Management Strategies for the Treatment of Schizophrenia

John M. Kane, M.D.

Considerable progress has been made during the past 10 years in the treatment of schizophrenia; however, the disease still represents a great challenge for the clinician. Frequently encountered problems include the patient who is only partially responsive to treatment or is treatment resistant and long-term relapse prevention. Patient compliance, long-term efficacy, drug dose, safety, and the duration of treatment are all important factors determining the degree of success of maintenance treatment in the prevention of relapse. This review discusses those aspects that should affect the clinicians' choice of treatment, including the recent introduction of atypical antipsychotics such as clozapine.

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Schizophrenia continues to produce enormous personal suffering, impaired social and vocational functioning, family burden, mortality, and cost to society. A meta-analysis of the outcome literature showed that in the past decade, only 36% of patients with schizophrenia have a favorable outcome with long-term improvement of their condition.[1] This figure illustrates that substantial challenges remain in the treatment of schizophrenia.

Nevertheless, considerable progress has been made during the past 10 years. Different domains of schizophrenia, such as cognitive function, have been recognized as disease characteristics of importance in assessing response to treatment and determining treatment outcome.[2] In addition, a series of atypical antipsychotics have been introduced. However, deciding the most appropriate treatment for a specific patient and illness phase remains a challenge for many clinicians, and the role of maintenance treatment for long-term relapse prevention continues to be fraught with obstacles, with controversy regarding indications, duration, and patient acceptance and compliance. This review discusses issues pertinent to the treatment-refractory patient and the prevention of relapse.

TREATMENT RESISTANCE

Studies in the 1960s demonstrated the substantial problem of treatment resistance to typical antipsychotics. Although approximately 70% of first- and multi-episode patients with schizophrenia derived significant improvement from treatment with typical antipsychotics, approximately 30% derived relatively little.[3] A subsequent study conducted by Kinon et al.[4] addressed whether such treatment-resistant patients would most benefit from a prolonged period of treatment to allow for patient variation in the time course of response, a higher dose of the treatment, or a switch to an alternative treatment. Acutely ill, hospitalized schizophrenic, schizophreniform, or schizoaffective patients were treated openly with the typical antipsychotic fluphenazine, 20 mg/day, and with prophylactic benztropine for 4 weeks. Patients with residual psychotic signs and symptoms were considered nonresponders, even if some improvement occurred, and were randomly assigned to 3 alternative treatment regimens. One group of patients remained on the same treatment, a second group of patients were administered fluphenazine, 80 mg/day, and the third group of patients received treatment with an alternative typical antipsychotic haloperidol, 20 mg/day. After 4 weeks' further treatment, only 9% of the patients were considered to be treatment responders. This poor response was surprising considering that the majority of clinicians would take one of these courses of action when faced with a treatment-resistant patient.

However, a higher response can be obtained if treatment-resistant or partially responsive patients are switched to an atypical antipsychotic such as clozapine. For example, the 6-week, double-blind, randomized study conducted by Kane et al.[5] of 268 patients who had previously failed to respond to at least 3 different neuroleptics found that 30% of patients improved following treatment with clozapine compared with only 4% of those who received a typical antipsychotic.

This study is typical of trials of clozapine treatment in that it is based on patients who were treatment resistant in not only one 4-week trial, but in multiple trials. However, a smaller, 10-week, double-blind, randomized study

From the Department of Psychiatry, Hillside Hospital, New York, N.Y.

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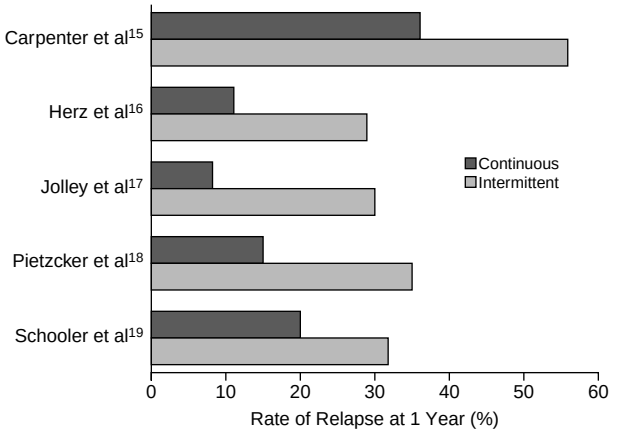
Reprint requests to: John M. Kane, M.D., Hillside Hospital, 59–75 263rd St., Glen Oakes, New York, NY 11004.

