Measuring Outcome in Schizophrenia: Differences Among the Atypical Antipsychotics

Collaborative Working Group on Clinical Trial Evaluations

The advent of the atypical antipsychotics marked a new era in the history of the treatment of psychotic disorders. To evaluate the published literature about the available atypical antipsychotics—clozapine, risperidone, olanzapine, and quetiapine—and select the most appropriate treatment for specific patients, physicians need to understand the outcome measures used in clinical studies, the pharmacologic differences that explain varying side effect profiles, and pharmacoeconomic assessments that are used in the decision-making process. While the atypical antipsychotics have established efficacy in the overall treatment of schizophrenia, they may differ in their effects on factors such as cognitive function, overall quality of life, adverse events, and hospitalization status. Each of these factors should be considered when weighing treatment options for an individual patient.

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Between the 1920s and the 1970s, the percentage of patients with schizophrenia who were rated as clinically improved nearly doubled.[1] These gains were mainly attributed to the development of new treatments such as neuroleptics, which were introduced in the 1950s, and of family and community intervention strategies. Today, excitement is stirring about the hope that outcome in schizophrenia will soon once again improve dramatically, this time because of the increasing use of the atypical antipsychotics.

A large body of literature has emerged from the numerous clinical trials required before a new antipsychotic receives Food and Drug Administration (FDA) approval. The atypical antipsychotics currently available are clozapine (which is approved for treatment-resistant and neuroleptic-intolerant patients only), risperidone, olanzapine, and quetiapine. Ziprasidone, zotepine, iloperidone, M100907, and several other agents are under development and should reach the marketplace in the near future. Sertindole was recently withdrawn in the United States because of cardiac side effects. To evaluate the published literature and select the most appropriate treatment for an individual patient, physicians need to understand the outcome measures used in clinical studies, the pharmacologic differences that explain varying side effect profiles among the newer antipsychotics, and pharmacoeconomic tools that are used to evaluate the atypical antipsychotics, which may have differing effects on factors such as cognitive function, overall quality of life, adverse events, and hospitalization status. Each of these factors should be considered when the risks and benefits of a specific treatment are weighed.

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OUTCOME MEASURES IN CLINICAL STUDIES

As part of the new drug approval process for antipsychotics, the FDA requires an assessment tool for total psychopathology such as the Brief Psychiatric Rating Scale (BPRS)[2] or the Positive and Negative Syndrome Scale for Schizophrenia (PANSS).[3] These scales measure specific types of symptoms such as positive, negative, and disorganization, as well as the overall pathology. Other scales, such as the Clinical Global Impressions (CGI)[4] for severity of illness and improvement, measure social function and mental status before and after treatment. When the trial includes hospitalized patients with schizophrenia, a tool such as The Nurses' Observation Scale for In-Patient Evaluation (NOSIE)[5] may be used to assess social function, appropriateness of behavior, and self-care. These three types of outcome measures should be sufficient to determine the short-term efficacy of an antipsychotic in a double-blind, controlled study in which the raters are well-trained.

These scales, however, fail to provide a complete picture of the effects of an antipsychotic on the extensive disabilities produced by schizophrenia, which involve cognitive dysfunction and diminished overall quality of life including employment status and social relationships. In addition, they fail to measure the change in the effects of the patient's illness on both society—in terms of the direct

and indirect costs of care—and the family and/or caretakers. By design, clinical trials generally last only 4 to 6 weeks, the cohort comprises an unusually homogenous group of patients because of rigorous inclusion and exclusion criteria, and the treatment setting and conditions, unlike real-world practice, are strictly controlled. Thus, clinical trials preclude assessment of the long-term impact of treatment with a particular antipsychotic on the patient's ability to function in society. While all the atypical antipsychotics that have received FDA approval show efficacy on measures of overall psychopathology, other factors such as cognitive function and overall quality of life may differentiate the atypical agents.

Cognitive Function

Cognitive abnormalities in schizophrenia, which include deficits in attention, learning, memory, and executive function, appear early in the course of schizophrenia and appear to be enduring characteristics of the illness. Many patients with schizophrenia show impairments in focusing attention, including difficulty maintaining vigilance to relevant information while disregarding unimportant material. This attentional deficit becomes more apparent as the tasks increase in complexity. Memory deficits in schizophrenia encompass many tasks, including story recall, verbal paired associate learning, and visual designs recall, which translate practically into the rapid forgetting of newly learned information. Executive function includes the capacity to both devise and carry out solutions to problems whose solutions are not immediately obvious, such as those that require abstract reasoning. Impairments in executive function are manifested as a failure to plan, to organize, and to learn from past experiences. The patient with schizophrenia is challenged more in using information than in processing information, and these problems include distractions (an inability to edit irrelevant data) and perseverations (difficulty in generating new strategies).

