Outcome in Schizophrenia: Beyond Symptom Reduction

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Although some patients with schizophrenia may have a single episode and recover, the vast majority remain ill and unable to work for life. In the United States, patients with schizophrenia use 2.5% of the annual total health care allocations. The atypical antipsychotics, particularly when combined with psychosocial treatment, hold the promise of improving outcome and reducing the economic burden on society. Both clinical outcome and cost effectiveness are best evaluated in the context of a comprehensive assessment of a range of meaningful outcome measures studied in clinical situations. Evidence exists that the atypical antipsychotics not only reduce positive and negative symptoms and cause fewer side effects than conventional neuroleptics, but also lessen cognitive impairment, lead to a better quality of life, and have antidepressant effects, all of which should result in improved outcome in patients with schizophrenia. Increasing the availability of the atypical agents should be cost effective for society by restoring productivity in some patients with schizophrenia.

(J Clin Psychiatry 1999;60[suppl 3]:3–7)

A prototypical schizophrenic patient will show mild, almost imperceptible impairments in social and cognitive function in childhood and adolescence. During the prodromal period, which is usually of 1 to 3 years' duration prior to the onset of positive symptoms, these impairments will become noticeable, and substance abuse will sometimes begin. The first psychotic episode, which generally occurs in late adolescence during college or the first years of work, often results in brief hospitalization and a return home. Although as many as 80% of individuals with schizophrenia are unable to return to school or work after resolution of that first episode,[1] patients often refuse recommended outpatient treatment. Recurrent crises and hospitalizations are likely over the next several years. Substance abuse occurs in about 40% to 70% of patients, and 10% to 15% will be incarcerated, often for long periods of time, reflecting the fact that the nation lacks adequate supported housing and hospital beds for the severely mentally ill. About 10% to 15% of people with schizophrenia in the United States will be homeless at some point during their lifetime, and 10% will take their lives, usually within the first decade of illness. Patients with schizophrenia often do not receive adequate treatment for ancillary medical problems, such as diabetes and heart disease, that affect them at the same rate as the general population.

Although about 20% or greater of patients may have a single episode from which they recover and then disappear into the general population,[2] the majority of individuals with schizophrenia remain ill for life. Some will have an episodic illness with symptom-free intervals, but others will remain chronically ill. Thus, schizophrenia is expensive in terms of lost productivity as well as the cost of care. In the United States, 2.5% of the total health care budget is spent on patients with schizophrenia, who occupy 25% of the hospital beds and consume 20% of Social Security benefit days. In 1993, the costs of schizophrenia in the United States were estimated to be 33 billion, including direct ($17.5 billion for hospitalization and health care and $0.5 billion for medication) and indirect ($15 billion for morbidity, mortality, and lost productivity) costs (Figure 1).[3]

The atypical antipsychotics hold the promise of dramatically improving outcome in schizophrenia for many patients, which will, by restoring patients to some degree of productivity, lessen the economic burden on the health care system. Efficacy studies of antipsychotics, which are required for regulatory approval, have examined the impact on symptomatology alone but failed to provide a valid assessment of risks and benefits to guide clinical decision-making and public policy. Both cost effectiveness and clinical outcome of novel antipsychotics are best evaluated in the context of a comprehensive assessment of a range of meaningful outcome measures studied in clinical situations.

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Presented at the closed symposium "Pharmacoeconomic Factors Related to the Treatment of Schizophrenia" held on April 8, 1998, in Chicago, Illinois, and supported by an unrestricted educational grant from Janssen Pharmaceutica and Janssen Research Foundation.

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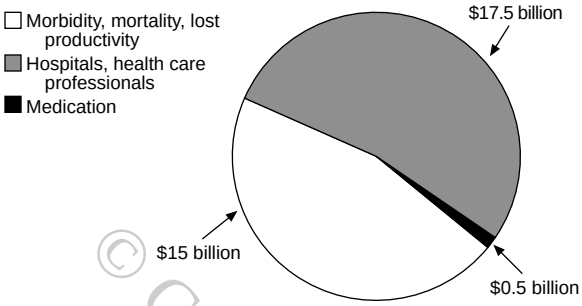
Figure 1. Distribution of Costs of Schizophrenia*



*Data from reference 3.

