Atypical Antipsychotics for Treatment of Depression in Schizophrenia and Affective Disorders

Collaborative Working Group on Clinical Trial Evaluations

Depression in schizophrenia may be partially responsible for the increased suicide rate in schizophrenic patients, which is more than 20 times higher than that found in the general population. Affective disorders in patients with schizophrenia are associated with a poor outcome, an increased risk of relapse, and a high rate of suicide. There is evidence that atypical antipsychotics may contribute to a reduction in suicidality, and although the new drugs are marketed for the treatment of schizophrenia, their novel psychopharmacologic effects suggest the possibility of other therapeutic applications. Recent studies of the efficacy of the novel antipsychotics found that these agents may produce an antidepressant effect in schizophrenia and may be used as either an adjunctive medication or an alternative to mood stabilizers in patients with affective disorders. *(J Clin Psychiatry 1998;59[suppl 12]:41–45)*

Depression in schizophrenia may be partially responsible for the increased suicide rate in schizophrenic patients, which is more than 20 times higher than that in the general population. The risk of suicide in schizophrenia exceeds that in all psychiatric disorders except major depression, and the annual suicide rate among schizophrenics is reported to be 0.4% to 1.1%.[1] The lifetime rate for suicide attempts is 25% to 55% in schizophrenic patients and the lifetime rate for completed suicide is approximately 9% to 13%.[1] Risk factors for suicide in this population include severe illness with frequent relapses and hospitalizations, poor social function (premorbid and current), a history of previous suicide attempts, significant depressive symptoms (particularly hopelessness), current substance abuse, and recent hospitalization. Awareness of effects of the illness, a sense of inadequacy in achieving goals, and fear of further mental deterioration are additional risk factors for suicide in the schizophrenic patient. Because these factors may lead to a sense of hopelessness, neuroleptic-resistant schizophrenic patients with persistent and severe positive symptoms may be at particularly high risk for suicide.

Various processes that contribute to the psychopathology of schizophrenia have been postulated and classified over the past 3 decades. In 1974, Strauss et al.[2] hypothesized that the 3 basic independent processes underlying schizophrenic symptomatology were positive symptoms, negative symptoms, and disorders of personal relationships. As research has developed over time, an expanded concept of schizophrenia has emerged. Recent factor analyses[3] have demonstrated 5 independent principal components in schizophrenia. In addition to the negative and positive components of the disorder, researchers are now studying an excited component (excitement, poor impulse control, tension, hostility, uncooperativeness), a cognitive component (difficulty in abstract thinking, disorientation, conceptual disorganization), and a depressive component (anxiety, guilt, depression, somatic concern, preoccupation). Depression in schizophrenia may involve the schizophrenic process itself, occur during remission from an acute psychotic episode (as in a postpsychotic depression),[4] be reflected in the negative symptoms of schizophrenia,[5] or be induced by conventional neuroleptics.[6] Patients who experience akinesia while taking conventional neuroleptics may experience an increase in depression (neuroleptic-induced dysphoria) that usually improves with successful treatment of the akinesia.[7] The novel antipsychotics are less likely to produce dysphoria and more likely to have an antidepressant effect than conventional antipsychotics. Therefore, in addition to demonstrated efficacy against positive and negative symptoms and a reduced incidence of extrapyramidal side effects (EPS) and tardive dyskinesia, there is now reason to believe that atypical antipsychotics may also be superior for treatment of depression in schizophrenia or schizoaffective disorder.

Although the atypical antipsychotics are marketed for the treatment of schizophrenia, their novel psychopharmacologic effects suggest the possibility of other therapeutic applications in mood disorders. Recent studies of the efficacy of the novel antipsychotics clozapine, risperidone, and olanzapine against depressive symptoms of schizophrenia and affective disorders will be reviewed in this ar-

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ticle. The effects of quetiapine and sertindole have yet to be assessed in this regard.

ASSESSMENT OF DEPRESSION

Scores on specific items of rating scales may be more useful than global scores for assessing depression in schizophrenia. In a discussion of the measurement of depression and negative symptoms in schizophrenia, Goldman et al.[8] stated that individual Hamilton Rating Scale for Depression (HAM-D) subfactors provided a better index of various symptom complexes than the total score, which was nonspecific. The authors reported that the HAM-D contained a depressive factor that correlated strongly with the Brief Psychiatric Rating Scale (BPRS) depression factor, and it also contained a negative symptom factor that correlated strongly with the Scale for the Assessment of Negative Symptoms (SANS) and the BPRS negative symptom factor.

