# Rationale and Guidelines for the Inpatient Treatment of Acute Psychosis

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For patients hospitalized with acute episodes of psychosis, rapid stabilization of intense positive symptoms, hostility, and agitation is typically a preeminent therapeutic goal. These goals often differ from those of the nonhospitalized patient with psychosis for whom long-term treatment goals such as improvement of negative symptoms, cognitive function, compliance, and reduction in side effect burden may be paramount. Therefore, when selecting an antipsychotic treatment for hospitalized patients, efficacy against positive symptoms and hostility as well as speed of therapeutic onset should strongly be considered. At the same time, selection of antipsychotic treatment in the inpatient setting should establish a definitive treatment that will address long-term goals effectively after discharge. This article presents the rationale and practical guidelines for selection of treatment regimens for patients hospitalized due to acute psychosis. *(J Clin Psychiatry 2000;61[suppl 14]:27–32)*



Patients hospitalized due to acute psychosis represent a population with a distinct clinical presentation and treatment challenges compared with most outpatients with chronic symptoms of a psychotic disorder.

## THERAPEUTIC GOALS IN THE ACUTE INPATIENT SETTING

Psychotic symptoms are categorized under 2 major domains: positive and negative. Despite recent evidence regarding the long-term impact of negative symptoms on functional outcome, positive symptoms remain the most predictive of acute hospitalization. As such, positive symptoms tend to predominate as high-priority targets for stabilization among hospitalized patients with acute psychosis. Agitation and hostility, which are often associated with positive symptoms, are also commonly identified as high-priority targets for stabilization in patients hospitalized for acute psychosis, particularly in the first days of inpatient treatment. For these reasons, efficacy against positive symptoms, psychotic aggression, and psychotic agitation must be given strong consideration when selecting treatment regimens for patients admitted to inpatient psychiatric facilities for stabilization of acute psychosis.

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Patients admitted to acute psychiatric inpatient facilities have intense symptoms, which may place them at greater risk of physical harm and further psychiatric decompensation. Therefore, the time required for the onset of therapeutic effects, a factor not strongly addressed in general treatment guidelines for psychiatric disorders, warrants strong consideration when choosing treatment regimens for the acutely hospitalized psychiatric population.

Despite the overarching need to stabilize positive symptoms and parapositive symptoms such as hostility and agitation on a rapid time course, consideration of treatment options for patients with psychosis in the acute phase of treatment must not ignore other important therapeutic goals, which may be less acute. These goals typically include improvements of negative symptoms and/or cognitive deficits associated with psychotic disorders such as schizophrenia. The long-term tolerability and safety profiles of treatment options must also be considered, since these will impact postdischarge compliance, and, therefore, they will ultimately impact treatment effectiveness (Table 1).

## SELECTING AN ANTIPSYCHOTIC DRUG

### Overview

Prior to the development of "atypical" antipsychotics, high-potency conventional ("typical") antipsychotics, for which haloperidol is the prototype, had been the treatment of choice for stabilization of acute psychosis among hospitalized schizophrenia patients. Indeed, haloperidol has become the "gold standard" typical antipsychotic against which most new antipsychotics are compared in studies that incorporate an active comparator. The one-time com-

**Table 1. Criteria for Selection of Antipsychotic to Treat Patients Hospitalized for Acute Psychosis**

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|---|
| Acute |
| Efficacy against positive symptoms |
| Efficacy against hostility and agitation |
| Speed of action (speed of titration) |
| Short-term safety/tolerability profile |
| Nonacute |
| Efficacy against negative symptoms |
| Efficacy against cognitive deficits |
| Long-term safety/tolerability profile |



mon practice of rapid titration of neuroleptics and use of high doses of haloperidol (20–80 mg) to control psychosis has fallen out of practice owing to evidence that such approaches are not more effective, and probably deleterious, compared with lower doses (2–10 mg daily) of haloperidol.[1] Little clinical or neuropharmacologic evidence justifies the use of haloperidol in doses higher than 5 to 10 mg per day in patients with acute psychosis.

