. The specific dispositions for patients in the clinical trial, including reasons for discontinuation, are discussed in detail elsewhere.[15] This design is problematic for an effectiveness or intent-to-treat analysis, since such analyses require data on the whole population for the full study period regardless of subjects' response status or adherence to treatment.[66,67]

Using a mixed linear model, we estimated values (based on all observed data) for missing SF-36 responses for both treatment responders and nonresponders who completed the SF-36 at baseline. The imputation method is described fully by Obenchain and Johnstone.[67] These estimates can be considered conservative in that they tend to reduce the estimated differences between the 2 groups (olanzapine and haloperidol) of patients. Thus, the model provides the minimum difference in scores between treatment groups.[67]

Analyses were conducted using the software SAS Proc Mixed.[68,69] Likelihood imputation methods were used for all subscales except for vitality and role limitations due to emotional problems. Due to the discrete nature of these data, likelihood-based models would not converge; thus, the imputation procedure using method of moments estimators was required.[69]

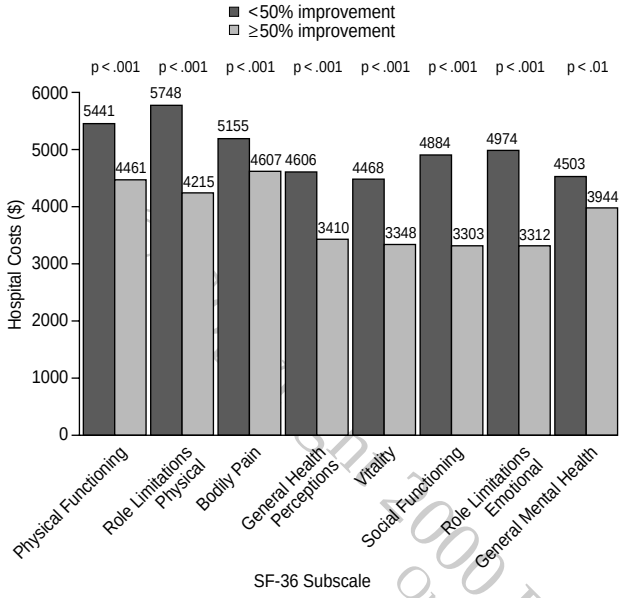
***Health-related functioning and medical cost outcomes.*** Initial analyses were conducted to explore the relationship of change in perceived health and functioning with hospitalization costs. Medical services were assigned an estimated cost in 1995 U.S. dollars based on a standardized list of prices for services.[55,70] Analyses of cost data include only U.S. patients (N = 812) to avoid difficulties in pooling cross-national data on health services delivery, utilization, and cost. Missing observations were imputed using the procedure described above.[55,70]

For each of the 8 SF-36 subscales, the Mann-Whitney test was used to analyze differences in costs, comparing patients who perceived major improvement in each scale with those reporting less-than-major improvement. Major improvement was defined as an increase of greater than 50% of possible improvement. Patients who, at the start of the study, had the maximum score on a given subscale were excluded from the analysis of that subscale, since there was no opportunity for improvement. The 6-week and 52-week time periods were used as analytic endpoints.

***Cost-effectiveness analysis.*** Eisenberg[71] suggested that the relative cost and effectiveness of clinical interventions can be jointly considered as a $3 \times 3$ contingency table that summarizes the 9 possible outcomes of a comparison of the cost and effectiveness of 2 therapies: lower clinical benefit at lower, equal, or higher cost; equal clinical benefit at lower, equal, or higher cost; and higher clinical benefit at lower, equal, or higher cost. A clear decision pathway for the choice of therapeutic options and the establishment of policy concerning access is implied by most of these possible scenarios. For example, if a novel agent is more effective and less costly than is standard medication therapy, one would be likely to adopt the novel agent as the treatment of choice. If the clinical benefit is equal, the choice of therapy can be made entirely on the basis of comparative cost. Rejection is implied if the clinical effect of the novel therapy is lower and at higher cost than standard therapy. However, if the novel agent is more effective and more costly, the decision to adopt the novel agent will not be as obvious. Moreover, it should be recognized that the results may vary depending on the types of costs and the particular aspect of effectiveness examined.

For purposes of analysis, this model can be simplified to include a $2 \times 2$ matrix of greater or lesser cost versus greater or lesser effectiveness. We conducted 2 ICER analyses; one for the physical health and functioning do-

**Figure 1. Differences in Hospital Costs at 6 Weeks for Patients Who Improved by 50% in Health Status vs. Patients Who Did Not Report Major Improvements[a]**




[a]Abbreviation: SF-36 = Medical Outcomes Study Short Form Health Survey.

main and a second for the mental health and functioning domain of the SF-36. For the first, we aggregated the 3 SF-36 subscales that loaded exclusively on the physical factor from a factor analysis of the SF-36 responses in the study population. These subscales were physical functioning, role limitations due to physical problems, and bodily pain. Similarly, the second ICER was calculated defining effectiveness as the aggregate of the 3 subscales that loaded exclusively on the mental health factor (i.e., general mental health, role limitations due to emotional problems, and social functioning).[12] A bootstrap analysis was used to evaluate the stability of both ICER statistics.