Impairments in learning, memory, language, and executive function persist during periods of remission even after conventional neuroleptic treatment has reduced an acute exacerbation of psychotic symptoms and impairments in attention. There is evidence from studies of high-risk, first-degree relatives of patients with schizophrenia that the presence of mild cognitive dysfunction may be a vulnerability factor in schizophrenia.[6] These cognitive deficits can be best evaluated with a battery of neuropsychological tests such as the Digit Symbol Substitution test, which measures attention; the Consonant Trigram and the Verbal List Learning Immediate and Delayed Recall tests, which assess secondary declarative memory; the Controlled Word Association test of verbal fluency; and the Wisconsin Card Sort Test (WCST) and the Wechsler Adult Intelligence Scales–Maze Test, which measure executive function. Such tests enable some degree of localization of dysfunction to specific regions of the brain. The frontal lobes, the temporal lobes, and the hippocampus are often involved in completing cognitive tasks.

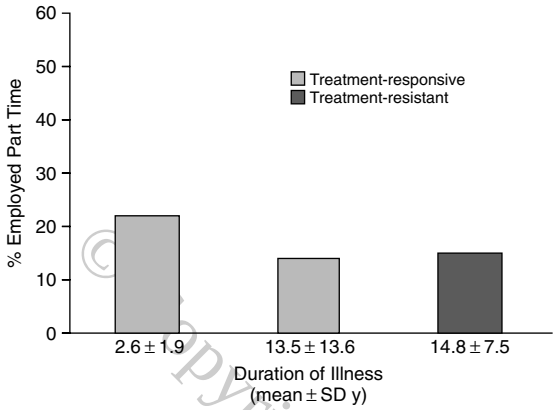
Since it is clear that cognitive dysfunction is a major factor in impaired social and work function, it is important to consider potential improvements in cognition when assessing the benefits of the newer antipsychotics. The atypical antipsychotics appear to be more effective than conventional neuroleptics in improving cognitive deficits in schizophrenia; this contributes to better overall quality of life in patients with schizophrenia, including employment status and social function.

Quality of Life

New pharmacologic treatments of schizophrenia have not only improved outcome on measures of general pathology but have also brought the issue of quality of life to the forefront. Quality of life measures, which assess changes in physical, functional, mental, and social health, are particularly relevant when treating patients with chronic disabling illnesses such as schizophrenia, which transforms the lives of patients for the worse. This illness is the determining factor in where and how patients live and work, how they relate to other people, and which, if any, daily activities they can accomplish and enjoy. While the incidence and lifetime prevalence of schizophrenia appear to be relatively similar across cultures, the clinical course tends to be more benign in developing countries where the environment is often supportive of those with impaired drive or mental functioning, whereas in the western world, individual accomplishment and productivity are stressed. Lehman[7] proposed a model for assessing quality of life in chronically ill mental patients in the United States, which included subjective and objective measures in the domains of work status, family and social relations, and other measures such as leisure activities, safety, finances, and health. The Quality of Life Scale (QLS),[8] another assessment tool in schizophrenia, evaluates functioning in four major categories: (1) Intrapsychic Functions, including sense of purpose, motivation, curiosity, anhedonia, aimless activity, and empathy; (2) Interpersonal Relations, which describes various aspects of interpersonal and social experience; (3) Instrumental Role, which assesses participation in employment or schooling; and (4) Common Objects and Activities, which is based on the assumption that participation in community life is reflected in the possession of common objects and the engagement in a range of regular activities.