The advent of atypical antipsychotics has had a major impact on the treatment of psychosis. Clozapine is the prototype of this category of antipsychotic drugs, which at present also includes risperidone, olanzapine, and quetiapine. Olanzapine and risperidone can be considered high-potency atypical antipsychotics, whereas clozapine and quetiapine can be considered low-potency atypical antipsychotics, since they respectively require relatively low doses and high doses to achieve antipsychotic effects. There is good evidence that at therapeutic doses, each of the 4 currently approved atypical antipsychotics produces fewer extrapyramidal side effects (EPS) than haloperidol.[2] Each of these agents has been shown to be equally efficacious or superior to haloperidol in the control of positive and negative symptoms and various cognitive deficits associated with schizophrenia. Therefore, atypical antipsychotics are in the process of replacing typical antipsychotics as first-line treatments for psychosis both in outpatient and acute inpatient settings. Exceptions to this general trend of preferential use of atypical antipsychotics over typical antipsychotics exist. The risk of fatal agranulocytosis associated with clozapine precludes the use of this drug use as a first-line agent. Furthermore, since no depot formulation of an atypical antipsychotic is currently available, a depot formulation of a typical antipsychotic (e.g., haloperidol decanoate) may provide important compliance-related advantages that outweigh the superior safety and efficacy associated with atypical antipsychotics in an individual with a history of poor treatment compliance.

## Global Symptoms of Psychosis

Acute treatment studies (8 weeks or shorter) indicate that clozapine, risperidone, and olanzapine are superior to haloperidol and that quetiapine is comparable to haloperidol when measuring global changes in the symptoms of psychosis, reflected, for example, by total scores on the Positive and Negative Syndrome Scale (PANSS) or the Brief Psychiatric Rating Scale (BPRS).[3] Three head-to-head comparisons of olanzapine and risperidone found that both drugs were comparable with regard to the therapeutic effects they produced on measures of overall psychosis.[4–6]

## Positive Symptoms

Acute treatment studies have consistently shown that clozapine[7,8] and risperidone[9–12] are more efficacious than haloperidol against positive symptoms. Other studies have shown olanzapine[13–15] and quetiapine[3,16] to be equally efficacious to haloperidol in the improvement of positive symptoms. Two of 3 studies directly comparing olanzapine and risperidone found that risperidone produced greater improvements in positive symptoms.[4,5] The third study found no significant differences between olanzapine and risperidone in their effects on positive symptoms.[6]

## Psychotic Hostility

In several studies, risperidone[17,18] and clozapine[19] have been shown to be more effective than haloperidol and other high-potency typical antipsychotics in controlling hostility associated with psychosis. The antihostility effects seem to be independent of their therapeutic effects on psychotic symptoms. In another study,[20] risperidone and haloperidol were equally efficacious in controlling hostility. Information regarding the specific antihostility effects of olanzapine and quetiapine is generally lacking.

## Negative Symptoms

Clozapine,[21] olanzapine,[14,15] and risperidone[9,22] have each been shown to be more efficacious against negative symptoms compared with haloperidol. Studies comparing quetiapine with haloperidol have shown quetiapine to be equally efficacious, but not superior, to haloperidol.[3,16] One study[6] directly comparing olanzapine and risperidone found that olanzapine produced greater improvement in negative symptoms measured by 1 of 2 negative symptoms scales used. Two other studies[4,5] found the therapeutic effects of olanzapine and risperidone on negative symptoms to be comparable.

## Cognitive Deficits

Various cognitive functions such as memory, executive function, attention, and verbal fluency are markedly impaired in patients with schizophrenia and other psychotic disorders. These cognitive deficits appear to be somewhat independent of psychotic symptoms, and improvement in psychotic symptoms does not necessarily produce improvement in cognitive deficits. Typical antipsychotics have limited ability to improve cognitive deficits associated with schizophrenia. In contrast, atypical antipsychotics have been shown to produce significant improvement of cognitive function in schizophrenic patients. Furthermore, available data suggest that the specific cognition-improving ef-

fects may differ among the various atypical antipsychotic drugs.[23] Published studies provide consistent evidence that clozapine improves attention and verbal fluency. Risperidone produces consistently positive effects on working memory, executive functioning, and attention. Preliminary evidence suggests that olanzapine improves verbal learning and memory, and executive function, but not attention, working memory, or visual learning and memory. Only highly preliminary data are available regarding the effects of quetiapine on cognitive function, and they suggest that it also has beneficial effects on certain cognitive domains.

