New Antipsychotic Agents: Emerging Clinical Profiles

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The past 5 years have witnessed an intense period of change in the pharmacotherapy of schizophrenia. Several new antipsychotic agents have become available for clinical use, and more are likely to appear over the next few years. The new agents require that clinicians treating patients with schizophrenia adopt new ways of thinking regarding the pharmacotherapy of this illness. Longer drug trials than have traditionally been used may be required to determine response to the newer agents, and response should be measured across negative symptoms, cognitive symptoms, and broader rehabilitative dimensions. Clozapine has an established role in treatment-resistant schizophrenia. Other new antipsychotics are being used with broader clinical indications. The relative efficacy of these agents, particularly in treatment-refractory patients, remains to be determined. The availability of the newer agents may represent an opportunity to reduce the incidence of tardive dyskinesia and to gain better management of comorbid substance abuse and aggression among schizophrenic patients. Significant cost savings could accrue from more effective disease management.

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Clinicians who care for persons with schizophrenia hardly need to be reminded that it is a debilitating, chronic illness. However, many of us are unacquainted with the extent of the economic impact of schizophrenia. Schizophrenia is a costly condition, in terms of both direct and indirect costs (see the article by Rice in this supplement[57]). Moreover, the costs associated with schizophrenia consume a disproportionate amount of resources available for the care of all individuals with psychological disorders.[1] The rapid development of the newer antipsychotic drugs for the treatment of schizophrenia has important therapeutic and economic implications for patients yet also poses challenges for clinicians to incorporate and synthesize new information into a coherent approach to the pharmacotherapy of schizophrenia.

Maintenance treatment studies of conventional antipsychotic agents show poor outcome and high relapse rates of 30% to 50% at 1 year, even in stabilized patients.[2] In a substantial proportion of patients, conventional antipsychotics exert limited therapeutic effects and psychotic symptoms persist (these patients are referred to as "partial responders"). Another group of patients, perhaps some 25% to 30% of patients, have an illness that is refractory to treatment with conventional neuroleptics. Only a minority of patients achieve "acceptable" outcome in terms of absence of psychotic symptoms and return of psychosocial function. Moreover, conventional antipsychotics are associated with extrapyramidal side effects (EPS), which are distressing and which compromise treatment compliance. Treatment is further complicated by the risk of tardive dyskinesia, estimated to emerge in 5% of patients annually for the first 5 years of treatment.[3]

The recent availability of new antipsychotic medications encourages optimism among clinicians and patients alike. Clozapine was the first atypical antipsychotic to be introduced into clinical practice (in the United States, in 1990). Risperidone has been available in the United States since 1993 for the treatment of psychosis. Olanzapine was introduced in 1996, and quetiapine in 1997. Sertindole has been available in England and other European countries since 1996. Sulpiride, amisulpride, and zotepine are other agents that are available in Europe but not the United States. Several other promising agents are at advanced stages of clinical evaluation.

These newer drugs differ from conventional antipsychotics both in receptor binding profile and in clinical profile. Moreover, ongoing clinical experience suggests that these agents may also differ among themselves. There is as yet insufficient information available from clinical trials that compare these new agents. Much of our current understanding is derived from scrutiny of pivotal clinical trials,[4–8] from subsequent clinical studies,[9] and from clinical experience and anecdotal observations. Nevertheless, with these resources it is possible to begin to explore the clinical profile of novel antipsychotics and compare them both with older congeners and with each other. This brief

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review attempts to summarize the current "state-of-play" for novel antipsychotic medications with respect to the important issues of the duration of clinical trials, effect on negative symptoms, dosing patterns, efficacy in treatment resistance, switching of medications, liability for and effect on tardive dyskinesia, and effects on particular patient subgroups who are "high users" of mental health services.