Kay and colleagues devised a 30-item Positive and Negative Syndrome Scale (PANSS)[9] in an effort to develop a tool to rate positive and negative symptoms as well as to introduce formal operational definitions for each item and anchoring points for each degree of severity. Lindenmayer et al.[3] proposed the introduction of a 5-syndrome model based on a reanalysis of factor analytic procedures used on 240 schizophrenic patients assessed with the PANSS and found that all 5 factors—positive, negative, excited, depressive, and cognitive—were both internally reliable and valid as a group when tested against independent demographic and historical variables. The risperidone multicenter trials, which combined use of the PANSS with systematic rater training, also confirmed the utility of the PANSS as a rating scale for multicenter studies of newer antipsychotics.

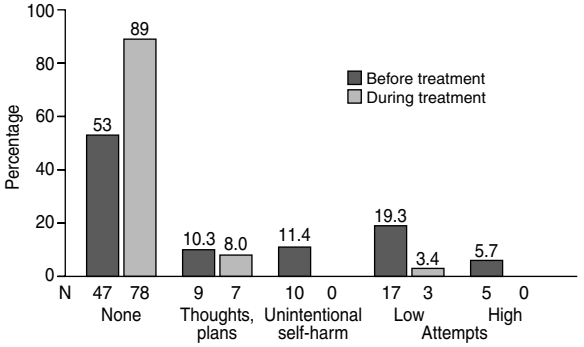
The Montgomery-Asberg Depression Rating Scale (MADRS) is a widely used scale that was specifically designed to be sensitive to changes over time.[10] The scale differs from the HAM-D rating scale in that it does not include somatic or psychomotor symptoms. However, it has high face validity because it measures some of the most important symptoms of depression such as sadness, inner tension, reduced sleep, lassitude, pessimism, and suicidal thoughts. The Calgary Depression Scale for Schizophrenia[11–13] is specifically designed for schizophrenia and is the scale of choice for the purpose of monitoring depression in schizophrenia.

ATYPICAL ANTIPSYCHOTICS

Clozapine

There is evidence that atypical antipsychotics may contribute to a reduction in suicidality and that the atypical antipsychotic clozapine may decrease suicidality (suicidal ideation, suicide plans, attempted/completed suicide) in part by an antidepressant action. Meltzer and Okayli[1] determined that completed suicide was rare in clozapine-treated patients. Of 101,900 clozapine-treated patients, there were 39 completed suicides, and the annual suicide rate appeared to be 0.09% to 0.18% compared with 0.4% to 0.8% in patients taking standard treatment. When the frequency of suicidality in a group of patients was compared 2 years before and during clozapine treatment, 89% of patients were without suicidal behavior during clozapine treatment as opposed to 53% in the 2 years before treatment started (Figure 1).[1] The mean ± SD follow-up period was 3.5 ± 1.6 years. Analysis of the HAM-D total scores of the 22 patients who made suicide attempts before taking clozapine demonstrated significant decreases 6 weeks after treatment started and at the last available rating.

Figure 1. Frequencies of Suicidality 2 Years Before and During Clozapine Treatment (N = 88)*



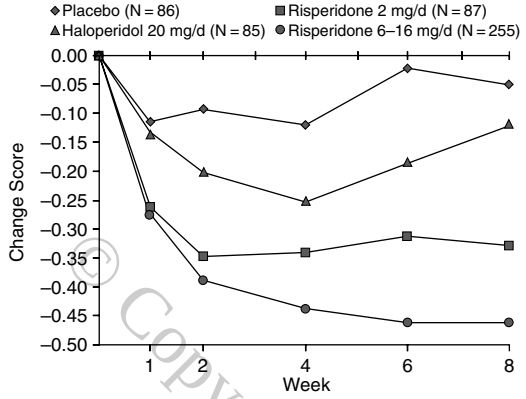
*Data from reference 1.

In an epidemiologic study,[14] the standardized mortality rates of various causes of death were compared in 67,072 current and former clozapine users. According to the 790 death certificates reviewed, mortality was lower during periods of clozapine use than during non-use, and it appeared that clozapine primarily reduced mortality in patients who had severe schizophrenia by decreasing the incidence of suicide. A clozapine-induced decrease in suicidality may be related to the relief of depression, hopelessness, and positive symptoms, as well as the development of a more optimistic view about prognosis for possible further improvement in psychopathology and tardive dyskinesia.[1]

