ABSTRACT

Schizophrenia is characterized by high relapse rates and difficulty with reintegration into the community, despite recent advances in disease management. Distinct challenges are encountered at each disease stage. During the early prodromal phase, subtlety of symptoms and the absence of frank psychosis may hinder diagnosis and prevent early psychologic and pharmacologic therapy. Stigma and the lack of social support networks prevent patients from obtaining appropriate care at every stage of the disease. Effective early treatment can help prevent or delay disease progression and psychotic episodes. A combined psychosocial and pharmacologic treatment approach can ameliorate symptoms of acute psychosis, and long-term therapy can prevent disease progression and promote patient rehabilitation. However, loss of efficacy and noncompliance are major contributors to the high recurrence rates of acute psychosis in patients with schizophrenia. Extrapyramidal symptoms and tardive dyskinesia are major side effects of the earlier-generation antipsychotics; while metabolic effects, such as weight gain, dyslipidemia, and diabetes, are major side effects of many second-generation agents. Effective management of schizophrenia will depend on several factors, including the availability of new-generation drugs with benign tolerability profiles and efficacy in improving cognitive symptoms; early diagnosis and prevention; intensive cognitive-behavioral therapy; and improved psychosocial support structures.

substance abuse. Deterioration can compound all of these challenges, making effective clinical management even more difficult.

**PREVENTING RELAPSE**

At the Intervention Research Center for the Study of Schizophrenia at the Zucker Hillside Hospital in Glen Oaks, New York, we have been working closely with first-episode patients experiencing their first treatment for this devastating illness and have had some promising results. In our cohort of patients treated with conventional antipsychotics plus intensive psychosocial interventions, treatment response was defined by the following 3 criteria: a rating of mild (≤3) on the psychotic symptom items on the Schedule for Affective Disorders and Schizophrenia-Change Version with psychotic and disorganization (SADS-C+PD) items; a Clinical Global Improvement (CGI) scale rating of much or very much improved; and a sustained level of improvement for 8 consecutive weeks. Control of positive symptoms within the cohort (n = 118) was generally good: approximately 87% responded by 1 year. However, median time to response was 9 weeks, which suggests that even among patients with first-episode schizophrenia where drug response is quite good, many patients may take several weeks or months to achieve a full response.

Although the temptation is to discontinue medication in patients with a good response during the first episode, the risk of relapse is a substantial clinical concern. Relapse criteria within this analysis included: a rating of at least moderately ill on the CGI (≥4); much or very much worse on the CGI improvement scale; and a rating of at least moderate (4) severity on 1 or more of the psychotic symptom items of the SADS-C+PD. Over 5-year follow-up, the relapse rate was 82%. The single most important predictor for relapse was discontinuation of medication (Table), with patients in that data subset showing a 5 times greater risk of relapse compared with patients who remained on medication. The hazard ratio for a second relapse among patients who discontinued medication was similar.

Whereas medication response is one aspect of patient recovery, formalized standards help clinicians assess the extent of recovery in individual patients. Recovery criteria developed by Liberman and colleagues require sustained improvement in positive and negative symptoms for at least 2 years. In addition to symptom remission, acceptable levels of appropriate role function, ability to perform day-to-day living tasks without supervision, and social interactions were also defined and required as part of the recovery designation. "Improvement" does not suggest normal function; patients may demonstrate improvement, yet remain highly impaired in each of these domains. Within our cohort of first-episode patients over a 5-year period, the recovery rate was only 17%.

Could we have reduced the amount of cumulative medication that our patients with schizophrenia took by treating them intermittently or only giving medication when early or prodromal signs of relapse were evident? A

<table>
<thead>
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<th>Year</th>
<th>Relapse Rate</th>
<th>Lower 95% Limit</th>
<th>Upper 95% Limit</th>
<th>Patients Remaining at End of Year (n)</th>
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<td>81.9</td>
<td>70.6</td>
<td>93.2</td>
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</table>

Adapted from Robinson et al.

