Formulary Decisions and Health Economics

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Because of increasing concerns about health care costs, physicians must consider the cost-effectiveness of a treatment strategy, as well as its efficacy and safety. The question of whether the greater expense of a newer drug is justified over the cost of a generic drug deserves a comprehensive evaluation. The determination of effectiveness and tolerability of the newer antipsychotics should be expanded to include quality-of-life issues, reintegration of the patient into the community, resource utilization, and medical costs. There are clear indications that patients who take atypical antipsychotics utilize fewer medical resources than patients who take typical antipsychotics; however, the positive outcomes of the newer drugs must be translated into cost benefits if formularies are to be intelligently controlled.
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Because of increasing concerns about health care costs, physicians must consider the cost-effectiveness of a treatment strategy, as well as its efficacy and safety.[1] Awareness of the cost-effectiveness of therapeutic strategies for patients who have schizophrenia is especially important because of the economic burdens an early onset and long-term course of illness place on society, the patient, and the health care system. Costs of treatment have been high, even among patients who were initially responsive to conventional neuroleptic care.

The study of pharmacoeconomics addresses the impact of medication costs on other direct treatment costs, on patient satisfaction and quality of life, and on indirect treatment costs (such as welfare). In 1986, Weiden and Olfson[2] estimated the cost of rehospitalization in neuroleptic-responsive schizophrenics in the United States. Within 2 years of being discharged from an index hospitalization, more than 80% of the cohort had been rehospitalized, and the aggregate cost of readmission for the group approached $2 billion. More than half (63%) of these costs were principally attributed to the loss of medication efficacy, with the majority of the remainder accounted for by medication noncompliance. In 1990, drug costs constituted only 2% of the direct costs of treatment for schizophrenic patients.[3] Although that percentage may increase to 10% by the year 2000, it is still a small slice of the total pie.

The question of whether the added expense of a newer drug is justified over the lower costs for a generic drug deserves a comprehensive evaluation. To focus only on a drug's expense is as biased as to focus only on its efficacy. The determination of effectiveness and tolerability of the newer antipsychotics should be expanded to include quality-of-life issues, reintegration of the patient—including social functioning, suicidality, employability, and productivity—resource utilization, and medical costs. Recognition of the impact of the newer drugs on social and economic measures may lead to a more comprehensive and accurate understanding of their value.

A recent publication of *The Medical Letter* [4] found that the atypical antipsychotics are substantially more expensive than conventional antipsychotics. The acquisition costs per month of 2 typical antipsychotics, haloperidol and chlorpromazine, were compared with acquisition costs per month of 2 atypical antipsychotics, olanzapine and risperidone (Table 1). The cost to the pharmacist for 30 days' treatment with the usual dosage, which was based on the average wholesale price in 1997, was approximately $68 (brand) and $9 (generic) for chlorpromazine 200 mg b.i.d.; $94 (brand) and $2 (generic) for haloperidol 5 mg b.i.d.; and brand prices of $317 for clozapine 100 mg t.i.d., $239 for olanzapine 10 mg q.d., $197 (100 mg t.i.d.) or $262 (200 mg b.i.d.) for quetiapine, and $253 for risperidone 3 mg b.i.d. The difference in acquisition costs has captured the attention of individuals in many institutions and state planning groups, especially those concerned with medication budgets. Some legitimately question if the newer medications are worth the greater expense. A discussion of health economics should include not only the topic of medication costs but, ultimately, the value of the newer antipsychotic medications.

A useful and heuristic view of antipsychotic agents has been proposed by Anthony F. Lehman, M.D. (Figure 1).[5] He proposes that antipsychotics benefit the *proximal* outcomes of positive and negative symptoms, disorganiza-

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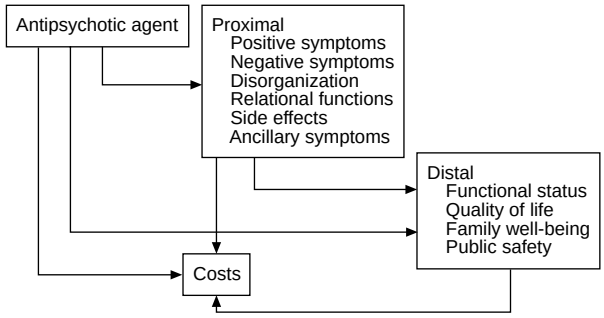
Table 1. Cost of Antipsychotic Drugs*