COST EFFECTIVENESS

The worldwide prevalence of schizophrenia is about 1%.[1] Thus, the disease, which is associated with chronic long-term disability, is extremely expensive in terms of both direct and indirect costs. Most individuals with schizophrenia in the United States will receive lifelong government subsidies in the form of Social Security Disability, Medicaid, and Medicare payments. The typical chronic patient generally has had between 6 and 30 hospitalizations in his or her life, each lasting from 1 to 4 weeks. However, both the number and duration of hospitalizations are declining steadily, as the nation limits inpatient care for severely mentally ill patients.

Medication has been the mainstay of schizophrenia treatment since the 1950s. The development and introduction of the first neuroleptic in 1954 led to the emptying of mental hospitals and the beginnings of community psychiatry in the 1960s. Implementation of deinstitutionalization in the 1960s was rarely planned properly, and inadequate resources were allocated to provide housing and rehabilitation programs that would monitor compliance and provide needed education and training. It has since become apparent that no medication alone can rehabilitate patients with schizophrenia; targeted education and community support are needed to complement pharmacotherapy. Appropriate medication is likely to help patients with schizophrenia take better advantage of rehabilitation programs. The course of schizophrenia is usually marked by discrete psychotic episodes. More extended hospitalizations are often desirable during psychotic exacerbation, but the necessary resources have become less available, mainly for financial reasons. State hospitals have been replaced with community treatment programs designed to stabilize a patient in crisis. Often only medication is offered, and that treatment is frequently rejected by patients with schizophrenia.

While conventional neuroleptics treat the positive symptoms of the illness, they fail to improve core deficits in cognition, motivation, pleasure, and affect. They also cause parkinsonian side effects that limit compliance. The search for new drugs with fewer parkinsonian side effects—especially tardive dyskinesia—led to the first atypical antipsychotic clozapine in 1991. Because of the side effect profile of clozapine—agranulocytosis develops in 1 in 100 patients—superior outcomes had to be demonstrated before it was approved. The discussions over the approval of clozapine represented the first serious look at issues involving risk versus benefits as well as cost-effectiveness of a specific antipsychotic treatment. The price of clozapine, significantly higher than that of conventional neuroleptics, was based both on an anticipated market of only 50,000 U.S. patients and on a perceived need to prepare for anticipated litigation, which, fortunately, did not occur. The clozapine price no doubt influenced the charge for the newer atypical antipsychotics—risperidone, olanzapine, and quetiapine—when they were approved.

Conventional neuroleptics cost about $0.80 to $2 per day, while the atypicals are priced between $6 and $13 per day. The additional costs have been justified, in part, by the argument that atypical antipsychotics reduce the overall costs of caring for patients with schizophrenia, particularly in terms of reducing the number of hospitalization days. This argument was valid for treatment-resistant patients in an era when psychosis or bizarre behavior routinely led to prolonged hospitalization, but not under managed care and a public policy of low reimbursements, which has led to a systematic reduction in the number of hospital beds and restrictions on the types of medication available for the seriously mentally ill in both the private and public sectors. Both managed care companies and some government agencies have used direct and indirect means to restrict access to mental health services and medication.

For example, an independent evaluation of TennCare,[4] the Tennessee program that provides public mental health services, by a group of state mental health agencies found that the capitation rate had been increased for the nonpriority population and decreased for the priority population. For the priority population (seriously and persistently mentally ill patients with moderate to severe disability ratings), an estimated 34% of the total capitation rate was available to be used for medication in lieu of services; the percentage for the nonpriority population (patients with psychiatric disorders that produce minor disability) was 57%.[5] These percentages translated into a 43% reduction in the number of units of service provided to both the priority and the nonpriority population, which had the paradoxical effect of making medication available but curtailing access to physicians and other health care providers who prescribe and monitor the medication. The evaluation also found that while controlled data support the use of olanzapine and risperidone as first-line treatments, these agents were available only for the treatment-