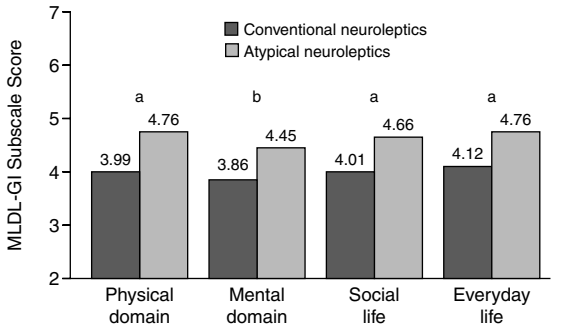
Occupational status is a factor in many quality of life assessments, and patients with schizophrenia often have a poor outcome when school or employment status is assessed, regardless of the duration of illness or degree of treatment-resistance. When the status of 3 groups of patients with a varying course of illness was compared, the percentage of patients employed part-time did not substantially differ: 20% of treatment-responsive patients who had been ill for a relatively short period, 17% of chroni-

Figure 1. Employment Status as a Function of Treatment Resistance and Chronicity*



*Data from H.Y. Meltzer and S. McGurk, unpublished data, 1998.

Figure 2. Quality of Life in Patients Treated With Conventional vs. Atypical Antipsychotics*



*From reference 15 with permission. Mean score on the Munich Quality of Life Dimensions List (range, 1 = very dissatisfied to 7 = very satisfied).
[a]$p < .05$.
[b]$p < .10$.

cally ill, treatment-resistant patients, and 12% of chronically ill, treatment-responsive patients held part-time jobs (Figure 1) (H. Y. Meltzer and S. McGurk, unpublished data, 1998). While both treatment-responsive groups had responded to conventional neuroleptics, 80% to 92% of patients remained severely disabled and unable to work.

There may be an association between cognitive impairment and occupational and social function in patients with schizophrenia. Meltzer et al.[9] examined the relationship between social and cognitive function in a group of 82 patients with schizophrenia and found that cognitive function appeared to be an important predictor of work status. Of this group, 15 were employed full-time or were in school, 13 worked part-time, and 54 were unemployed. The scores on the WCST-Category subtest were significantly higher for those employed full-time than for those working part-time or unemployed. Cognitive impairment may also be related to social disability in patients with schizophrenia. Social functioning requires such cognitive skills as face and affect recognition, recall of past interactions, executive functions, and language skills. Social problem-solving requires higher level reasoning, episodic and semantic memory, sustained attention, and high processing capacity. Jaeger et al.,[10] in a review of the literature, reported that neuropsychological deficits are predictive of social and occupational dysfunction and may explain the poor outcome from traditional vocational rehabilitation programs. Social and occupational function can be specifically assessed by such scales as the Level of Functioning Scale,[11] the Global Assessment Scale,[12] and the Social and Occupational Functioning Assessment Scale, which is contained in the DSM-IV.[13]

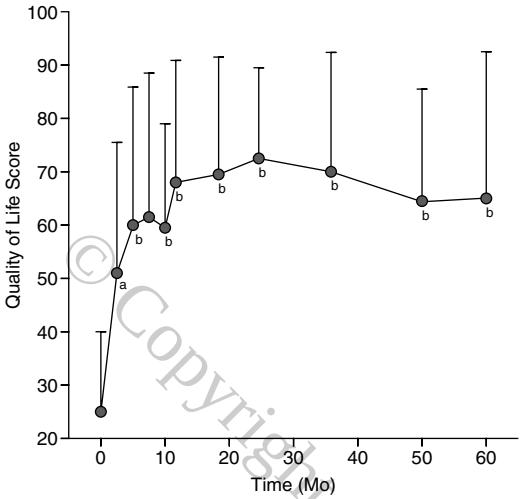
The reduced quality of life suffered by most schizophrenic patients is due partially to the manifestations of schizophrenia and partially to the adverse effects of conventional neuroleptic therapy. Recent studies[14,15] provide evidence that atypical antipsychotics may be associated with better outcome on quality of life measures than traditional neuroleptics. Meltzer[14] reported significant improvement in quality of life as assessed by the QLS and reduced rehospitalization and family burden as compared with baseline in a group of neuroleptic-resistant patients treated with clozapine. Franz et al.[15] used a modified version of the Munich Quality of Life Dimensions List (MLDL)[16] (scale ranging from 1 = very dissatisfied to 7 = very satisfied) to compare quality of life in hospitalized patients treated with conventional neuroleptics versus that of patients treated with clozapine, risperidone, or zotepine. The group treated with atypical antipsychotics had significantly higher scores in general quality of life as well as the domains of physical well-being, social life, and everyday life (Figure 2). Patients taking atypical antipsychotics were also prescribed fewer sedatives and anticholinergics than those taking conventional neuroleptics. When the atypicals were evaluated separately, a higher general quality of life was observed in patients taking clozapine or risperidone but not zotepine. Atypical antipsychotics have allowed some patients to resume a level of function that would be considered within the low normal range because it includes stable interpersonal relationships, varied social activities, some level of employment, and living with family members.