![Table. Relapse Rates for First Relapse](image)

**Figure 1. Uninterrupted Therapy Ensures Optimal Outcome**

number of studies have been conducted to test this hypothesis. Even with intensive management of the patient and the family, most studies found that continued pharmacologic treatment was far more successful in preventing relapse and repeated hospitalization compared with intermittent or targeted treatment (Figure 1). Data from the new-generation drugs (risperidone, olanzapine, quetiapine) show that many patients are still not responding adequately to treatment. A review of clinical trial data for these agents shows that as many as 20% to 30% discontinue use of medication due to lack of efficacy. Moreover, a substantial proportion of patients are not achieving the minimal level of clinically significant improvement (Figure 2).

**Patients Who Fail Therapy**

Remarkably few studies of new-generation drugs have been conducted in patients who have failed to respond to 1 or 2 drugs. Among such agents, clozapine was the first to demonstrate superiority in the management of treatment-refractory patients. Other second-generation drugs have not replicated the early effects reported for clozapine in nonresponders. A recent study of aripiprazole vs perphenazine is the only study to date in which treatment resistance to typical and atypical antipsychotics was rigorously established. Schizophrenic patients who had previously failed therapy with 2 or more drugs (≥1 of which was a typical agent), and who then failed therapy with either risperidone or olanzapine over a 6-week period were included in the study.

Specifically, 300 patients found to be treatment resistant with both retrospective and prospective assessment were randomized to receive either aripiprazole (mean dose 25-30 mg daily) or perphenazine (mean dose, 30-40 mg daily). At 6 weeks, a 27% and 25% clinical response rate was reported for aripiprazole and perphenazine, respectively (response was defined as ≥30% improvement in Positive and Negative Syndrome Scale [PANSS] or in CGI by 1 or 2). Comparable improvement in PANSS scores was observed in both treatment groups. A trend toward greater quality-of-life response was observed with aripiprazole (36% vs 21%; P = .052). Incidence of reported adverse events was similar between the 2 treatment groups (≥10% of patients), with the incidence of extrapyramidal side effects being higher with perphenazine.

As clinicians, our hope is that the new generation of antipsychotic medications will not only improve adherence because of better tolerability, but also help to prevent psychotic relapse and exacerbation. Our recent meta-analysis reviewing findings from long-term trials...
involving new-generation drugs and a first-generation comparator suggests that there is reason for hope.27 Viewed in aggregate, these studies show a significant reduction in relapse rates favoring atypical antipsychotics over conventional therapies.

Adding to this body of literature is a recent long-term study of the newest addition to the class of atypical therapeutic agents, aripiprazole.27 This study was a 52-week, randomized, double-blind, active-controlled trial that enrolled 1452 patients with acute relapse of chronic schizophrenia. The analysis of the mean change in the PANSS positive subscale score showed that there was no significant difference between the aripiprazole and haloperidol treatment groups at any time point (Figure 3). These data demonstrated long-term improvement of positive symptoms with aripiprazole similar to that achieved with haloperidol. Using the Montgomery Asberg Depression Rating Scale (MADRS) for depressive signs and symptoms, initially similar improvement was reported for both drugs. As the study progressed, the reduction in MADRS total score was significantly greater among patients treated with aripiprazole at weeks 6 through 10, and then at weeks 26 and later. Negative symptom improvement was also greater with aripiprazole.

**CONCLUSION**

Clinical trial data informs clinical practice. It can help us to determine how best to use atypical antipsychotics and what to expect in terms of efficacy and adverse events. In my opinion, the newer medications do provide a better framework for recovery in schizophrenia. However, the facilitation of recovery requires individualized treatment planning that includes psychosocial and vocational therapies. Too often we do too little in these areas, and ultimately fail to provide optimum care to patients with this illness. As clinicians, it is imperative for us to adopt a long-term perspective and to form a sound therapeutic alliance with our patients and their families. Finally, much work remains in terms of educating the public about the nature and progression of this disease and ensuring that we provide the necessary resources to deliver the care that is available.

**REFERENCES**