LENGTH OF DRUG TRIALS

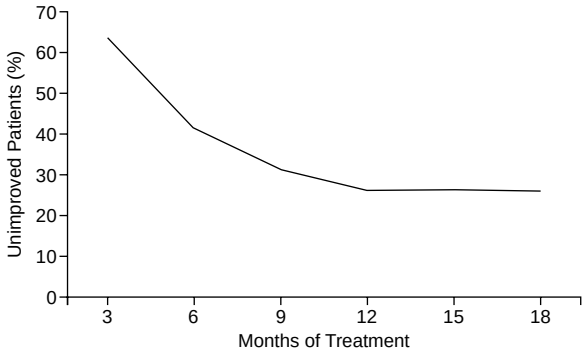
Since the new atypical antipsychotics are more expensive to prescribe than conventional drugs, how long to continue therapeutic trials, particularly when patients fail to respond after several months, is an important concern.[10] To evaluate these agents properly, a longer follow-up period is needed than the 6 to 8 weeks that is traditionally used with older antipsychotics. For example, short-term studies of clozapine suggest that 35% of patients respond within an approximately 3-month time frame,[9] while long-term studies suggest that approximately 60% of patients respond after 1 year or more of treatment.[11–13] In a study that followed patients taking clozapine for 78 weeks, the overall response rate was 73% (Figure 1).[11] Although the lack of rigorous maintenance studies has been pointed to as a cautionary note in interpreting these results,[10] a recent, exemplary, 1-year double-blind comparative clinical trial of clozapine and haloperidol noted a 1-year response rate of 40% for clozapine-treated patients.[13] Data also are accruing for the other new antipsychotics: Lindstrom and colleagues[14] reported a favorable 1-year outcome for patients receiving risperidone.

It will be of considerable interest to determine the optimum duration of clinical trials for each new drug and to examine whether it differs between agents. On present evidence, it appears prudent to allow a 2- to 4-month trial before switching to another drug or trying an augmentation strategy.

EFFECT ON NEGATIVE SYMPTOMS

Another area of concern is whether the atypical antipsychotics improve negative symptoms, but here again the data are not as clear-cut as one would like. Clozapine was shown in the multicenter trial to have an effect significantly superior to that of chlorpromazine in the treatment of negative symptoms[4]; similar effects in comparison with the chosen conventional antipsychotic have been shown in the pivotal trials of risperidone,[5] olanzapine,[6] quetiapine,[7] and sertindole.[8] However, in each instance the lower rates of EPS with the novel antipsychotics raises the possibility that the observed effect on "negative" symptoms is derived predominantly from a lower propensity for EPS. Statistical scrutiny of these effects by path analysis can shed some light on this issue and suggests that novel antipsychotics also exert a beneficial effect on primary negative symptoms,[15] but such analyses are far from conclusive. On the other hand, it is possible that real improvements in negative symptoms occur over time and are the result of enhanced social contact and psychosocial treatments for patients who are less distracted by positive symptoms and are newly able to engage in these therapies. An observation that improvement in negative symptoms occurred in the second year of clozapine treatment in the context of an outpatient psychosocial program is consistent with this notion.[12] This is an important distinction. Studies that address this are required for each of the new drugs.

Figure 1. Time Course at Response for 100 Clozapine-Treated Patients*



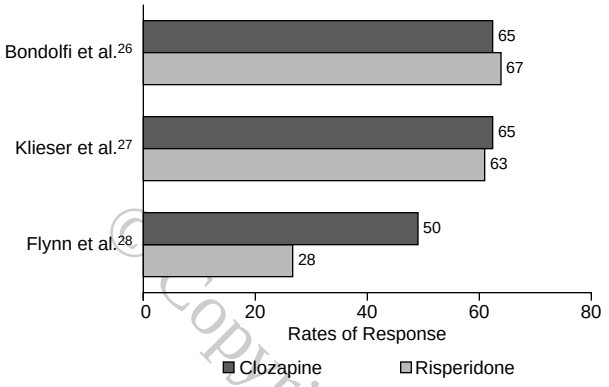
*Adapted from reference 11, with permission. After 78 weeks, overall rate of response was 73%.

