Common Treatment Goals of Antipsychotics: Acute Treatment

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When a patient with an acute exacerbation of schizophrenia is admitted into the hospital, the target symptoms include pathologic excitement/agitation and exacerbated psychotic symptoms. The goal of hospitalization becomes attenuation of these symptoms to a level compatible with safe discharge. The mainstay of stabilization is antipsychotic treatment. A risk/benefit analysis of the conventional versus the newer antipsychotics favors the use of the newer agents as first-line drugs. These newer antipsychotic agents represent the first significant advance in the pharmacologic treatment of schizophrenia in the past four decades. They are at least as effective as conventional agents and are clearly superior from a safety perspective. Because of short inpatient stays, the challenge for clinicians is to provide an adequate treatment period without aggressively escalating the dose.

(J Clin Psychiatry 1998;59[suppl 19]:5–8)

With the introduction of antipsychotics in the mid-1950s, the treatment of schizophrenia shifted from chronic inpatient settings to the community, and the majority of patients with schizophrenia are now cared for outside the hospital. Pharmacologic treatment with antipsychotic agents remains the mainstay of the management of schizophrenia. However, despite adequate treatment with conventional antipsychotics, significant psychopathology and functional impairment persists in most patients, and relapse rates remain high, averaging between 15% to 20% annually.[1] The past few years have seen significant treatment advances, first with the introduction of clozapine in 1989 for treatment-refractory patients with schizophrenia, then with the introduction of risperidone in 1994 as the first atypical antipsychotic for routine use, and most recently, the introduction of olanzapine, which also qualifies as a first-line atypical antipsychotic. We are currently in the midst of a fundamental change in the treatment of schizophrenia, with more atypical antipsychotics soon to be approved for use in the U.S. market. Not only do these first-line agents have a much improved side effect profile in comparison with the conventional antipsychotics, which may translate into increased patient acceptability and compliance (with possible reduction in relapse rates), but they also offer the potential for an increased spectrum of efficacy against a broader range of symptoms including negative symptoms,[2–4] comorbid depression,[5,6] and cognitive impairment.[7]

In this article, the clinical issues involved in the management of an acute exacerbation of schizophrenia will be reviewed, with a special emphasis on clinical factors that affect the choice of antipsychotic agents (i.e., conventional versus novel).

GOALS OF ACUTE TREATMENT

The goals of inpatient treatment vary to some degree with the stage of illness. In first-episode patients, two important goals are to rule out organic causes of manifest symptomatology and establish the diagnosis. On the other end of the spectrum are treatment-refractory patients, who pose unique therapeutic challenges. Neither of these specific patient subtypes will be discussed here. In this article, it is assumed that the diagnosis of schizophrenia has been established, and the patient is suffering an acute symptom exacerbation of an otherwise stable chronic illness. When such a patient is admitted into the hospital, the overarching and immediate goal is symptom attenuation to the point of safe discharge in as short a time as possible. The target symptoms fall into two broad categories: pathological excitement/agitation and exacerbated psychotic symptoms. A secondary, but equally important, goal of hospitalization is to lay the foundation for long-term treatment success.

CONSIDERATIONS FOR OPTIMIZING TREATMENT WHEN CHOOSING AN ANTIPSYCHOTIC

Because antipsychotic treatment is the cornerstone of stabilization, the choice of antipsychotic becomes the criti-

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Supported in part by a NARSAD Young Investigator Award.

Presented at the symposium "The Routine Use of Atypical Antipsychotic Agents," held July 25, 1997, Dallas, Tex., which was supported by an unrestricted educational grant from Eli Lilly and Company.

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cal decision point of clinical management. Several factors should be considered when choosing an antipsychotic so as to optimize treatment for a particular patient. Among these considerations are a patient's prior treatment response including both objective response and subjective experience; history of propensity to develop side effects, e.g., parkinsonian side effects, sedation, orthostasis, anticholinergic side effects, weight gain, and neuroendocrine complications related to prolactin elevation; severity and rapidity of relapse upon medication discontinuation and, especially, a history of dangerousness to self or others when relapsed; level of insight into illness and recognition of need for ongoing antipsychotic treatment; history of compliance; active drug/alcohol abuse; severity of negative symptoms; and presence of risk factors for tardive dyskinesia (e.g., elderly female patients). In addition to the factors listed above, one has to consider not only goals of acute treatment but also goals of maintenance treatment. Decisions made in the inpatient service tend not to be changed in the outpatient setting—if a patient is discharged on a conventional agent, he or she is likely to be continued on that agent as an outpatient.