**Speed of Onset of Antipsychotic Effect**

There is a dearth of comparative data about the relative therapeutic time course associated with the various antipsychotics. One study[24] comparing clozapine and risperidone found risperidone produced clinically significant antipsychotic effects more rapidly. However, even if it is assumed that at therapeutic doses all antipsychotics produce antipsychotic effects with a similar time course, it is likely that significant differences among the antipsychotics in the time required to achieve therapeutic doses translate into differences in the number of days required to produce antipsychotic effects. Indeed, evidence from bipolar patients hospitalized for acute manic symptoms suggests that time to reach therapeutic doses of mood stabilizers predicts time to onset of therapeutic effects for these drugs.[25] Therapeutic doses of high-potency typical and atypical antipsychotics can usually be achieved within the first 3 days of hospitalization and often on the first day. In a recent open-label study,[26] my colleagues and I found that risperidone can be titrated to therapeutic doses within 24 hours in hospitalized psychiatric patients with acute psychosis by using a rapid-loading regimen that is safe and highly tolerated. The minimal number of days needed to achieve therapeutic doses of clozapine or quetiapine remains to be determined; however, our experience suggests that, unlike olanzapine and risperidone, rapid titration regimens aimed at achieving therapeutic doses of quetiapine in hospitalized patients by the second day are not well tolerated. Extrapolating from this, it is reasonable to assume that using a high-potency antipsychotic may induce antipsychotic effects earlier than low-potency antipsychotics.

While many general guidelines for the treatment of psychosis recommend monotherapy trials of at least 3 weeks before consideration of dose or medication changes, this is often impractical when treating acute psychotic patients in an inpatient setting. Evidence indicates that antipsychotics produce significant improvements if not their full therapeutic effect in patients with acute psychosis within 1 to 2 weeks.[27] Therefore, an earlier decision point (e.g., 10–14 days) regarding the efficacy of a treatment regimen seems appropriate, particularly if at that point there is no improvement whatsoever.

**Acute Tolerability/Safety**

Evidence consistently indicates that each of the atypical antipsychotics is superior to the typical antipsychotic comparators in regard to induction of EPS.[27] However, the atypical antipsychotics are not without some side effects. Clozapine has a strong propensity to produce hypersalivation, orthostatic hypotension, and urinary changes. Risperidone may have a higher propensity for inducing akathisia.[5] Olanzapine has a higher propensity than placebo for inducing dry mouth and somnolence. Quetiapine has a propensity to induce somnolence and orthostatic hypotension.

**Chronic Tolerability/Safety**

While they may not have an impact during an acute hospitalization, antipsychotic drugs can produce long-term adverse effects that manifest after inpatient stabilization of acute psychosis during the postdischarge, maintenance phase of treatment. These chronic side effects have the potential to negatively influence patients' compliance rates. Chronic use of typical antipsychotics such as haloperidol carries a significant risk of tardive dyskinesia, the occurrence of which is estimated at 5% per year. The rates of tardive dyskinesia with chronic use of atypical antipsychotics are substantially lower than with typical antipsychotics. The risk of agranulocytosis associated with clozapine use is estimated at less than 1% in the first year of treatment.[28] While this is a small percentage, the potential morbidity and mortality associated with agranulocytosis has precluded use of clozapine as a first-line antipsychotic. Preclinical studies revealed a higher incidence of corneal cataracts in dogs administered chronic quetiapine compared with placebo, but experience with humans suggests that this is not a material risk that needs to be considered when selecting among the antipsychotics.[29] A significant problem, which has emerged with the chronic use of some antipsychotics, is weight gain. Strong evidence now exists for significant weight gain in patients taking clozapine[30] and olanzapine.[14,27] Evidence to date indicates that risperidone and quetiapine are substantially less problematic in regard to weight gain than clozapine and olanzapine.[4,27,31] Furthermore, clozapine and olanzapine use has been linked to abnormalities in glucose metabolism, including hyperglycemia, diabetic ketoacidosis, and diabetes in some patients taking these antipsychotics.[32,33] Patients taking risperidone have been found to have a higher incidence of elevated prolactin than patients taking other atypical antipsychotics,[6] but few patients with elevated prolactin levels experience symptoms.

**Conclusion**

The high-potency atypical antipsychotics risperidone and olanzapine seem best suited as first-line antipsychotic treatment of inpatients with acute psychosis owing to the fact that they have been shown to have superior efficacy and fewer side effects compared with haloperidol and do not carry the agranulocytosis risk associated with cloza-

pine. Furthermore, both risperidone and olanzapine can be administered at therapeutic doses without the need for a lengthy titration schedule. Several differentiating factors should be considered when selecting between these 2 agents. The current evidence for the efficacy of risperidone against positive symptoms and hostility is stronger than for olanzapine. Significantly more weight gain and incidences of hyperglycemia and diabetic ketoacidosis are associated with olanzapine than with the other atypical agents. On the other hand, risperidone has a higher propensity than olanzapine to produce EPS, hyperprolactinemia, and akathisia at doses above 4 to 6 mg/day.