The positive effects of atypical antipsychotics on the quality of life assessments appear to be long-term. H. Y. Meltzer (unpublished data, 1998) found that the mean scores on the QLS increased substantially at the beginning of clozapine treatment. These increases were maintained during a 5-year study of 23 neuroleptic-resistant schizophrenic patients (Figure 3).

PHARMACOLOGY AND ADVERSE EFFECTS

Although the traditional neuroleptic drugs were the mainstay for treating schizophrenia for 30 years, they have many adverse effects that often lead to noncompliance and

Figure 3. 5-Year Outcome of Clozapine Treatment of the Quality of Life Scale Score *



*Data from H.Y. Meltzer, unpublished data, 1998.
[a]p < .001.
[b]p < .0001.

discontinuation.[17] These include neurologic side effects such as extrapyramidal symptoms (EPS) and tardive dyskinesia, anticholinergic side effects, and sexual dysfunction. The newer agents are termed atypical because of the broader range between the dose that controls symptoms and the one that produces EPS; with the conventional neuroleptics, the range between the therapeutic dose and the toxic dose is narrow. However, the atypicals also differ in their receptor binding profiles (Figure 4).[18,19] Haloperidol is primarily a D_2 antagonist, while clozapine and olanzapine have a broad spectrum of activity, including preferential antagonist activity at 5-HT_{2A} receptors. Risperidone principally combines D_2 and 5-HT_{2A} activity, and it has been theorized that 5-HT_{2A} antagonism is the reason why risperidone produces fewer EPS at lower doses. Quetiapine is also more potent as a 5-HT_{2A} than D_2 antagonist but is mainly potent at histaminic and adrenergic receptors. Ziprasidone and zotepine are also more potent as 5-HT_{2A} than D_2 antagonists. More well-designed head-to-head investigations are needed to see how these differences in receptor binding translate into differences in the incidence and severity of adverse effects of the various atypical agents, since separate clinical trials do not provide a reliable basis for comparing drugs because of varying dosages, titration schedules, patient populations, and nonspecific factors.

EPS and Tardive Dyskinesia

Originally, it was thought that motor side effects were an inevitable result of antipsychotic treatment. These side effects, which include akathisia, dystonia, parkinsonism, and tardive dyskinesia, are major reasons for noncompliance with antipsychotic treatment because they place an additional burden on schizophrenic patients. Ultimately, the theory that motor side effects were inevitable was challenged, and eliminating EPS and tardive dyskinesia became a goal in the development of new antipsychotics. The definition of an "atypical antipsychotic" includes having a lower risk for causing EPS and tardive dyskinesia than traditional neuroleptics.

However, lower risk does not translate into no risk, and the research designs for investigational antipsychotics generally call for any EPS to be scored, including those that appear within the first few weeks of treatment. Patients entering clinical trials have often been previously treated with conventional neuroleptics and have EPS that carry forth from this treatment. In several clinical trials for the new antipsychotics, EPS were assessed as present at least once in 10% to 20% of placebo-treated patients.[20–24] Although some of these ratings are made early in the study when the prior antipsychotics are still washing out, the statistical effect is to raise the incidence of EPS in placebo-treated patients, which makes it difficult to determine if an investigational drug carries liability for minor EPS.