## RESULTS

### Health Status and Medical Costs

Results of the exploratory analysis of health-related functioning and hospital costs at 6 weeks are shown in Figure 1. For each of the 8 SF-36 domains, patients who achieved at least 50% of the possible improvement over baseline in the first 6 weeks of treatment had significantly lower hospitalization costs. At 52 weeks, patients who reported at least a 50% improvement since baseline in perceived physical functioning, general health, and vitality had significantly lower hospitalization costs. The 52-week differences in hospital costs for the 2 groups of patients (i.e., those who perceived a 50% improvement versus those who did not) were $9878 for physical functioning ($p < .05$), $8991 for general health perceptions ($p < .05$), and $11,384 for vitality ($p < .01$). These analyses affirm the close relationship between patients' perceived functional status, use of health services, and costs of care to the system.

**Table 1. SF-36 ICER Results Over 52 Weeks (savings benefit ratios)[a]**

| Effectiveness Measure | Cost Difference ($) | Effectiveness Difference | Savings per 1 Interval (Point) of Improvement ($) | % Bootstrap Results in Ideal Olanzapine Quadrant |
|---|---|---|---|---|
| Physical health factor | –9386.87 | 5.75 | 1632.50 | 89 |
| Mental health factor | –9386.87 | 1.66 | 5654.74 | 62 |

[a]Abbreviation: ICER = incremental cost-effectiveness ratio.

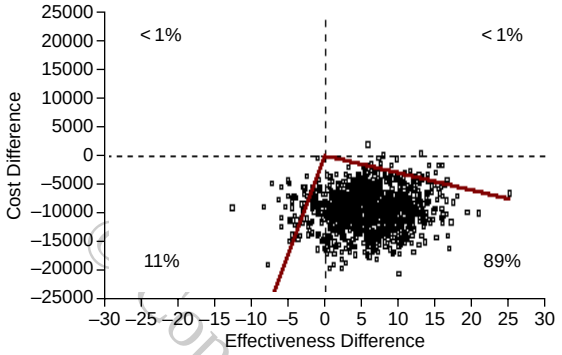
### ICER Results Comparing Olanzapine and Haloperidol Treatment

A second set of analyses evaluated the difference between olanzapine-treated and haloperidol-treated patients in the total cost of care and functioning. ICER results are summarized in Table 1. The calculated cost difference between this sample of olanzapine- versus haloperidol-treated patients was $9386.87 over 52 weeks. The daily cost of hospitalization varies across systems; we have used an estimate of $599 per day.[72,73] This suggests that a large savings in hospital costs was experienced by patients treated with olanzapine, representing more than 15 days in hospital annually. In the effectiveness measures, the olanzapine-treated patients' improvement was a mean difference of 5.75 units greater on the physical health and functioning factor and 1.66 units greater on the mental health and functioning factor over 52 weeks compared with the haloperidol-treated patients.

This combination of greater effectiveness and lower cost produces an unusual cost-effectiveness ratio, where improved effect is associated with extra savings rather than extra cost. Dividing the mean difference in the cost of care between the treatment groups by the mean difference in effectiveness, the ICER for olanzapine versus haloperidol treatment shows a savings of $1632.50 per point of change in the SF-36 physical health and functioning score, and a savings of $5654.74 per point in the mental health and functioning composite score.

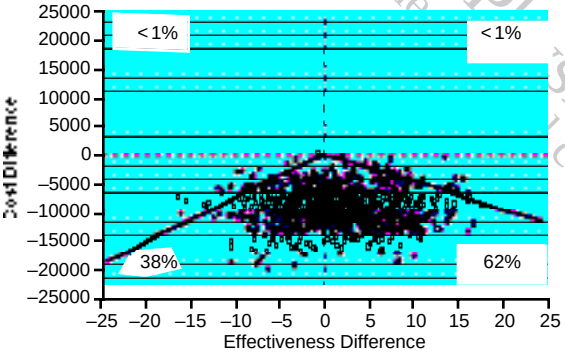
Figures 2 and 3 display the variability in cost and effectiveness outcomes as a result of the resampling procedures. The ICER confidence region is represented by the wedge-shaped area on each cost-effectiveness plane. The cost-effectiveness results for the physical composite are highly stable. Resampling 25,000 times led to an observed rate of negative estimates (indicating that olanzapine therapy was more effective at lower cost than was haloperidol therapy) of 89%. For the mental health and functioning index, the comparable rate was 62%. Finally, Figures 4 and 5 place the analyses within the context of the $2 \times 2$ cost-effectiveness decision matrix described above.