DOSAGE

Dosage is another important management issue that needs further study. The optimum dosages of the new atypical agents have not been adequately determined. The current maximum recommended dosage of clozapine is 900 mg daily. Some clinicians are still wary, because of concern regarding seizures, to prescribe up to this dosage. While some patients may not tolerate this dosage, optimizing the dose of clozapine over time to an effective and tolerable level is important to prevent patients from plateauing as "partial responders." Monitoring plasma clozapine levels can be helpful; available evidence suggests that achieving a plasma level of 350–420 ng/mL increases the patient's chance of a good response.[9] Many clinicians now use serial plasma clozapine levels as a guide in maintenance dosing.

Clinicians are now prescribing risperidone at dosages lower than the 6 mg daily recommended from the multicenter trials. Recommended dosages for olanzapine are between 5 and 20 mg daily, but many clinicians are now using it to treat severe schizophrenia at doses that well exceed 20 mg. Thus far, monitoring of plasma risperidone levels or plasma olanzapine levels has not been incorporated into routine clinical practice. Recent studies suggest that monitoring plasma levels for risperidone and olanzapine may prove to have clinical utility.[16,17]

Figure 2. Percentage of Treatment-Resistant Schizophrenic Patients Responding to Clozapine or Risperidone



MANAGEMENT OF TREATMENT-REFRACTORY PATIENTS

Contrary to the traditional concept of refractoriness emerging gradually during the course of schizophrenia, it may occur close to the onset of the illness. Studies using brain imaging and biological measures reveal that a substantial proportion of patients with first-episode schizophrenia exhibit brain changes similar to those observed with long-standing treatment-resistant disease.[18] Moreover, it is recognized that patients with treatment-refractory illness account for a disproportionate share of the economic burden of schizophrenia.[19]

Clozapine is the treatment of choice for patients with treatment-refractory schizophrenia.[4] Naturalistic follow-up studies[11,12] and more recent, well-controlled maintenance studies[13,20] confirm the superior efficacy of clozapine in this patient population. Less is known about the efficacy of other novel antipsychotics in treatment-resistant schizophrenia. Additionally, there are few comparative studies of clozapine and other novel agents. Studies in this subgroup show variable rates of response to risperidone (11% to 53%) and no obvious correlation between trial duration (which ranged from 6 to 12 weeks) and response.[21–25] Comparative data show that response rates were higher for clozapine than for risperidone (Figure 2).[26–28] In one study showing comparable response,[26] there was no clear definition of "treatment-resistance," and the dose of clozapine was modest. There are few data available on the efficacy of olanzapine in treatment-refractory patients. In the recently published multicenter study of olanzapine, fewer patients taking olanzapine than taking haloperidol discontinued the drug because of lack of efficacy.[6]

Results from a comparative study of olanzapine (25 mg) and chlorpromazine (1200 mg) show a 7% response rate for olanzapine in treatment-resistant patients; none of the chlorpromazine-treated patients were considered to be responders.[29]

Both quetiapine and sertindole are effective antipsychotics with a favorable EPS profile,[7,8] but no information from clinical trials in treatment-refractory schizophrenia is yet published concerning the use of either agent in treatment-resistant patients.

SWITCHING MEDICATIONS

Patients and families who become discouraged with the long-term nature of schizophrenia or the burden of monitoring procedures (such as the white cell counts required during clozapine treatment) may request that treatment be switched to another newly approved antipsychotic, even in the face of satisfactory symptom control with their current therapy. Before a change is made for these or other reasons, several questions must be addressed:

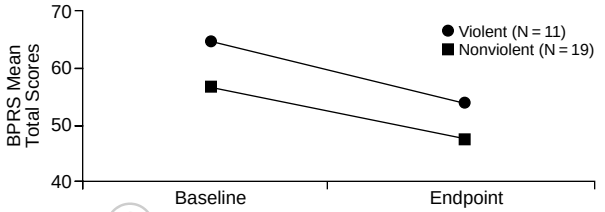
- Is there adequate information available about the new agent to define its place in the treatment of this patient?
- What is the dissatisfaction with current treatment (e.g., poor response, intolerance)?
- What are the target symptoms (e.g., persistent positive, negative, or cognitive symptoms) that may improve or worsen as a result of a switch?