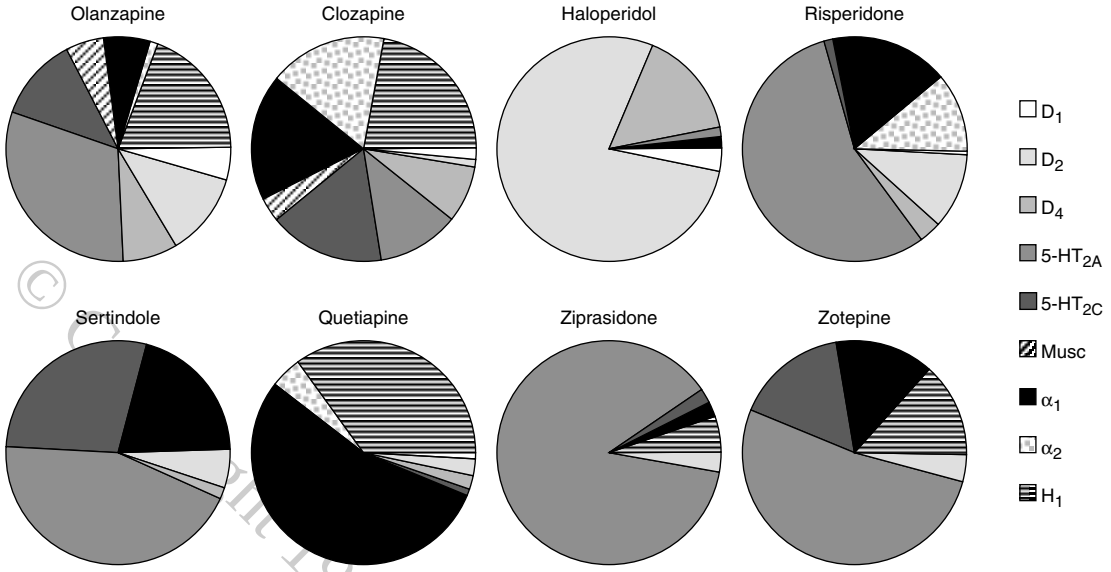
Common measures of EPS and tardive dyskinesia used in clinical trials include the Barnes Akathisia Scale,[25] the Extrapyramidal Symptom Rating Scale,[26] the Simpson-Angus Neurologic Rating Scale,[27] and the Abnormal Involuntary Movement Scale (AIMS).[28] Clozapine was the first atypical antipsychotic to clearly demonstrate a low EPS profile in a clinical trial.[29] Risperidone has a low EPS liability in the dose range of 2 to 6 mg/day,[23,24] and Kopala et al.[30] found no clinically significant EPS in a group of first-break patients receiving 2 to 4 mg/day of risperidone. Similarly, the incidence of EPS in clinical trials of olanzapine[20,21] and quetiapine[22,31,32] was lower than with placebo.

Tardive dyskinesia, which is characterized by involuntary hyperkinetic movements during or shortly after stopping pharmacotherapy, is experienced by about 20% of patients who receive extended treatment with traditional neuroleptics, and thus is also likely to be present at baseline in some patients who enter clinical trials for the newer agents. In theory, antipsychotics with low EPS potential will also have low risk for tardive dyskinesia. Support for this theory is provided by a prospective study of neuroleptic-treated elderly patients,[33] which showed that patients with few EPS were less likely to develop tardive dyskinesia than those with severe EPS. Since tardive dyskinesia, which is potentially irreversible, usually occurs later in treatment, long-term studies are needed to assess its prevalence.

Other Adverse Effects

Adverse events are routinely determined in clinical trials by using laboratory analyses, patient self-report, and a variety of assessments as part of the safety evaluation of a new agent. The incidence of a particular side effect occurring with the new agent is measured against the incidence occurring with placebo and/or the comparison agent. Anti-

Figure 4. Relative Binding Profile of Haloperidol and the Atypical Antipsychotics*



*Data from references 18 and 19.

cholinergic side effects such as blurred vision, dry mouth, urinary hesitation, constipation, confusion, possible cognitive impairment, and sometimes tachycardia occur often with high-milligram, low-potency neuroleptics, and the newer agents also are associated with a variety of anticholinergic side effects.[34] Olanzapine has a dose-related increase in constipation and dry mouth.[20]

Sexual dysfunction, often related to increased prolactin, has long been recognized as a side effect of antipsychotic treatment but until recently was not routinely assessed as part of the safety evaluation of clinical trials. Risperidone increases serum prolactin levels; however, these higher levels have not been found to be significantly correlated with the emergence of possible prolactin-related side effects.[35] Increases in prolactin during treatment with olanzapine[20,21] are small and transient, if they exist at all. Prolactin levels decreased slightly during quetiapine treatment.[22] Clozapine does not increase prolactin.

Since cardiovascular side effects, e.g., effects on blood pressure and myocardial conduction, occur frequently during treatment with conventional neuroleptics, evaluation of these effects are included in the design of clinical trials for newer antipsychotics. Orthostatic hypotension, the most common cardiovascular side effect, can occur during treatment with any conventional or atypical antipsychotic but is generally of concern primarily in the treatment of children and the elderly. Changes in electrical conduction of the myocardium, often identified as prolongation of the QT interval, is another cardiovascular side effect that is of concern. Sertindole produces a dose-related prolongation of the QT interval.[36] Although this has not been definitely linked to increased morbidity and mortality, the application for approval of sertindole has been withdrawn in the U.S. pending further studies of its risk-benefit ratio.

