Olanzapine and the New Generation of Antipsychotic Agents: Patterns of Use

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As the new generation of atypical antipsychotics becomes available, the limitations of the older typical agents become apparent. The new medications, which have benefits other than the alleviation of positive symptoms of schizophrenia, may also be beneficial for psychotic disorders that have responded poorly to conventional neuroleptics. This article will describe the potential use of the atypical antipsychotics, especially olanzapine, for affective mood disturbances in schizophrenia, psychotic depression and mania, first-break schizophrenia, comorbid schizophrenia and substance abuse disorders, dementia in the elderly and those with late-onset schizophrenia, and behavioral problems in patients with mental retardation or developmental delays. *(J Clin Psychiatry 1997;58[suppl 10]:18–21)*

The typical antipsychotic medications are effective for the majority of patients suffering from chronic psychotic conditions, such as schizophrenia. However, as the new generation of antipsychotic medications, or atypical antipsychotics, become available, we are becoming more aware of the limitations of these older typical agents. Also, because these newer medications show greater benefits than alleviation of positive symptoms, we can broaden our thinking about how we treat patients with chronic mental illness. In this article, I will review aspects of psychotic disorders that have not responded well to typical antipsychotic medications and suggest how the new atypical agents might be used, with an emphasis on the potential patterns of use for olanzapine.

USE FOR AFFECTIVE MOOD DISTURBANCES IN SCHIZOPHRENIA

The prevalence of depressive features in populations with schizophrenia may be as high as 25% to 50%.[1] Martin et al.[2] found that almost 60% of patients with schizophrenia who were followed up had experienced a depressive episode during the course of their illness. The effects of depression can be devastating in the lives of patients suffering from schizophrenia and contribute to a high suicide rate. Depression affects both patients' satisfaction with life and their ability to function in society.[3,4]

The etiology of depression in schizophrenia is complex. It can involve the schizophrenic process itself, for example, as in a schizoaffective disorder[5] or postpsychotic depression[6] that occurs during remission from an acute psychotic episode. Negative symptoms also could cause or be a part of a depression syndrome.[7] Medications are another likely cause of depression.[8] The typical antipsychotic medications have been shown to induce depression, and the drug-induced extrapyramidal symptom of akinesia can appear to be depression.[8,9]

The treatment of depression in schizophrenia is controversial and difficult. Some subgroups of patients with schizophrenia may benefit from antidepressants, such as imipramine, administered concurrently with a neuroleptic medication.[10,11] Mood stabilizers, such as lithium and carbamazepine, also have been used successfully in selected patients.[12,13]

Currently, the atypical antipsychotic medications are being used as a single therapy to treat both psychotic symptoms and depression in schizophrenic disorders. Hillert et al.[14] showed that depressive symptoms improved clinically in many patients receiving risperidone.

In an international, multicenter trial comparing olanzapine with haloperidol, the effects of medications on depression were assessed in 1996 inpatients and outpatients in 17 countries.[15] These patients had DSM-III-R diagnoses of schizophrenia, or schizophreniform or schizoaffective disorders and received 5 to 20 mg/day of olanzapine or haloperidol in an open-label extension of an acute, double-blind trial. To assess depression, the clinicians used the Montgomery-Åsberg Depression Rating Scale (MADRS),[16] which involves a 10-item interview with ratings of 0 for "no problem" to 6 for "extreme problem." This scale was developed and validated to measure changes in depressive symptoms in schizophrenic popula-

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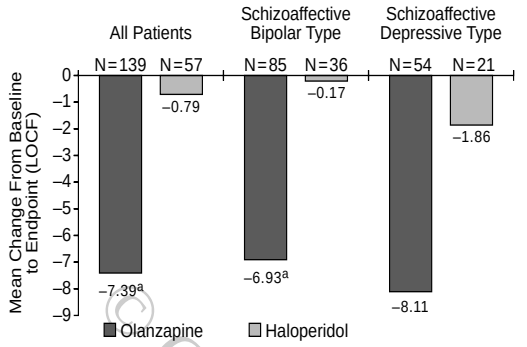
Figure 1. Mean Change in MADRS Total Score During the Acute Phase of Treatment With Olanzapine vs. Haloperidol*



*Data from reference 18. Abbreviations: LOCF = last observation carried forward; MADRS = Montgomery-Åsberg Depression Rating Scale.
[a]p < .001.

tions. Thus, when used appropriately, this scale can separate the symptoms of depression from specific schizophrenic complaints and symptoms.

At baseline, 55% of the subjects had at least moderate levels of depression according to the MADRS (scores ≥ 16), indicating that depression was common in this population.[15] After 6 weeks of treatment, MADRS scores of these moderately depressed patients improved significantly more (p = .001) in the olanzapine group than in the haloperidol group. The results of path analysis suggested that most (67%) of olanzapine's efficacy in treating depression was a direct effect instead of an indirect effect of improvements in extrapyramidal symptoms, or positive and negative symptoms.[17]

Of the 1996 patients studied in the acute multicenter trial, 300 had a diagnosis of schizoaffective disorder; of these, 177 were diagnosed as schizoaffective, bipolar type, and 123 were diagnosed as schizoaffective, depressive type.[18] After 6 weeks, patients in this subgroup who were treated with olanzapine had significantly greater improvements (mean = –7.39) in MADRS scores than patients treated with haloperidol (mean = –0.79) (p < .001) (Figure 1). Improvements in MADRS scores were significantly different between treatments in the bipolar type subgroup, but not in the depressive type subgroup. However, the numbers of patients in the latter group were small (54 receiving olanzapine and 21 receiving haloperidol).