Most of the clinical information required to make the decision regarding choice of antipsychotic agent is not available at the time of admission. Like all clinical decisions, this choice involves a risk/benefit analysis that has to be individualized for a particular patient on the basis of the available information. The risk/benefit analysis is conducted along the dimensions of efficacy and safety. The newer agents (risperidone and olanzapine) are at least as effective as haloperidol in improving global psychopathology and psychotic symptoms, are superior in the treatment of negative symptoms,[2–4] and are possibly superior in the treatment of comorbid depression.[5,6] From the safety perspective, both these agents have a clearly reduced risk of extrapyramidal symptoms (EPS)[2,3]; olanzapine has a reduced risk of elevating serum prolactin compared to haloperidol[8]; and initial data suggest that both drugs are associated with a reduced risk of causing tardive dyskinesia.[9,10] The improved side effect profile of these agents should make them more acceptable than conventional antipsychotics to patients, and provide at least the potential for improved compliance, although this remains to be demonstrated.

One potential limitation of the newer as opposed to the older agents is the clinical impression that they may not be as effective in the treatment of acute pathologic excitement and agitation associated with the exacerbation of a psychotic episode. This may in part be due to the lack of availability of short-acting formulations that can be administered intramuscularly. In acutely disturbed patients who cannot be verbally redirected, who may be violent, and who may have to be medicated over objection, a short-acting parenteral formulation with guaranteed systemic delivery has distinct clinical advantages. This potential shortcoming of the newer agents can, to a large extent, be overcome with concomitant benzodiazepine use for control of agitation. Another advantage of the older agents is that two of them (haloperidol and fluphenazine) are available in long-acting depot formulations, which provide an added clinical flexibility in certain patient types, including patients with a clear history of noncompliance not related to medication side effects, those with a history of severe relapses upon medication discontinuation (especially if they become dangerous to themselves or others), and patients with active substance abuse, who are more likely to be noncompliant with oral regimens.

Other than for patients who are candidates for long-acting depot formulations, the overall superior risk/benefit ratio of novel versus traditional agents favors one of the newer agents as the drug of first choice for inpatient treatment of an acute exacerbation of schizophrenia. Not only are these drugs better tolerated but they also appear to have a broader spectrum of efficacy. An acute exacerbation resulting in hospitalization is the ideal time to give a trial of one of the newer agents because relapse, the major risk of an outpatient medication switch, has by definition been obviated in this situation.

ACUTE TREATMENT

At the time of submission of this article, two novel agents that qualify as first-line agents for routine use were available in the U.S. market, risperidone and olanzapine. Approval by the Food and Drug Administration (FDA) for three other novel antipsychotics is expected shortly: quetiapine (Zeneca Pharmaceuticals), sertindole (Abbott Laboratories), and ziprasidone (Pfizer). Because only risperidone and olanzapine have FDA approval at the time of this writing, only these drugs will be discussed. The choice of which of these agents to use is largely one of personal preference. Both are effective antipsychotics, are well tolerated with a relatively benign EPS profile (at recommended doses), and have a low potential for pharmacokinetic drug/drug interactions at the level of the cytochrome P450 isoenzyme system. Risperidone causes relatively more prolactin elevation, while olanzapine causes more weight gain. These and other side effects may guide selection for a particular patient.

Risperidone should be initiated at a dose of 2 mg/day and increased over 3 to 7 days to a target dose of 3 to 4 mg/day. Olanzapine can be initiated at a dose of 10 mg/day, and this is also the therapeutic dose for some patients. Although the time course of antipsychotic response varies considerably, in general, 1 to 2 weeks of treatment are required for initial response, with several weeks being required for optimum symptom attenuation. This is true for conventional as well as newer agents.[2,3] Rapid dose escalation does not seem to increase the rapidity of onset of clinical antipsychotic effect and has the potential for greater toxicity due to increased risk of side effects. The

clinician should, therefore, resist the urge to escalate the dose in the absence of notable improvement in the first 1 to 2 weeks of treatment on the false hope that this will translate into increased efficacy.