Risperidone

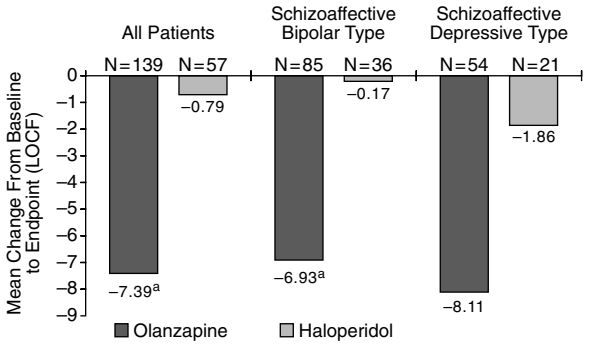
The antidepressant effects of risperidone may differ from those of clozapine.[15] Risperidone combines potent dopamine D_2 and serotonin 5-HT_2 receptor antagonist properties.[16] On the basis of the hypothesis that the 5-HT_2 receptor-blocking activity of risperidone would produce clinical antidepressant activity, Hillert et al.[17] treated 10 patients who had DSM-III-R major depression with psychotic features (N = 7) and schizoaffective disorder, depressive type (N = 3), with risperidone. Four (57%) of 7 patients with psychotic depression and all 3 patients with

Figure 2. Mean Changes in PANSS Anxiety/Depression Scores in Factor Analysis of Risperidone Data*



*Reprinted from reference 18, with permission. Abbreviation: PANSS = Positive and Negative Syndrome Scale.

Figure 3. Mean Change in MADRS Total Score During the Acute Phase of Treatment With Olanzapine vs. Haloperidol*



*Data from reference 21. Abbreviations: LOCF = last observation carried forward; MADRS = Montgomery-Asberg Depression Rating Scale.
[a]p < .001.

the depressive type of schizoaffective disorder displayed significant reductions in ratings for depressive symptoms, measured by BPRS scores, and for psychotic symptoms, measured by BPRS, SANS, and Scale for the Assessment of Positive Symptoms scores.

The effects of risperidone on the 5 dimensions of schizophrenia derived by factor analysis was reported by Marder et al.[18] Combined data of the 2 pivotal controlled trials of risperidone for schizophrenia[19,20] were analyzed to determine whether risperidone differed qualitatively from the conventional antipsychotic haloperidol.[18] Risperidone produced significantly ($p \leq .05$) greater improvements than haloperidol on all 5 dimensions. Symptoms of anxiety and depression were slightly reduced with placebo and haloperidol; in contrast, risperidone at doses of both 2 mg/day and 6 to 16 mg/day produced considerable improvement (Figure 2). In these dimensions, significantly greater improvement was seen in risperidone-treated patients (6–16 mg/day) than in haloperidol-treated patients on 3 of the 4 individual items (depression, anxiety, and tension) included in the anxiety/depression scores.

Olanzapine

Olanzapine has also been shown to be effective in ameliorating the depression that is sometimes associated with schizophrenia. In an international multicenter trial[21] that compared olanzapine with haloperidol, the effects of depression were assessed in 1996 inpatients and outpatients with schizophrenia and schizoaffective disorder. Clinicians used the MADRS and included a specific item interview with ratings of 0 to 6 for levels of depression. This scale was developed and validated to measure changes in depressive symptoms over time. At baseline, 55% of the subjects had at least moderate levels of depression (scores ≥ 16 on the MADRS), which indicated that depression was common in this population. After 6 weeks of treatment, MADRS scores of these moderately depressed patients improved significantly ($p = .001$) more in the olanzapine group than in the haloperidol group. The results of path analysis suggested that most of the efficacy of olanzapine in treating depression (67%) was a direct effect, instead of an indirect effect of improvement in EPS, positive, or negative symptoms. Of the 1996 patients studied in the trial, 300 had a diagnosis of schizoaffective disorder; 177 were diagnosed as schizoaffective, bipolar type; and 123 were diagnosed as schizoaffective, depressive type. After the 6-week acute treatment phase, patients in the depressed subgroup had significantly ($p < .001$) greater improvements in MADRS scores (mean = –7.39) than patients treated with haloperidol (mean = –0.79) (Figure 3). Along with the other novel antipsychotics, olanzapine appears to have a beneficial effect on the depressive component of schizophrenia.

AFFECTIVE DISORDERS

Affective disorders are common in patients with schizophrenia and are associated with a poor outcome, an increased risk of relapse, and a high rate of suicide. In depressed and actively psychotic schizophrenic and schizoaffective patients, treatment with a combination of neuroleptics and antidepressants may be less effective than neuroleptics alone. At doses comparable with those effective in schizophrenia, clozapine may be as good or better than conventional neuroleptics in schizophrenic patients who have psychotic mood disorder or schizoaffective disorder. In patients with high BPRS anxiety/depression scores, risperidone has been shown to be more effective than haloperidol.