OTHER USES FOR ATYPICAL ANTIPSYCHOTIC MEDICATIONS

Psychotic Depression and Mania

Patients with affective disorders who are treated with typical antipsychotic medications are at greater risk for developing severe forms of tardive dyskinesia or movement disorders than patients who do not have affective disorders.[19] If atypical antipsychotic medications, such as olanzapine, are less likely to cause tardive dyskinesia, as suggested by the results of recent studies,[20,21] these agents should be preferable to typical agents for the treatment of psychotic symptoms in people with these mood disorders. Zarate et al.[22] showed that the atypical antipsychotic clozapine was an effective mood stabilizer, reducing the number of affective episodes and rehospitalization, in patients with refractory bipolar disorders. More research with other atypical agents is needed.

First-Break Schizophrenia

We could logically assume that the outcomes of schizophrenia treatment will be better if early treatment is more effective, although data to support this assumption are scarce. We hope that atypical antipsychotic medications will be the medication of choice at the time of the first diagnosis, but considerably more research will be necessary before the standard of care changes. Early results suggest that atypical medications will be more acceptable because of greater efficacy and fewer side effects. Thus, patients will take them more consistently. Sanger et al.[23] have analyzed the data from the acute trial comparing olanzapine with haloperidol. Eighty-one of the 1996 patients met the criteria for first-episode psychosis; 56 were randomly assigned to receive olanzapine, and 25 were randomly assigned to receive haloperidol. Even in this relatively small group, the Brief Psychiatric Rating Scale (BPRS) scores, BPRS negative scores, Positive and Negative Syndrome Scale (PANSS) total scores, and the Simpson-Angus Neurologic Rating Scale for Extrapyramidal Symptoms total scores were significantly better for the patients receiving olanzapine (Table 1). Further studies will determine if these differences in efficacy continue over time.

Schizophrenia and Substance-Abuse Disorders

Substance-abuse disorders are the most common comorbid conditions for people with schizophrenia. In the Epidemiologic Catchment Area (ECA) study,[24] the estimated lifetime prevalence of substance abuse was 47% among people with schizophrenia. This problem is associated with treatment noncompliance and excessive costs for patients, their families, health care systems, and society.[25]

Clearly, medications alone will not solve the problems of substance abuse but should be the main part of a treatment plan that involves multiple service components, such as monitoring patients' compliance with therapy and drug avoidance. Buckley et al.[26] found that neither a history of substance abuse nor concurrent moderate substance abuse adversely affected the positive response to clozapine treatment. In their study, the rate of substance abuse was apparently lower during treatment. These results are promising and suggest the need for expanded prospective studies of

Table 1. Mean Change From Baseline to Endpoint (LOCF) in First-Break Schizophrenic Patients (N = 81) Treated With Olanzapine vs. Haloperidol*

Score	Mean Change Score	p Value
BPRS total		
Olanzapine	–15.4	.007
Haloperidol	–8.7	
BPRS negative subscale		
Olanzapine	–2.2	.03
Haloperidol	–0.8	
PANSS total		
Olanzapine	–25.77	.01
Haloperidol	–16.12	
Simpson-Angus total		
Olanzapine	–0.45	.001
Haloperidol	4.16	

*Data from reference 23. Abbreviations: BPRS = Brief Psychiatric Rating Scale; LOCF = last observation carried forward; PANSS = Positive and Negative Syndrome Rating Scale; Simpson-Angus = Simpson-Angus Neurologic Rating Scale.

this and other atypical antipsychotic medications in this population.

Dementia in Elderly Populations and Late-Onset Schizophrenia

Elderly patients are more susceptible to extrapyramidal side effects and tardive dyskinesia than younger patients.[27] Antipsychotic medications are the most frequently prescribed medication for this population, even with the attempts to reduce their use through regulations.[28] Recent studies suggest that atypical antipsychotic medications may be better than typical antipsychotic medications for agitated dementia and late-onset schizophrenia in these patients.

Behavioral Problems in Patients With Mental Retardation or Developmental Delays

Schizophrenia is a well-established diagnosis in people with mental retardation or developmental delays, occurring at a rate of two to three times the rate found in the general population.[29] Neuroleptic medications are still the major pharmacologic agent used to treat schizophrenia symptoms in this population, although concerns about overtreatment have reduced their use significantly over the past decade. Five years ago, I found that 40% of the people with mental retardation in the state of Connecticut were receiving antipsychotic medications.

Probably because of the organic nature of these disorders, these people are more susceptible to side effects from typical antipsychotic medications than people with schizophrenia who do not have these disabilities. Side effects include movement disorders, depression, and the other side effects observed with typical antipsychotic medications. Therefore, atypical medications, which pose an apparently lower risk of side effects, are being investigated as promising agents in these populations. Vanden Borre et al.[30] have shown in a double-blind, placebo-controlled study that risperidone is an effective add-on therapy for behavioral disturbances in patients with mental retardation.

CONCLUSION

Olanzapine is an atypical antipsychotic that has been shown to be effective for the negative symptoms of schizophrenia and to have a mild side effect profile. As a result, it has been tried or considered for patients who have a prominent depressive component to their psychosis and whose disease process or age puts them at increased risk for the serious side effects of typical antipsychotics such as extrapyramidal symptoms or tardive dyskinesia.

As clinicians gain more experience with olanzapine and other atypical agents, it seems inevitable that they will become widely used to treat a variety of psychotic conditions, including affective mood disturbances in schizophrenia, psychotic depression and mania, first-break schizophrenia, comorbid schizophrenia and substance-abuse disorders, dementia in the elderly, late-onset schizophrenia, and behavioral problems in patients with mental retardation or developmental delays.

Drug names: carbamazepine (Tegretol and others), clozapine (Clozaril), haloperidol (Haldol and others), imipramine (Tofranil and others), olanzapine (Zyprexa), risperidone (Risperdal).

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