In general, if symptoms are controlled with current therapy and the patient has a high level of functioning (this distinction remains to be properly clarified in the context of new antipsychotics and therapeutic expectations), switching medications is inadvisable. If the decision is made to switch drugs, slow cross-tapering of agents over weeks or months, rather than direct change, is appropriate.[30–32]

TARDIVE DYSKINESIA

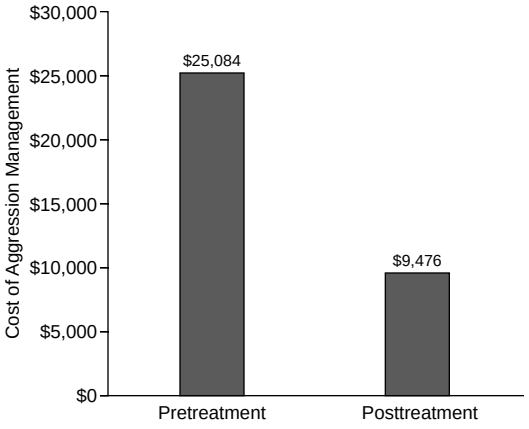
Treatment with conventional antipsychotics is a known risk factor for the development of tardive dyskinesia.[3] Extensive clinical data on the use of clozapine indicate no proven case of tardive dyskinesia.[9] On the other hand, there is evidence that clozapine may diminish involuntary movements in patients with more severe tardive dyskinesia or tardive dystonia.[33] It may take several months of clozapine treatment before this advantage becomes apparent.[34] Whether a dose-dependent improvement in tardive dyskinesia occurs with the use of clozapine is under investigation. Data available on other novel antipsychotics are encouraging and suggest a lower incidence of treatment-emergent tardive dyskinesia,[35] but the present data are insufficient to draw conclusions regarding their treatment effects on tardive dyskinesia. However, if the trend for lower rates of tardive dyskinesia with newer agents is con-

Figure 3. Response to Clozapine in Nonviolent and Violent Schizophrenic Patients as Measured by the Brief Psychiatric Rating Scale (BPRS)*



*Adapted from reference 49, with permission.

Figure 4. Cost Analysis of Aggression Reduction During Clozapine Therapy Among 11 Patients With Schizophrenia



firmed, then the role of older antipsychotic medications will diminish further. If EPS is a significant risk factor for tardive dyskinesia,[3] then the low rates of EPS with new drugs may in time translate into a lower risk for tardive dyskinesia during maintenance therapy. More research is needed here.

SUBSTANCE ABUSE

The rate of substance abuse among schizophrenic patients is high, and drug abusing schizophrenic patients are a notoriously difficult group to treat.[36] Moreover, there is now evidence that this group may have a higher propensity to develop tardive dyskinesia during treatment with conventional antipsychotics.[37] The use of clozapine in substance-abusing schizophrenic patients has been encouraging. It has been suggested that clozapine may diminish craving.[38,39] A study of alcohol abusers with schizophrenia found that 50% stopped drinking while taking clozapine.[40] Some data suggest that diminished substance abuse among patients taking clozapine may be attributable to improved functioning and self-control.[41] Recently, data have been presented showing that schizophrenic patients with a history of substance abuse achieved a good response to olanzapine.[42] To date, no formal studies have established the effects of risperidone, quetiapine, sertindole, or other novel antipsychotics on substance abuse among schizophrenic patients.