**Figure 2. Incremental Cost-Effectiveness Outcomes on Physical Health Factor[a]**




[a]Olanzapine minus haloperidol, 1000 bootstrap replications on a cost-effectiveness plane. The SF-36 physical health factor includes physical functioning, role limitations due to physical health problems, and bodily pain.

**Figure 3. Incremental Cost-Effectiveness Outcomes in Mental Health Factor[a]**




[a]Olanzapine minus haloperidol, 1000 bootstrap replications on a cost-effectiveness plane. The SF-36 mental health factor includes social functioning, role limitations due to emotional problems, and mental health.

**Figure 4. Percent of Bootstrap Replication Results at 52 Weeks in Each Cost-Effectiveness Quadrant: Physical Health[a]**

| Effectiveness Physical Health Factor | Hospital Costs: Haloperidol Less Costly | Hospital Costs: Olanzapine Less Costly |
|---|---|---|
| Olanzapine More Effective | < 1% | 89% |
| Haloperidol More Effective | < 1% | 11% |

[a]The SF-36 physical health factor includes physical functioning, role limitations due to physical health problems, and bodily pain.

**Figure 5. Percent of Bootstrap Replication Results at 52 Weeks in Each Cost-Effectiveness Quadrant: Mental Health[a]**

| Effectiveness Mental Health Factor | Hospital Costs: Haloperidol Less Costly | Hospital Costs: Olanzapine Less Costly |
|---|---|---|
| Olanzapine More Effective | < 1% | 62% |
| Haloperidol More Effective | < 1% | 38% |

[a]The SF-36 mental health factor includes social functioning, role limitations due to emotional problems, and mental health.

## DISCUSSION

Individuals with schizophrenia typically experience serious impairments in mental, social, and physical functioning. The direct and indirect costs of these impairments are a significant burden for the individual patient, his or her family, private insurers, and public health care systems. Second generation antipsychotics, including olanzapine, have demonstrated increased levels of effectiveness and tolerability compared with first generation antipsychotics. Increasingly, research on the effectiveness of these medications is broadening its scope to include distal, patient-centered outcomes of care such as perceived health status, quality of life, and employment or other forms of participation in the community. Ultimately, such research may point the way to an emergent standard of care that establishes full social reintegration as the primary expectation for treatment outcome and the standard for evaluation of the effectiveness of new therapies.

The impact of the second generation antipsychotics on the total cost of care received by patients with schizophrenia is another important outcome of interest. The usual analysis of cost-effectiveness ratios assumes that the newer and ostensibly more expensive technology will not be entirely offset by lower subsequent service utilization costs, that is, the usual analysis reveals the extra cost associated with a unit of patient improvement. In this study, olanzapine displayed both cost and effectiveness advantages over haloperidol. This was particularly the case when effectiveness was defined by physical health and functioning. Olanzapine treatment reduced average annual hospital costs in this analytic sample by $9387 relative to haloperidol treatment. Our results may best be described as a savings/benefit ratio in that olanzapine was associated with both hospital cost savings and greater overall effectiveness.

The striking findings for physical health and functioning seem important for the longer term view of medication treatment outcome. Olanzapine may hold great promise for affecting the physical aspects of functioning, which have important implications for health service utilization. The somewhat less robust but still notable effects for the mental health factor are likely to represent the complexity

of mental health functioning over long treatment intervals. The physical aspects of functioning may be less subject to fluctuating environmental variables such as social support and be more straightforwardly determined by medication effects.

This study examined only the "main effects" of medication treatment. It is important to examine the interaction of medication and other types of treatment interventions as well. Indeed, second generation medications may allow for more optimal responses to psychosocial or vocational interventions.

This study also adds to the body of accumulating empirical evidence that "subjective" patient experiences of outcome (e.g., reported levels of health and functioning) are not only valuable from the individual patient perspective,[74] but can also be linked to tangible endpoints of medical resource utilization and cost.[50] Thus, assessing perceived health and functioning (as well as other indices of functional status) can provide very useful information for treatment and policy decisions.

Future intervention studies should include patient functioning as an effectiveness domain. Patient-centered effectiveness domains that could be considered in cost and effectiveness analyses are numerous. Examples include measures of activity status, quality of life, alcohol or illicit drug use, and neuropsychological functioning.

The study of economic and functional outcomes associated with novel antipsychotic therapies will undoubtedly continue to grow, and the research questions will need to be addressed at progressively earlier stages of investigation. Data on patient functioning and resource utilization must continue to be linked to capture the full economic and humanistic value of second generation antipsychotic medications.

*Drug names:* haloperidol (Haldol and others), olanzapine (Zyprexa).

*Disclosure of off-label usage:* The authors of this article have determined that, to the best of their knowledge, no investigational information about pharmaceutical agents has been presented herein that is outside Food and Drug Administration–approved labeling.

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