Table 1. Relapse Rate of Successfully Maintained Schizophrenic Outpatients Following Treatment Discontinuation

Study	No. of Patients	Time in Remission (y)	Follow-Up Off-Drug Treatment (mo)	Relapse Rate (%)
Hogarty et al[8]	41	2–3	12	65
Johnson[9]	23	1–2	6	53
Dencker et al[10]	32	2	24	94
Cheung[11]	30	3–5	18	62
Johnson[12]	60	1–4	18	80
Wistedt[13]	16	0.5	12	100
Mean				76

Figure 1. Relapse Rates With Continuous or Intermittent Maintenance Treatment



of 39 partially responsive patients reported that 44% of the patients improved following treatment with clozapine compared with only 6% of those treated with haloperidol.[6] Further large-scale, controlled studies of atypical antipsychotics, such as clozapine, are required to determine the most effective strategies for the treatment of the patient who is partially responsive or resistant to treatment with typical antipsychotics.

PREVENTION OF RELAPSE

Even if first-episode patients do respond to treatment, approximately 80% will experience a second episode within the following 5 years.[7] This high rate may be because patients are administered maintenance treatment for an insufficient duration or because of early treatment withdrawal. There are few controlled trials, but it is evident that antipsychotic drugs can significantly reduce the risk of relapse in first-episode patients, at least for the first year or two. However, many first-episode patients discontinue antipsychotic medication owing to a variety of reasons, sometimes with the agreement of their families and even their mental health professionals.

On average among multiepisode patients, 76% relapse within a year or two of discontinuing treatment, even if they have been in remission for long periods of time (Table 1).[8–13] The consequences of psychotic relapse are considerable in the subsequent course of illness, social and vocational functioning, family burden, and cost to society. Therefore, there is a need to identify the optimum strategy for maintenance treatment, one that includes not only medication but also psychosocial treatment and vocational rehabilitation.

Patient Compliance

A number of factors, particularly patient compliance, determine the extent of success of maintenance treatment. Even in controlled trials where patients are initially compliant, approximately 1 in 3 become noncompliant within 1 year,[14] and one would expect noncompliance rates to be higher in the general patient population. Issues contributing to noncompliance include psychosocial factors, such as embarrassment and stigma; psychological and cognitive factors, such as a patient's denial that he or she even has an illness, lack of insight, and lack of information; and pharmacologic factors, such as lack of efficacy and adverse effects. Some of these issues, such as denial of illness, which is a particular problem during the early phases of schizophrenia, and lack of insight, may be a component of the illness itself. Other factors are more readily addressed, such as the provision of information on the expected benefits, limitations, and adverse effects of the treatment. Furthermore, patients need to be made aware of the importance of prophylaxis, that if they are feeling well they still need to continue treatment to prevent recurrence of illness.

Intermittent vs. Continuous Treatment

In consideration of problems with noncompliance and side effects, it was proposed that patients with schizophrenia might be better managed in the long term by allowing them to discontinue medication when they were feeling well and only reinstitute treatment if they experienced early signs of relapse, the so-called targeted or intermittent strategy. This strategy seemed promising since some patients with schizophrenia do have a characteristic pattern of relapse, and their families or caregivers could be educated to detect early signs of relapse. Appropriate intervention at this stage could possibly prevent the relapse from becoming more severe. In this manner, patients could be off medication for a period of months or years, thereby reducing the long-term risks and subjective dysphoria associated with medication.