AGGRESSION

The management of persistent aggression among patients with schizophrenia is problematic. Conventional antipsychotics have tranquilizing effects, but beyond their sedative and antipsychotic effects they do not appear to target hostility preferentially. In addition, akathisia and delirium from the use of high doses of conventional antipsychotics complicate the management of aggression. Several adjunctive agents have been tested in clinical trials, but none has emerged as clearly superior.[43]

There is now an impressive and consistent literature showing that clozapine is an effective treatment option for this patient subgroup.[44–50] This is a robust effect, maintained over time, and does not appear to be merely an advantage of the sedative effects of clozapine.[46] An analysis of data from New York's state hospitals suggested that clozapine exerts a selective effect on aggression beyond the overall improvement in psychosis.[45]

Buckley and colleagues[49] examined this issue in a study of 30 schizophrenic patients (11 with comorbid aggression, 19 without) who were long-stay (mean length-of-stay 11 years) in a state facility. When the 6 months before therapy are compared with the first 6 months of clozapine treatment, mean episodes of seclusion and restraint for the aggressive group decreased from 15.0 to 6.4. Time spent in seclusion and restraint dropped from 100.4 hours to 37.9 hours. The overall response to clozapine, as measured on the Brief Psychiatric Rating Scale (BPRS), was compared in patients with aggression (N = 11) and those without aggression (N = 19). Interestingly, both groups showed a similar response to clozapine in terms of decrement in total BPRS scores (Figure 3). The observation that the improvement in aggression was not associated with an overall superior antipsychotic response to clozapine in the violent group is suggestive that clozapine may possess specific antiaggression efficacy.

More recently, as part of a larger project, Buckley and I. Sharma, R.N., have examined the economic impact of clozapine's effect on aggression in this same patient group (unpublished data, 1998). Time spent by psychiatrists, nursing staff, hospital police, and other staff in managing each episode of seclusion and restraint was documented, and the cost of service for each discipline was determined based on hourly salary rates. Data were also collected on physical injuries to patients or staff, property damage, and emergency use of psychotropic medications. The cost analysis for these 11 patients is shown in Figure 4. The cost of the management of aggression during the first 6

months of clozapine treatment was $1419 lower per patient. Since the majority of this reduction was attributable to less staff time being spent managing aggression in these patients, this is best considered a cost-efficiency rather than a cost savings. Nevertheless, these data are of interest and buttress the argument for the availability of novel antipsychotics in state facilities in spite of their impact on hospital pharmacy budgets.

Reports have also been published on the efficacy of risperidone in treating aggression.[51–53] An analysis of the United States multicenter trial of risperidone suggested a selective effect of risperidone upon hostility in patients with schizophrenia.[51] Buckley and colleagues,[53] in a modest case-control study, showed comparable efficacy between risperidone and conventional antipsychotics. Jeanblanc and colleagues[52] suggested that risperidone may be a useful option in managing dementia-related aggression. Preliminary results of a large, placebo-comparative multicenter trial of risperidone in dementia show benefit in controlling aggressive behavior.[54] Analyses of the hostility scores from the multicenter trials of olanzapine and of quetiapine suggest a benefit in managing aggression.[55,56] However, clinical trials generally exclude patients who have the propensity for serious aggression. Therefore, studies in more persistently aggressive patients are warranted. Clozapine's advantage in this patient group emerged once it became available in state hospitals. Determining the role of novel antipsychotics in schizophrenic patients with persistent aggression is important because of the recalcitrant nature of their illness and the economic impact of protracted hospitalization. Additionally, if the atypical antipsychotics are helpful in ameliorating aggression in schizophrenia, they also may be of benefit in other nonpsychotic conditions where aggression is a significant behavioral component.

CONCLUSION

Novel antipsychotics represent a significant treatment advance for patients with schizophrenia and have potential to improve clinical outcomes and decrease overall treatment costs when used over the long term. Refinements in dosing and the use of these agents in specific subpopulations of patients with schizophrenia will in time result in a more rational and cogent pharmacotherapy of schizophrenia. Additionally, ongoing and future studies will determine the role of atypical antipsychotics in patients with mood disorders, other nonpsychotic conditions, behavioral disturbance, and neurologic conditions. It is likely that these expanding roles for novel antipsychotics will evolve simultaneously with a decline in the use of and specific indications for conventional antipsychotic medications.

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

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