## DOSING OF ANTIPSYCHOTIC DRUGS

Based on early clinical trials, the initial recommended optimal dose for risperidone was 6 mg/day; olanzapine, 10 mg/day; and quetiapine, 300 mg/day. Postmarketing experience with these drugs has produced shifts in the doses considered optimal for each of these drugs. The mean prescribed dose of risperidone has demonstrated a downward trend and is currently approximately 4 mg/day. In contrast, the typical prescribed dose of olanzapine and quetiapine has demonstrated an upward trend to 15 to 20 mg/day and 300 to 600 mg/day, respectively.[34] There is some evidence that the optimal doses of antipsychotic drugs for stabilization of acute exacerbation of positive symptoms and psychotic hostility/agitation are higher than optimal doses for long-term maintenance of these symptoms and amelioration of negative symptoms and cognitive deficits.[35] A useful strategy is to use higher doses of antipsychotics during the hyperacute phase of inpatient treatment when positive symptoms, hostility, and agitation predominate and then reduce the dose as these symptoms come under control.

Another important factor that has emerged as a consideration when selecting psychotropic medication and the optimal dose is the potential interaction with other drugs. With regard to selecting an antipsychotic, one potentially important consideration is the fact that clozapine and olanzapine are metabolized predominately by the CYP1A2 cytochrome P450 liver enzyme. This enzyme is strongly induced by tobacco smoke, and studies have revealed that cigarette smoking can produce significant fluctuations in the plasma levels of clozapine, and therefore it is likely that olanzapine is similarly influenced by smoking.[36] These findings are particularly noteworthy since there is a very high prevalence of smoking among patients with psychotic disorders and regular patterns of tobacco intake may be disrupted during acute hospitalization.

## COMBINING ANTIPSYCHOTICS

The practice of using more than one antipsychotic concomitantly to treat psychosis is widespread. However, the scientific rationale and empirical justification for such combinational use of antipsychotics are lacking. In fact, many of the dual antipsychotic treatments used are pharmacologically irrational. Examples of this are the concomitant use of 2 high-potency atypical antipsychotics such as olanzapine and risperidone, or a high-potency atypical antipsychotic with a high-potency typical antipsychotic such as haloperidol. Current understanding of the pharmacologic mechanisms underlying the therapeutic effects of antipsychotics has implicated binding of dopamine-2 ($D_2$) and serotonin-2 ($5\text{-}HT_2$) receptors as important features. When prescribing either of the available high-potency atypical antipsychotics at therapeutic doses, high occupancy levels of $D_2$ and $5\text{-}HT_2$ brain receptors are achieved. Concomitant use of another antipsychotic, whether it is a typical or an atypical antipsychotic, can accomplish little other than greatly increase the likelihood of side effects experienced by a patient. Furthermore, the therapeutic advantages of atypical antipsychotics over typical antipsychotics may be related the ratio of brain $5\text{-}HT_2$:$D_2$ binding achieved with monotherapy using these drugs. Combining antipsychotics is likely to disrupt the $5\text{-}HT_2$:$D_2$ binding ratios for both compounds. In so doing, it is possible that optimal therapeutic effects of either drug will not be realized. Thus, it is best to avoid combining antipsychotics in favor of sequential trials of monotherapy with different antipsychotics. A few rational exceptions to the general rule of avoiding combining antipsychotics may exist. In patients who are receiving therapeutic doses of low-potency atypical antipsychotics such as quetiapine or clozapine, adding low doses of a high-potency antipsychotic with strong $D_2$ binding affinity may be clinically useful. The reason for this is that binding studies of clozapine and quetiapine indicate that even at therapeutic doses, these antipsychotics may not produce the level of $D_2$ binding in the brain that is observed with high-potency typical and atypical antipsychotics.[37,38] Therefore, adding a high-potency antipsychotic with a strong $D_2$ binding affinity, such as risperidone or haloperidol, may increase brain $D_2$ binding and augment the efficacy of a low-potency antipsychotic in patients who have not fully responded to a monotherapy trial with the low-potency drug.