This hypothesis has been tested in a number of large-scale studies, all of which found that relapse rates with intermittent treatment were approximately twice as high as those with continuous treatment (Figure 1).[15–19] In the largest and most comprehensive study, including 3 treatment

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alternatives, over 300 patients were randomly assigned under double-blind conditions to placebo or to the depot antipsychotic fluphenazine, at either a standard (12.5–50 mg every 2 weeks) or a low (2.5–10 mg every 2 weeks) dose.[19] Patients assigned to placebo treatment were administered fluphenazine if they showed early signs of relapse, with the hope that a full psychotic episode could be prevented. In addition, patients were randomly assigned to 1 of 2 different types of family therapy, supportive or the more intensive applied family therapy. Patients who received the standard dose did the best in terms of relapse rate, with those who received placebo experiencing the highest relapse rate, significantly higher than with the other 2 regimens. Similarly, the targeted treatment group had a significantly higher rate of rehospitalization compared with the standard- and low-dose treatment groups. Therefore, the early intervention strategy did not prevent the relapse from becoming severe or subsequent rehospitalization. There was no significant difference between the standard dose and the low dose in preventing rehospitalization. Although family therapy has an important recognized benefit when combined with antipsychotic medication, with an additive effect in reducing relapse rates and improving psychosocial functioning, no difference was found between the less intensive multifamily group therapy and the more intensive home family visits in this study.

The early ambivalence regarding maintenance treatment was partly due to consideration of the risk of developing tardive dyskinesia with the typical antipsychotics. However, studies using clozapine treatment show that it is not associated with the development of tardive dyskinesia and may actually improve any preexisting symptoms.[5] Preliminary studies of other new atypical antipsychotics have found encouraging results as well.[20] Therefore, continuous maintenance treatment with an atypical antipsychotic may be the best strategy to prevent relapse in patients who are compliant with treatment. Nevertheless, some patients may refuse to comply with long-term treatment, and in these situations, an intermittent strategy may be the best treatment option, provided that the patients and family are educated to look for early signs of relapse and proceed with early treatment intervention.

Minimum Effective Dose

Concerns regarding side effects and compliance also inspired studies to establish the minimum effective dosage requirements for maintenance treatment. Six studies assessed the minimum effective dose of fluphenazine or haloperidol required for maintenance treatment.[21–26] Stable outpatients in relative remission were randomly assigned under double-blind conditions to different doses of fluphenazine or haloperidol maintenance treatment using long-acting, injectable forms of the drugs (so that compliance was not an issue). The lowest dose of haloperidol was 25 mg once per month, and the lowest dose of fluphenazine was 1.25 to 5 mg every other week. The relapse rate with 25 mg of haloperidol approached 60%, which, interestingly, corresponds with positron emission tomography data showing a 70% striatal dopamine D_2 receptor occupancy with haloperidol doses of 30 to 50 mg once a month.[27] Although the brain areas involved may be different, receptor occupancy may correlate with maintenance of clinical remission. A dose of 50 mg of haloperidol appeared to be the minimum effective dose, with a significantly lower rate of relapse than a 25-mg dose, although this dose was previously suspected to be too low to be effective. However, even with the highest doses tested in these studies, approximately 15% to 20% of patients relapsed within 1 year.

Since the introduction of the atypical antipsychotics, determination of the rate of relapse and the minimum effective dose may be less relevant. Preliminary data on long-term outcome and relapse prevention have indicated that treatment with clozapine is associated with a lower rate of relapse than prior treatment with typical antipsychotics such as haloperidol and fluphenazine[28] in patients who are already treatment refractory. Furthermore, the study by Essock et al.[29] found reduced rates of hospitalization after clozapine treatment in comparison with usual treatment with conventional antipsychotics.

Duration of Maintenance Treatment

Another question regarding the prevention of relapse is the appropriate duration of maintenance treatment. There still seems to be a general reluctance to recommend long-term maintenance medication despite convincing evidence that even first-episode patients will relapse upon treatment discontinuation. The American Psychiatric Association treatment guidelines[30] suggest only 1 year or more of maintenance treatment after remission of a first episode of schizophrenia. This reluctance to prescribe long-term treatment may, again, be partly due to concern about adverse effects, but clinicians need to recognize that this situation has improved with the introduction of the atypical antipsychotics.