Drug	Usual Dosage (mg)	Cost ($)
Chlorpromazine[a]	200 bid	8.88
Thorazine (SK Beecham)		67.56
Haloperidol[a]	5 bid	1.76
Haldol (McNeil)		93.50
Clozapine		
Clozaril (Novartis)	100 tid	317.03
Olanzapine		
Zyprexa (Lilly)	10 qd	239.18
Quetiapine		
Seroquel (Zeneca)	100 tid	196.56
	200 bid	262.08
Risperidone		
Risperdal (Janssen)	3 bid	253.46

*Adapted from reference 4. Costs to the pharmacist for 30 days' treatment with usual dosage based on wholesale price according to *Drug Topics Red Book* 1997 and December 1997 *Update*.
[a]Generic drug.

Figure 1. Hypothesized Outcomes of Antipsychotic Agents*



*From reference 5.

tion, relational function, side effects, and ancillary symptoms such as anxiety and depression, hostility, and dysphoria. In addition to the symptom-oriented proximal outcomes, antipsychotics benefit *distal* outcomes such as functional status, quality of life, family well-being, and public safety. This implies a causal and temporal cascade of outcomes in which success with proximal outcomes may lead to success in more distal outcomes. The more distal the outcome, the more likely that extrinsic factors other than the treatment of interest also exert influences. This means that intervention efforts are likely to be stronger and more immediate on proximal than on distal outcomes. Nonetheless, distal outcomes may be of major importance, and hence, even moderate effects on these outcomes may be important to detect. For example, some treatments may enhance patients' ability to return to work; others treatments may not. Such a difference is important to patients, their families, and employers, and this difference may have economic impact on society as well.

DEFINITION OF QUALITY OF LIFE

The concept of quality of life has formerly been construed by many clinicians as soft and indefinable. There has been not only difficulty devising instruments and choosing outcome criteria to measure quality of life but also skepticism about the validity of self-report from schizophrenic individuals, along with the absence of a conceptual model to link quality of life with treatment, especially neuroleptic treatment.[6] With the development of excellent assessment scales and conceptual models, such as the one proposed by Lehman,[5] clinicians can measure quality of life more realistically.

Clinicians are just beginning to embrace the whole issue of quality of life. Because of the implications that newer antipsychotics improve patients' quality of life, many clinicians currently include quality-of-life assessments in the clinical evaluation, and explicit quality-of-life measures will likely be included in future treatment plans. Quality of life has been defined by Testa and Simonson as "the physical, psychological, and societal domains of health, seen as distinct areas that are influenced by a person's experiences, beliefs, expectations, and perceptions."[7(p835)] The physical domain includes clinical symptoms, function, and disability; the psychological domain includes positive and negative symptoms and behavior; and the societal domain includes work, daily instrumental roles, and personal behavior. Each of the 3 domains can be measured in 2 dimensions—objective measures of functioning and subjective perceptions of health.

Data are scarce on quality-of-life issues as they relate to the successful treatment of psychotic patients. Examples of available data include a study[8] of quality of life as a predictor of rehospitalization in 559 seriously mentally ill persons who were assessed at 2 and 12 months after an index hospital discharge, and 2 studies[9,10] of quality of life in deinstitutionalized patients who were followed for a period of several years after discharge. In the first study,[8] patients who were and were not rehospitalized between 2 and 12 months postdischarge were compared on subjective and objective quality of life, symptom severity at first follow-up, and previous rehospitalization. The patients who were rehospitalized had more severe symptoms and were more likely to have a history of hospital admissions than the patients who were not rehospitalized. Rehospitalized patients reported more dissatisfaction with family relations and were more likely to report an arrest in the previous 2 months. The 2 groups did not differ in other quality-of-life domains or in global quality of life.

In the study reported by Okin and Pearsall,[9] 53 state hospital patients were discharged to group homes in the community in the late 1970s and were followed up at 3 and 11 years to assess quality of life and several other dimensions of their community experience. The 30 patients living in noninstitutional settings at the 11-year follow-up believed that their quality of life outside the hospital had improved in the extent of their social networks, the quality

of the environment in which they lived, and their capacity to meet their own basic needs. In a longitudinal study by Okin and colleagues,[10] various dimensions of the lives of chronically mentally ill patients were examined immediately before and several years after discharge from a state hospital into well-staffed, structured, community resident settings. Fifty-five percent of the patients needed hospital readmission, but the total sample spent only 11% of the time after discharge in the hospital. At follow-up, patients showed substantial improvements in cognitive and social functioning, and 94% expressed a preference for life in the community.