In the first few days of hospitalization, the treatment goal is to manage agitation and pathologic excitement. Frequently, lack of efficacy on this symptom domain is equated to lack of antipsychotic effect of the agent. To control pathologic excitement and agitated behavior, robust doses of adjunctive benzodiazepines are very useful. Lorazepam in doses up to 10 mg per day is highly effective and safe. It is well absorbed orally, or intramuscularly should this route of administration be necessary. Adequate doses of adjunctive benzodiazepines are probably underutilized in large part because of the exaggerated risk of the potential for dependence or drug-seeking behavior. Once behavioral control is achieved (usually within the first few hours to days), the benzodiazepine dose can be gradually decreased and eventually discontinued. In patients with a definite history of substance abuse or patients who are imminently violent and who refuse oral medication, concomitant short-term treatment with injectable forms of conventional antipsychotics may be clinically justified to achieve behavioral control. Again, once this is achieved, the conventional drug should be discontinued and the patient maintained on the newer agent alone.

If after 2 weeks of treatment no improvement is evident in core psychotic symptoms, the dose of risperidone should be increased to 6 mg/day (if not already at this dose) and olanzapine to 15 to 20 mg/day. These doses should be maintained for 4 to 6 weeks and the patient monitored for clinical response. It is important to recognize that these dosing guidelines are based on group data; individual variability is possible (e.g., because of a variable first-pass effect), and patients may require more or less than these doses.

In the absence of a clinical response at this time, the clinician should seriously consider switching to a different agent. At least with the older agents, the literature does not support the utility of dose escalation,[11] especially if patients already have clinical evidence of mild EPS.[12] In this situation, a trial of the other atypical agent should be considered, although the effectiveness of this strategy has not been demonstrated in controlled trials. The only intervention with proven efficacy in these treatment-refractory patients is clozapine.

The time course of treatment described above appears to immediately be at odds with the reality of length of acute hospital stays, which range anywhere between 7 to 21 days. External mandates (e.g., by health maintenance organizations) do not, however, alter the time course of antipsychotic action. In this era of cost containment, the goal of inpatient hospitalization in many instances becomes control of acutely disturbed behavior, with only the very early stages of therapeutic antipsychotic effect evident before a patient has to be discharged. The challenge for clinicians is to achieve behavioral control, reach an optimum antipsychotic dose, and ensure that the patient does not represent an acute danger to self or others prior to discharge, while resisting the natural urge to escalate the antipsychotic dose in the hope that this will result in more rapid symptom resolution. Full antipsychotic response will, in most cases, not occur until after discharge.

It is also important in the inpatient setting to address issues such as housing and financial status of the patient, which will surely threaten therapeutic gains of antipsychotic treatment if they are not resolved. Other stressors that might have contributed to the relapse need to be identified and addressed. Along similar lines, a thorough assessment should be made of family dynamics, the family's (or other caregiver's) understanding of the patient's illness, and the need for ongoing family psychoeducation/therapy. If necessary, appropriate referrals should be made, as most of these interventions will have to be done in the outpatient setting.

CONCLUSION

The newer first-line antipsychotic agents represent significant advances in side effect profile and efficacy. In controlled, randomized clinical trials, they are at least as effective as older agents in the treatment of exacerbated psychotic symptoms and are more effective in the treatment of negative symptoms. We no longer have to accept parkinsonism as a necessary, inseparable accompaniment of therapeutic antipsychotic effect. These newer drugs are not just older agents recast with an improved side effect profile. They are fundamentally different at several levels: in their receptor binding profiles[13]; in their neuroanatomically selective action on dopamine tracts involved in mediation of emotion and cognition as assessed by electrophysiologic studies[13] and studies of immediate-early gene expression[13]; in animal behavioral models[14]; and lastly, in their broader spectrum of efficacy.[2,3]

The relevant question is no longer "Who are candidates for these newer agents?" but rather, "In which patient type should we *not* use these drugs?" At this time, the only groups of patients in which the older agents are preferable are those in whom there is a clear indication for a long-acting depot formulation of haloperidol or fluphenazine, or a history of excellent response to a conventional agent with minimal side effects. As long-acting formulations of the newer agents are developed, it will be even more difficult to find justification for any use of the older agents. We look forward to the introduction of other novel agents for the treatment of schizophrenia, the most severe of mental illnesses.

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

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