Table 1. Important Outcome Measures in Schizophrenia

Positive, negative, and disorganization symptoms
Cognitive dysfunction
Mood symptoms
Morbidity, mortality, and suicide
Work function
Social function
Quality of life
Hospitalization
Family and societal burden
Direct and indirect costs

resistant, and that clozapine, an established agent for the treatment-resistant, was seldom used. The national experience is similar to that of Tennessee. For treatment-resistant patients with schizophrenia, conventional antipsychotics are used for 60% of patients, while clozapine is used for 25%, risperidone for 10%, and olanzapine for 5%.[6]

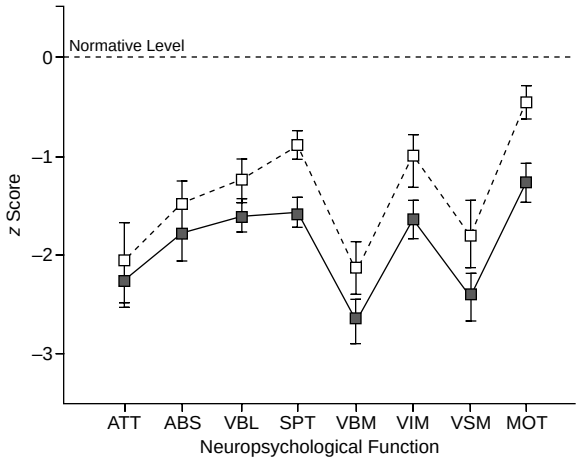
OUTCOME

Outcome in schizophrenia has been persistently poor. A survey of 20th-century outcome studies[7] showed that before the introduction of the first antipsychotic in 1954, recovery with underlying mild psychotic symptoms and social functioning returning to premorbid level occurred in about 35% of patients. The introduction and widespread use of antipsychotics in the next 3 decades led to improvement in an additional 13.1% of patients to a total of 48.5% of patients. However, the average rate of favorable outcome inexplicably declined to 36.4% after 1990; this decline may reflect less availability of psychiatric services and perhaps resulted from the reemergence of narrow diagnostic criteria.

The overall mortality rate in schizophrenia is 3 to 4 times that of the general population. A 20-year follow-up of all first-episode patients with schizophrenia diagnosed between 1966 and 1967 in Iceland[8] revealed that 22% had died; 9% had committed suicide. The majority of the patients with schizophrenia experienced serious difficulties in achieving a satisfactory quality of life. At the end of the study in 1987, 51% remained unmarried and 32% of those who had married were divorced. Symptoms persisted in 71% despite neuroleptic treatment, and social relationships were impaired in 95% of the patients. However, 35% worked 5 months per year or more, a rate substantially higher than in the United States, where only about 15% of individuals with schizophrenia work part-time or full-time.[9]

When outcome in schizophrenia is measured exclusively in terms of remission of positive symptoms, most patients treated with conventional neuroleptics are rated as much improved. Conventional antipsychotics initially reduce psychotic symptoms in 60% of all patients and in 70% to 85% of those experiencing their first episode of illness.[3] But during maintenance treatment, 60% of patients eventually relapse and need additional hospitalization, although

Figure 2. Neuropsychological Profile for Neuroleptic-Naive Patients With First-Episode Schizophrenia (N = 37) and Previously Treated Patients (N = 65) Relative to Healthy Controls (N = 131)*

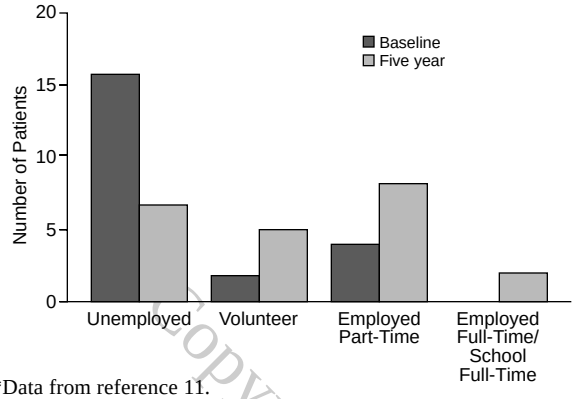


*From reference 10, with permission. Open squares = neuroleptic-naive patients with first-episode schizophrenia; closed squares = previously treated patients; dashed line = healthy controls. Abbreviations: ATT = attention-vigilance, ABS = abstraction-flexibility, VBL = verbal intelligence and language function, SPT = spatial organization, VBM = verbal memory and learning, VIM = visual memory, VSM = speeded visual-motor processing and attention, MOT = fine manual motor functions.