MEDICATION EFFECTS ON QUALITY OF LIFE

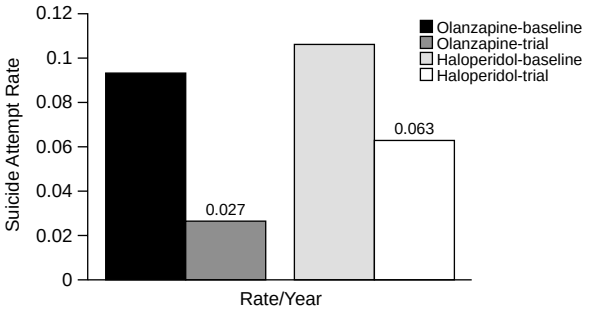
Studies of medication effects on quality of life are relatively rare—one such study by Meltzer et al.[11] showed that the use of clozapine in patients who continued treatment for at least 2 years (compared with a dropout group) led to marked improvement in Brief Psychiatric Rating Scale (BPRS)[12] total scores, Positive and Negative Symptom Syndrome Scale (PANSS)[13] scores, Global Assessment Scale (GAS)[14] scores, and Quality of Life Scale (QLS)[15] scores. Moreover, work functioning, capacity for independent living, and rehospitalization rates were improved in the schizophrenic patients who took clozapine. One study[16] that showed comparable improvement in quality of life between clozapine and haloperidol in chronically refractory patients would likely have shown a significant advantage to clozapine after a longer follow-up time (the patients were followed for 12 months).

An open-label study[17] that used postmarketing surveillance data found that risperidone produced a significant increase in scores on the QLS and Global Assessment of Functioning (GAF)[18] scales in a Spanish population. A recently published German inpatient study[19] measured patients' subjective quality of life by maze testing and found that clozapine and risperidone—but not zotepine—were superior to haloperidol in the preservation of cognitive function. Other studies are emerging that imply that atypical antipsychotic medications have more positive effects on the quality of life of schizophrenic patients than do the typical antipsychotics.

OLANZAPINE INTERNATIONAL TRIAL DATA (STUDY HGAJ)

The premarketing olanzapine studies found statistical superiority for olanzapine over haloperidol on a number of quality-of-life measures. The multicenter international trial data (Study HGAJ)[20] came from 1996 inpatients and outpatients who had DSM-III-R diagnoses of schizophrenia, schizophreniform disorder, or schizoaffective disorder. Patients were required to have a minimum BPRS score of 18 (items extracted from the PANSS and scored 0–6) and/or be intolerant of current antipsychotic therapy (excluding haloperidol). The double-blind trials were conducted in 174 investigative sites in 17 countries. Patients were randomly assigned to receive 5 to 20 mg/day of either olanzapine or haloperidol for an initial period of 6 weeks. Responders could continue double-blind therapy for an additional 46 weeks to a maximum of 1 year. The primary efficacy analysis was determined by the mean change from baseline to endpoint in total scores on the BPRS. Secondary analyses included comparisons of the mean change in positive and negative symptoms, comorbid depression, extrapyramidal symptoms, and overall drug safety. Additional rating scales for patient evaluations included the QLS, Barnes Rating Scale for Drug-Induced Akathisia (BAS),[21] Simpson-Angus Neurologic Rating Scale,[22] Abnormal Involuntary Movement Scale (AIMS),[23] Clinical Global Impressions scale (CGI),[24] and the Montgomery-Asberg Depression Rating Scale (MADRS).[25] Another outcome instrument was a resource utilization questionnaire that emphasized suicide attempts, employment and schooling status, and use of medical resources.