PHARMACOECONOMIC OUTCOME

Increasing concern about the costs of health care in the United States has made the assessment of cost-effectiveness an issue in selecting an antipsychotic. Understanding the cost-effectiveness of a particular treatment is especially important for schizophrenia, which imposes a large economic burden on the patient, the health care system, and society because of its early onset, devastating effects, and long-term course. Data on the cost-effectiveness of new antipsychotics are essential for maintaining the availability of the atypical agents in managed care formularies.

Several different types of cost-effectiveness analyses can provide information about a new medication. The quality of the data about the cost-effectiveness of a specific schizophrenia treatment is generally associated with the duration of the study; i.e., the most useful data come from studies of direct and indirect costs over the long-term. The gold standard is the medical effectiveness study, a prospective randomized trial designed to obtain cost-effectiveness information. Information can also be obtained by collecting cost data during the typical double-blind randomized controlled efficacy trial. Another approach is the retrospective study, which is often easier to carry out than to interpret. Retrospective studies include secondary analyses of large clinical data bases, analyses of completed clinical trials that add retrospective cost estimates, and studies of cohorts of treated patients either by themselves or matched to retrospective comparison groups.

To date, studies of the atypical antipsychotics indicate they are more cost-effective than traditional treatment, primarily because of a sharp reduction in the number of inpatient days.[37] Meltzer et al.[38] collected retrospective data on 96 treatment-resistant patients with schizophrenia for 2 years before and 2 years after they started clozapine treatment. Information about the cost of inpatient and outpatient treatment, housing, and family burden was gathered through direct interviews and questionnaires. The authors found that the cost of treatment was significantly decreased in the patients who continued taking clozapine for 2 years, primarily because of decreased hospitalization. In another retrospective analysis, Chouinard and Albright[39] used data from the Canadian arm of the North American Risperidone Trials and conducted a utility analysis to assess the relative gains in patient quality of life as well as the reduced costs for risperidone versus haloperidol. They found that risperidone-treated patients obtained more than twice as many quality-adjusted years as haloperidol-treated patients and that the incremental drug treatment cost divided by the incremental benefit of risperidone versus haloperidol yielded a favorable cost-utility ratio for risperidone.

Since inpatient costs comprise a large proportion of the expense in treating a patient with schizophrenia, studies comparing number of days of hospitalization provide useful data for analyzing the cost-effectiveness of a specific treatment. Addington et al.[40] conducted a retrospective analysis of a cohort of risperidone-treated patients. They compared the number of hospital days during 1 year of treatment with risperidone with the number in the preceding 365-day period when the patients were receiving conventional antipsychotics and found that the mean number of hospital days was reduced from 106 before risperidone treatment to 85 days in the year after treatment began.

Initial efficacy trials usually fail to provide ideal information for those who are investigating the cost-effectiveness of an agent in a clinical setting. Most efficacy trials include a narrow population of carefully selected patients who are free of the comorbid conditions and compliance problems that are prevalent in clinical practice. However, once a product has been shown to be safe and efficacious in short-term reduction of symptoms (the requirement for marketing an agent in the United States), broader questions of cost-effectiveness attract attention. Some of these questions can be answered by including measures of cost in the research design of clinical trials. Others will only be answered after a medical effectiveness study, a randomized trial that has the primary purpose of determining relative cost effectiveness of one agent versus another, is conducted.

CONCLUSION

Because of the increasing demand for the newer atypical antipsychotics, the annual national expense for antipsychotics is expected to grow dramatically in the next 10 years. To be able to select with confidence among these newer agents, clinicians have to evaluate the rapidly increasing body of literature about the atypical antipsychotics and understand how the pharmacology affects the side effect profile in order to choose treatments that are likely to both improve quality of life and be cost-effective. The advent of the atypical antipsychotics, which appear to improve quality of life in patients with schizophrenia, has marked a new era in the history of the treatment of schizophrenia. However, atypical antipsychotics have important clinical differences that are still being defined. Well-designed head-to-head trials of the atypical agents will provide physicians with needed information to make appropriate clinical decisions about the treatment of their patients with schizophrenia.

Drug names: clozapine (Clozaril), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal).

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DISCLOSURE OF OFF-LABEL USAGE

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