adding specific psychosocial treatments to medication can reduce the rate of rehospitalization. About 30% of patients treated with conventional antipsychotics fail to improve over time and are labeled treatment-refractory. When only positive symptoms are measured, many dimensions of schizophrenia are omitted from the equation (Table 1). When new treatments are being assessed, it is important to also evaluate their effects on negative symptoms and disorganization; cognitive dysfunction; mood symptoms; morbidity, mortality, and suicide; work and social function; quality of life; hospitalization status; family and societal burden; and direct and indirect costs of illness.

Broadly speaking, there are 3 targets for treatment at the level of phenomenology: psychotic symptoms, e.g., delusions, hallucinations; negative symptoms, e.g., withdrawal, lack of pleasure and motivation; and a range of cognitive impairments, which are fundamental to the illness. Poor outcome in most dimensions of schizophrenia is present and independent of the severity of positive symptoms from the beginning of the illness. Saykin et al.[10] examined neuropsychological performance of first-episode, neuroleptic-naive patients with schizophrenia and showed that from the onset of illness, schizophrenic patients performed 1 to 2 standard deviations below healthy controls in tests of verbal memory and learning, attention-vigilance, and speeded visual-motor processing and attention. When the results were compared with those of a group of unmedicated, previously treated patients with schizophrenia, the cognitive profiles were nearly identical (Figure 2). These cognitive

Figure 3. Five-Year Follow-Up of 23 Clozapine-Treated Patients*



*Data from reference 11.

deficits, which are apparent in newly diagnosed schizophrenia, greatly impair the ability of individuals with schizophrenia to function in society. 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 mean ± SD of 2.6 ± 1.9 years, 17% of treatment-responsive patients who had been ill for 13.5 ± 13.6 years, and 12% of treatment-resistant patients who had been ill for 14.8 ± 7.5 years.[11] Even among the patients who had responded to conventional neuroleptics, 80% to 83% remained severely disabled and unable to work. Scores on the Quality of Life Scale, which assesses activities of daily living, work and social function, and interpersonal relationships, were also similar across these 3 patient groups.

My colleagues and I[12] have found a strong association between cognitive impairment and occupational function in patients with schizophrenia. Abstraction, the ability to shift mental sets and grasp fundamental principles of organization, is measured in the Wisconsin Card Sort Test (WCST). Despite the presence of symptomatology, some patients with schizophrenia maintain a WCST score of between 4 and 6 (healthy controls generally score 5 or 6), and these are the patients who are most likely to remain employed. We found that cognitive function was an important predictor of work status in 82 patients with schizophrenia, of whom 15 were employed full-time or were in school, 13 worked part-time, and 54 were unemployed. Scores on the WCST-Category subtest were significantly higher for those employed full-time than for those working part-time or unemployed. When atypical antipsychotics are combined with a psychosocial treatment program, gains in function are often maintained. McGurk and I[11] followed 23 clozapine-treated patients for 5 years. At baseline, 4 were employed part-time; the number employed part-time or full-time increased to 11 after 5 years (Figure 3). However, the ability of patients to work is often dependent on government laws and policies such as, for example, when the gain of a part-time, minimum-wage job leads to the loss of health insurance or assisted housing.

Cognitive function often improves in patients treated with atypical antipsychotics.[13–16] Fujii et al.[13] reported significant improvements on prorated Wechsler Adult Intelligence Scale-Revised (WAIS-R) full scale, verbal, and performance IQ scores and on the similarities and digit symbol subtests in 10 treatment-resistant patients who had been treated with clozapine for a minimum of 1 year. Similarly, Hagger et al.[14] found that cognitive impairment decreased in 36 treatment-refractory patients with schizophrenia at both 6 weeks and 6 months after clozapine therapy began. Improvement was reported in tests of memory, executive function, and attention. Risperidone had greater beneficial effect than haloperidol on verbal working memory at 4 weeks, even after changes in the effects of benztropine cotreatment, in psychotic symptoms, and in negative symptoms were controlled.[15] When maze tests were used to determine the effects of conventional versus atypical antipsychotics on cognition, patients taking clozapine or risperidone showed better performance than untreated patients or those taking haloperidol or fluphenazine.[16]