Longer periods of maintenance treatment are generally recommended for patients who have experienced 2 or more episodes of illness, but again the recommended period may be inadequate to prevent relapse. In general, recommendations are for 5 years or at least 5 years; however, data on the long-term course of schizophrenia do not suggest that this disease is resolved in 5 years. Obviously, it is difficult to carry out controlled trials of 5 years or more in duration, but this issue does require clarification so clinicians can give a clear message to their patients and patients' families.

Cost of Relapse

The hospital costs arising from maintenance phase relapse, caused by loss of efficacy or noncompliance, are

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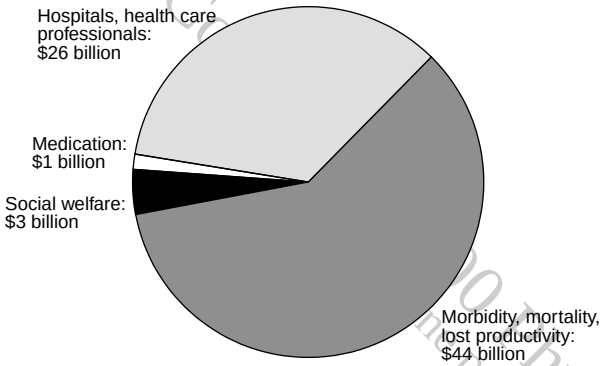
Table 2. Estimated Hospital Costs From Maintenance Phase Relapse[a]

	Costs in US Dollars (% of Total Cost)		
Variable	Year 1	Year 2	Year 3
Loss of efficacy	800 (68)	400 (54)	1200 (63)
Noncompliance	370 (32)	335 (46)	705 (37)
Total cost	1170	735	1905

[a]Adapted from reference 31, with permission.

Figure 2. Distribution of Costs Associated With Schizophrenia[a]



[a]Data from reference 32. Values given in US dollars.

considerable (Table 2).[31] Nevertheless, many clinicians are required to minimize their costs by reducing hospital stays, and in many cases the reimbursement available for other forms of treatment has also declined. If costs due to rehospitalization could be reduced, more funds for psychosocial treatment and vocational rehabilitation and housing would be available.

Compared with the enormous costs associated with health care and morbidity, mortality, and lost productivity, the cost of medication is minimal (Figure 2).[32] Therefore, an improvement in outcome or reduction in relapse rates would more than offset the costs of more expensive medications. However, this is not frequently recognized, since the money for these different expenditures is not provided by a single source. Hopefully, the next decade will bring more rational solutions to some of the problems faced in health care that should enhance the ability of clinicians to treat schizophrenia in the most effective manner.

CONCLUSIONS

Schizophrenia remains a difficult disorder to treat; however, some of the challenges faced by the clinician are being addressed. Treatment resistance continues to be a significant problem, although the introduction of the atypical antipsychotic clozapine improved the outcome for such patients. Recent studies have demonstrated that schizophrenia is a long-term problem and that continuous maintenance treatment is critical for the prevention of relapse, with 80% of first-episode patients relapsing within 5 years of discontinuing treatment. However, such long-term therapy necessitates an effective, well-tolerated treatment with a high patient compliance. Again, the atypical antipsychotics represent an advance in this area. They are not associated with the same risk of tardive dyskinesia that has caused clinicians' reluctance to prescribe long-term treatment with the typical antipsychotics. Indeed, treatment with clozapine has been associated with a lower rate of relapse and a reduced incidence of hospitalization. Furthermore, any reduction in the considerable costs due to relapse and subsequent hospitalization should readily compensate for any increase in drug expenditure. Overall, these results indicate that the more judicious or widespread use of atypical antipsychotics such as clozapine could improve the outcome for patients with schizophrenia.

Drug names: benztropine (Cogentin and others), clozapine (Clozaril, Leponex), fluphenazine (Prolixin and others), haloperidol (Haldol and others).

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