## CONCOMITANT MEDICATION USE

When treating hospitalized patients who have acute psychosis, there is often a strong need to address symptoms such as agitation and insomnia, particularly early in the course of inpatient treatment. One strategy that is often used involves selecting antipsychotics with the propensity for sedation to target these symptoms. This strategy has several potential liabilities. First, sedation or other side effects of an antipsychotic may limit the ability to titrate that drug to optimal doses for an antipsychotic effect. Furthermore, sedation, which may be desirable during the hyperacute stage of hospitalized treatment, may become a liabil-

ity as the patient's insomnia is lessened during the course of hospitalization. Using one medication to target psychosis as well as insomnia limits a physician's ability to flexibly adjust medication doses to maintain optimal treatment of both symptoms that may respond at differential rates during hospitalization. Therefore, selecting an antipsychotic based on its sedating or other side effects should be avoided in favor of selecting an optimal antipsychotic based on its direct therapeutic efficacy against psychotic symptoms. Separate supplemental medication should be used to target insomnia and agitation that is not controlled by the antipsychotic alone. Benzodiazepines such as lorazepam are very useful for management of psychotic agitation. High-dose β-blockers such as propranolol have been used successfully to control excessive psychotic excitation and hostile behavior in some psychotic patients.[39] Diphenhydramine, trazodone, benzodiazepine hypnotics, and nonbenzodiazepine hypnotics (e.g., zolpidem, zaleplon) are useful to counteract insomnia associated with acute psychosis in the inpatient setting. These medications should be titrated downward and discontinued when possible as agitation and insomnia decrease during the course of inpatient treatment.

## AUGMENTATION STRATEGIES

Relatively few scientifically established options are available to practitioners wanting to augment the effects of an antipsychotic drug. In some studies, benzodiazepines have been shown to potentiate the effects of typical antipsychotic drugs.[40] Another strategy frequently employed is the addition of an anticonvulsant mood-stabilizing agent such as valproate or divalproex sodium. The use of valproate has not been tested in a controlled experimental fashion to date. Nevertheless, clinical experience suggests that in some patients with acute symptoms of psychosis, the addition of valproate or divalproex sodium or another mood stabilizer can be helpful in augmenting the antipsychotic effects of typical and atypical antipsychotics. Therefore, this is a reasonable option to consider when patients do not respond adequately to monotherapy with antipsychotics.

## RECOMMENDED GUIDELINES

- Use risperidone, 4 to 6 mg/day, or olanzapine, 10 to 20 mg/day, titrated to achieve therapeutic doses on day 1 or day 2 if possible. (Consider another antipsychotic if an individual patient has had a poor response or adverse reaction to risperidone or olanzapine in the past or if the patient is known to have a good response to another antipsychotic.)
- Symptoms favoring a choice of risperidone are prominent positive symptoms, hostility, agitation, obesity, smoking, hyperglycemia/diabetes.
- Symptoms favoring a choice of olanzapine are history of EPS or akathisia vulnerability.
- Use lorazepam or a comparable benzodiazepine to control for breakthrough agitation.
- Use diphenhydramine, trazodone, a benzodiazepine, or a nonbenzodiazepine hypnotic to target insomnia.
- Titrate doses of all psychotropic medication downward during the course of hospitalization as symptoms come under control, with the goal of discharging patient on antipsychotic monotherapy if possible (risperidone, 2–4 mg/day; olanzapine, 10–15 mg/day).
- If monotherapy with the initial antipsychotic does not produce any evidence of improvement by day 10 of hospitalization, consider adjusting dose, switching to another antipsychotic monotherapy, or augmenting monotherapy with a mood stabilizer such as divalproex sodium.
- Consider converting the patient to a depot antipsychotic such a haloperidol decanoate prior to hospital discharge if postdischarge compliance with oral medication is anticipated to be problematic.

*Drug names:* clozapine (Clozaril and others), diphenhydramine (Benadryl and others), divalproex sodium (Depakote), haloperidol (Haldol and others), lorazepam (Ativan and others), olanzapine (Zyprexa), propranolol (Inderal and others), quetiapine (Seroquel), risperidone (Risperdal), trazodone (Desyrel and others), zaleplon (Sonata), zolpidem (Ambien).

*Disclosure of off-label usage:* The author of this article has determined that, to the best of his knowledge, divalproex sodium has not been approved by the U.S. Food and Drug Administration as augmentation for antipsychotic treatment; lorezepam is not approved for sleep or agitation; and propranolol is not approved for the treatment of aggression.

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