Figure 2. Number of Suicide Attempts Per Year for Olanzapine- Versus Haloperidol-Treated Patients*

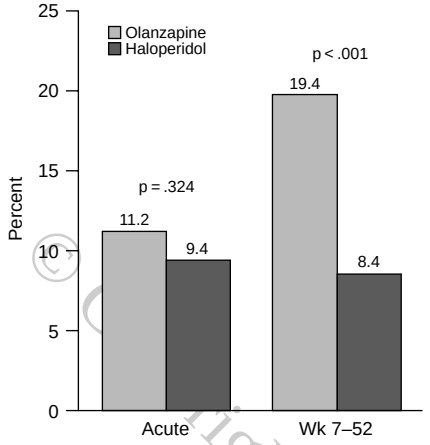


*Data on file, Eli Lilly and Company. The olanzapine rate was calculated as a function of 17 suicide attempts in 627 patient months. The haloperidol rate was calculated as a function of 12 suicide attempts in 190.25 patient months.

A striking view of the beneficial effect of olanzapine, compared with that of haloperidol, is apparent when a functional measure of quality-of-life issues such as suicide attempts per year is assessed (Figure 2). When the annual suicide attempt rates were measured at baseline and again at follow-up in the extended protocol, a 2.3-fold difference in decreased suicide attempts occurred in olanzapine-treated patients compared with haloperidol-treated patients. These data are consistent with studies of clozapine and suicidality reported by Meltzer and Okayli.[26]

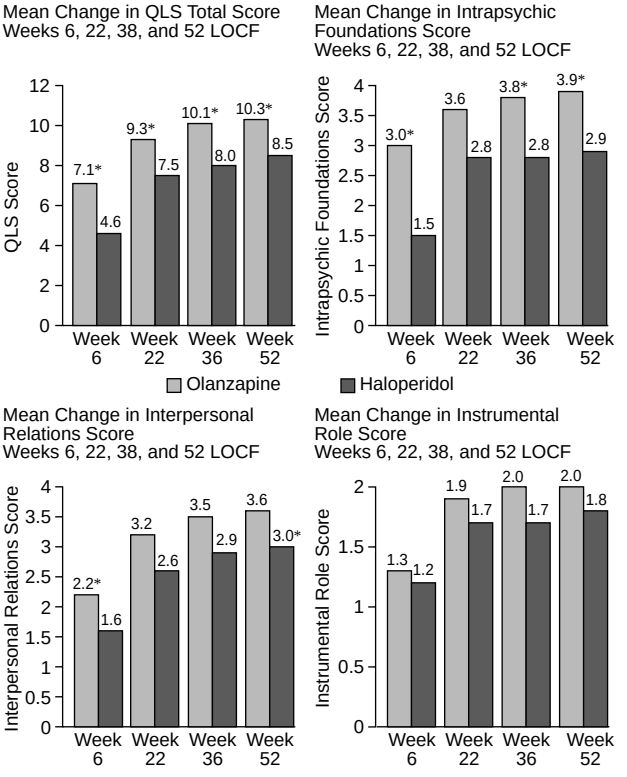
Work status, defined as part-time or full-time employment, was also evaluated as another measure of quality of life (Figure 3).[27] At baseline—the beginning of the study—the number of employed olanzapine-treated patients was similar to the number of haloperidol-treated patients. However, at the end of the 52-week extension program,

Figure 3. Percentage of Employed Olanzapine- Versus Haloperidol-Treated Patients*



*Data from reference 27. Doses of both olanzapine and haloperidol were 5, 10, 15, or 20 mg/day.

Figure 4. Olanzapine Versus Haloperidol: Long-Term Follow-Up†



†Data from reference 28.
*Analysis of variance, p < .05 vs. haloperidol.

the percentage of employed patients was twice as high for olanzapine-treated patients as haloperidol-treated patients. Although these findings are encouraging, it remains troublesome that only 20% of the overall schizophrenic population was employed on a part-time or full-time basis at the end of 1 year.

The conclusions drawn from the international data analysis were that olanzapine-treated patients, compared with haloperidol-treated patients, demonstrated a significantly greater mean change (p = .05) in QLS total scores, including both acute and long-term improvements in such quality-of-life measures as intrapsychic foundations, interpersonal relations, and instrumental role category (Figure 4).[28] The international olanzapine studies were not aimed at efforts to rehabilitate schizophrenic patients; rather, they were drug studies that focused primarily on acute and long-term antipsychotic effects. I suspect that a comparative study of atypical versus typical antipsychotics—performed in a vigorous rehabilitation setting—would demonstrate an even greater positive effect of olanzapine. The beneficial acute and long-term effects of the atypical antipsychotics provide an appropriate preparation of patients for rehabilitation. This added advantage poses a challenge for policy makers to provide suitable programs and facilities that will allow patients to benefit from early rehabilitation.