Along with increased cognitive function, quality of life also can be improved by treating patients with atypical antipsychotics versus conventional neuroleptics, which should lead to better overall outcome. In one 4-month study,[17] scores on a standardized quality-of-life interview were higher in patients treated with clozapine or risperidone than in those treated with conventional antipsychotics or zotepine. Hamilton et al.[18] reported improved quality of life over 46 weeks in patients who were treated with olanzapine, and Aronson[19] reported improved quality-of-life as assessed by decreased hospitalization in 3 risperidone-treated patients, 2 with chronic schizophrenia and 1 elderly patient with the behavioral disturbances of dementia.

Atypical antipsychotics have been associated with a decrease in suicidality, which may be associated with antidepressant effects of these agents. Clozapine has been reported to produce a marked reduction in the incidence of suicide attempts in neuroleptic-resistant patients followed for 2 years.[20] Before treatment started, 47 patients were without suicidal thoughts, 9 had thoughts or plans of suicide, 10 had completed acts that resulted in self-harm, 17 had made attempts that had a low probability of fatal outcome, and 5 had made attempts that had a high likelihood of fatality. After 2 years of treatment, 78 were without suicidal thoughts, 7 had thoughts or plans or suicide, 3 had made attempts that had a low probability of fatal outcome, and 0 had either completed acts that resulted in self-harm or made attempts that had a high likelihood of being fatal. The overall incidence of low and high probability suicide attempts decreased from 22 (25.0%) of 88 patients in the 2

years before clozapine therapy started to 3 (3.4%) of 88 patients after 2 years of clozapine treatment. The decrease in suicide attempts was associated with a reduction in feelings of hopelessness and depression, improvement in psychosis and tardive dyskinesia, and medication compliance. While data are still lacking about the reduction of suicidality with the other atypical antipsychotics, there is preliminary evidence that risperidone[21] and olanzapine[22] have beneficial effects on the depressive component of schizophrenia. These antidepressant effects are likely to help reduce the incidence of suicidality in patients treated with risperidone and olanzapine.

CONCLUSION

The atypical antipsychotics have proven efficacy in the treatment of schizophrenia, and they also have a more favorable side effect profile than the conventional antipsychotics, which is likely to improve compliance. For example, in the North American fixed-dose trials, patients taking 6 mg/day of risperidone showed a significant decrease ($p \leq .01$), compared with patients taking 20 mg/day of haloperidol, in overall psychopathology as measured by the Positive and Negative Syndrome Scale.[23,24] Additionally, the atypical antipsychotics—risperidone, olanzapine, and quetiapine—have a substantially lower risk of extrapyramidal symptoms (EPS) compared with conventional neuroleptics. EPS are often the cause of noncompliance with conventional agents.

The use of the atypical antipsychotics to treat schizophrenia has been increasing regularly. Currently, only a slight majority (54%) of new prescriptions of antipsychotic drugs are written for typical neuroleptics, while 46% of new prescriptions are for atypicals: 25% are written for risperidone, 17% for olanzapine, and 4% for clozapine.[11] In many patients with schizophrenia, including those who have been treatment-resistant for many years, latent cognitive and social abilities return when the patients respond to an atypical antipsychotic.

John Nash, Ph.D., as a 20-year-old graduate student did research on game theory, for which he eventually won the Nobel Prize. He developed schizophrenia 10 years later. After 30 years of intermittent psychosis, he recovered remarkably and has been able to function exceptionally well. He serves as a reminder that people with schizophrenia may be able to regain their inherent capacity to contribute to society. Increasing the availability of the newer medications will improve the outcome for many people with schizophrenia. Many groups, including family members, are working hard to promote awareness of the fact that the use of the atypical antipsychotics should not be limited due to their costs, since they appear to be the more cost-effective antipsychotics in the long run because of increased improvements in outcome for patients with schizophrenia.

Drug names: benztropine (Cogentin and others), clozapine (Clozaril), fluphenazine (Prolixin and others), haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal).

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