From the extended protocol of almost 2000 patients in the multicenter international trial data (Study HGAJ),[20] comparison costs were determined between olanzapine and haloperidol in the acute and extended phases of treatment.[1] The sample subset for the evaluation of cost outcomes consisted of 817 patients who had a DSM-III-R diagnosis of schizophrenia and resided in the United States. Data on patients' use of medical services, including protocol-specific physician and other services, were collected throughout the duration of the trial. Utilization data were collected on the number of hospitalizations and inpatient length of stay experienced by patients, as well as the numbers of day hospital treatment sessions, visits to the emergency room, appointments with psychiatrists and other mental health providers, home visits by health professionals, and the use of study and concomitant medications. Services and medications were assigned an estimated cost in 1995 dollars, using standardized list prices. The cost of an average daily dose of haloperidol was estimated to be $0.08 per day and the cost of olanzapine was estimated to be $7.58 per day, based on the average wholesale price of the medication. Mean medical costs per month for the olanzapine-treated group and the haloperidol-treated group were compared during the acute phase of treatment (weeks 1–6) and during the maintenance phase (weeks 7–52) for patients who demonstrated a successful response only.

During the acute phase (weeks 1–6), the medication costs of haloperidol were unquestionably less than that of olanzapine (Table 2).[1] However, during that same time period, a $615 per month reduction in inpatient mean medical costs and a $25 per month reduction in outpatient mean medical costs were estimated for the olanzapine-treated patients compared with the haloperidol-treated patients. The total mean medical costs per month for the acute phase of treatment were assessed at $431 less in

Table 2. Mean Medical Costs Per Month: Acute Phase (Weeks 1–6)*

Cost	Olanzapine Mean, $ N = 546	Haloperidol Mean, $ N = 260	Difference, $ (Olanzapine – Haloperidol)	p Value
Inpatient	3789	4404	–615	.337
Outpatient	445	470	–25	.743
Medication	219	10	209	< .001
Total medical	4453	4884	–431	.501 (.026)[a]

*From reference 1.
[a]Significance value for log-transformed total medical costs.

Table 3. Mean Medical Costs Per Month in Responders During Double-Blind Extension (Weeks 7–52)*

Cost	Olanzapine Mean, $ N = 270	Haloperidol Mean, $ N = 74	Difference, $ (Olanzapine – Haloperidol)	p Value
Inpatient	802	1205	–403	.393
Outpatient	332	486	–154	.269
Medication	219	9	210	< .001
Total medical	1354	1699	–345	.483 (.160)[a]

*From reference 1.
[a]Significance value for log-transformed total medical costs.

olanzapine-treated patients than in haloperidol-treated patients, which demonstrated a statistical superiority of olanzapine over haloperidol (p = .026).

During the double-blind extension period (weeks 7–52), the same parameters were measured. During the 1-year follow-up period, the acquisition cost of olanzapine was again clearly greater than that of haloperidol (Table 3).[1] However, during the same time period, the reduction in inpatient mean medical costs of $403 per month in olanzapine-treated patients probably compensated for the elevated medication costs. Outpatient mean medical costs were reduced by $154 per month in olanzapine-treated patients, and total mean medical costs during the extension phase were $345 per month less in olanzapine-treated patients as compared with haloperidol-treated patients. A larger sample would likely have shown a statistically significant difference in this parameter.

OTHER ATYPICAL ANTIPSYCHOTICS

The positive outcome of newer atypical antipsychotic treatment must be translated to cost benefits if formularies are to be intelligently controlled. To that end, there are 2 substantial issues. The first issue is whether the outcomes created by the various agents are the same. On the basis of the olanzapine multicenter international data,[20] the atypical antipsychotics are associated with better patient outcomes than the typical antipsychotics. The second issue is whether atypical antipsychotics are superior to standard treatments from an economic standpoint. Several studies have attempted to address this subject. Meltzer et al.[11] were among the first to publish an economic study of patients who responded to clozapine. Because the subjects were responders, the study was slightly weighted toward a beneficial outcome; nevertheless, in patients who continued clozapine treatment for at least 2 years, mental health costs demonstrated a savings of $8702/year per patient. Although this study failed to demonstrate the impact of clozapine in a vigorous, prospective randomized design, it was a definite beginning.

Another clozapine study, conducted at the Connecticut State Hospital, has been published by Essock et al.[29] Sixty percent (N = 483) of 803 long-term inpatients with a diagnosis of schizophrenia or schizoaffective disorder met the Food and Drug Administration-approved criteria for treatment with clozapine, as judged by review of past medication trial records and by the responsible physicians. This percentage included nonresponders and those who were intolerant of other medications. At the end of 1 year, 76% were still taking clozapine. The clozapine-treated patients and the usual care (typical antipsychotics) comparison group were discharged at similar rates (27% vs. 30%). However, once the patients were discharged, the clozapine-treated patients, who were taking about 500 mg/day, were less likely to be readmitted than the usual care patients (p = .001). The translation of these data to cost savings should be available at a later date.

The Veterans Administration (VA) study[16] was conducted in 15 VA medical centers. It was a prospective, randomized, double-blind, comparative trial of clozapine (N = 205) and haloperidol (N = 218) treatment in patients with refractory schizophrenia. The patients, who received maximally tolerated dosages of drugs (mean ± SD clozapine dose = 422 ± 211 mg/day; mean ± SD haloperidol dose = 21 ± 7 mg/day), were followed for 12 months. Clozapine-treated subjects had higher treatment-retention rates, greater symptomatic improvements in both positive and negative symptoms, and fewer—though less well tolerated—extrapyramidal side effects. The total annual health care costs were $2441 (not statistically significant) lower in clozapine-treated patients compared with haloperidol-treated patients. Thus, the high acquisition costs of clozapine are probably compensated for by a decrease in total health care costs; moreover, use of the drug may ultimately keep overall expenses down.

Albright et al.[30] reported similar findings from the Saskatchewan Health Linkable databases. A total of 146 patients who failed to respond to or were unable to tolerate conventional antipsychotics were assessed in a retrospective review of direct treatment costs 10 months before and 10 months after initiation of risperidone therapy. Improvements noted in the risperidone-treated patients included fewer hospital admissions, decreased length of hospital stay, and fewer physician visits. An annual cost savings of $7925 (Canadian dollars) per patient was estimated. Since the study was uncontrolled, it is impossible to de-

termine whether the savings were the result of actual drug effects or of overall improved treatment (i.e., "cohort effects").

A study of sertindole-treated patients by Nabulsi et al.[31] attempted to answer that question. A retrospective, nonrandomized mirror-image study was conducted of open-label phase 2 trial (sertindole) subjects (N = 35) versus a usual care (typical antipsychotic) comparison group (N = 40). Comparison was made of the number of hospital days 12 months before treatment and 12 months after crossing over from double-blind to open-label sertindole. Although both patient groups—the sertindole-treatment group and the usual care group—had reduced inpatient utilization, the annual number of hospitalized days was lower for the sertindole-treated patients (4.3) than for the usual care group (18.4). Sertindole is not available for use in the U.S. at this time.

CONCLUSION

There are clear indications that patients who take atypical antipsychotics utilize fewer medical resources than patients who take typical antipsychotics. Atypical antipsychotics provide benefits to patients in the form of lesser frequency of delivery of inpatient and outpatient services and the fewer number of visits to health care professionals.

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 investigational studies. The prospective randomized clinical trial framework provides a powerful inferential tool for the evaluation of economic as well as clinical hypotheses, but the adaptation of this design to meet both types of objectives presents both opportunities and challenges to researchers. It is important to ensure that complementary or potentially opposed design objectives of classical clinical trials and economic studies are carefully considered in the development and conduct of studies, and that the implications of these design decisions are appreciated in the interpretation of findings.

In well-controlled responder studies, the beneficial outcomes of atypical antipsychotic treatment have compensated for the high acquisition costs of the atypical agents. Data of cost studies, along with quality of life and resource utilization data, should clearly demonstrate the economic value of atypical antipsychotic medications. When clinicians are challenged to justify increased formulary costs of the newer antipsychotics, they must provide a total picture, not only in terms of dollar value but also in terms of the improved quality-of-life experiences of patients who take the drugs and of the patients' families.

Drug names: chlorpromazine (Thorazine and others), clozapine (Clozaril), haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal).

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Disclosure of Off-Label Usage

The author of this article has determined that, to the best of his clinical estimation, no investigational or off-label information about pharmaceutical agents has been presented that is outside Food and Drug Administration–approved labeling.