Bipolar Disorder

A growing number of studies over the past decade have shown that clozapine may be effective for the acute and prophylactic treatment of some patients with bipolar disor-

der. Tohen and Zarate[22] conducted a meta-analysis involving primarily retrospective and open-label studies of clozapine from 1973 through 1995. Patients in manic or psychotic phases of schizoaffective or bipolar disorder were significantly more likely to respond to clozapine than patients with schizophrenia (71.2% of 315 affective patients vs. 61.3% of 692 schizophrenic patients; p = .0006). In the same review, patients in the manic and mixed-psychotic state of illness were more likely to respond to clozapine than patients with major depressive syndromes (72.2% of 79 manic and mixed patients vs. 51.7% of 58 depressed patients; p = .001).

In an effort to assess whether clozapine was effective in patients with schizoaffective disorder or psychotic mood disorders, McElroy and colleagues[23] surveyed treatment response to clozapine in 85 consecutive patients including 14 with bipolar disorder. Response to clozapine was assessed by 2 scales: a 4-point scale that measured patient functioning and improvement—determined by interview with the primary clinician—and the BPRS, which was administered at baseline and quarterly thereafter. Response to clozapine on the 4-point scale was significantly (p = .02) better in the bipolar group than in the schizophrenic group. The mean ± SD improvement in total BPRS score from baseline to the last available determination was 21.8 ± 14.7 for patients with bipolar disorder.

Suppes et al.[24] reported a study of 7 patients with dysphoric mania who showed marked symptomatic and functional improvement with clozapine treatment. The chronically disabled patients had diagnoses of bipolar disorder characterized by dysphoric mania with psychotic features and were refractory to standard treatments and anticonvulsants. During a 3- to 5-year follow-up period, most of the patients maintained substantial gains in psychosocial function, and 6 of the patients who continued the medication required no further hospitalization. The remarkable improvement of these severely ill patients suggests that clozapine may have utility in the treatment of bipolar illness as well as schizophrenia.

Hillert and colleagues[17] first reported that the novel antipsychotic risperidone reduced psychotic and affective symptoms in patients with DSM-III-R major depression with psychotic features or schizoaffective disorder, depressive type. Keck et al.[15] evaluated the response to risperidone in 11 patients with bipolar disorder (7 manic, 2 mixed, 2 depressed), all of whom received mood stabilizers in addition to risperidone. Response was determined according to a 4-point scale used in previous studies, and all but 2 of the patients with bipolar disorder responded to risperidone. The authors concluded that risperidone may be a useful alternative or adjunctive treatment for patients with bipolar disorder when used in conjunction with mood stabilizers. Ghaemi et al.[25] also reported the acute treatment of 14 outpatients with bipolar I disorder with adjunctive risperidone for approximately 6 weeks. Nine (64%) patients were much improved on the basis of Clinical Global Impression scores, and Global Assessment of Functioning scores improved from a mean ± SD of 48.2 ± 4.9 to 58.8 ± 7.3 (t = 4.49, p = .0006, paired t test). Treatment was well tolerated and no patient experienced worsening of mood symptoms while receiving risperidone.

Studies suggesting that olanzapine may have a role in the treatment of affective symptoms are also beginning to emerge. Tohen and Zarate reviewed a database of bipolar patients treated with olanzapine[22] and noted a significant reduction in scores on the HAM-D in comparison to those in patients treated with placebo. In a subanalysis of a larger database, a 6-week, double-blind study of patients with schizoaffective disorder and bipolar mania revealed that olanzapine-treated patients had a mean 6.06 decrease in the BPRS mania score compared with a 3.36 mean decrease for the haloperidol group (p = .251). Schizoaffective depressed type patients had a 3.59 mean decrease with olanzapine and a 0.33 mean decrease with haloperidol (p < .0001).[22] In a retrospective chart review,[26] 150 consecutive patients newly treated with olanzapine were assessed for their response to the drug and for clinical factors associated with that response. A total of 47 patients had a diagnosis of bipolar disorder with psychotic features (20 manic, 14 depressed, 13 mixed type); levels of response were assessed according to a 4-point scale, and all but 8 patients with bipolar disorder showed a moderate-to marked response.

Mania

The initial treatment of acute psychotic mania, especially when accompanied by severe agitation, often involves both a mood stabilizer and an antipsychotic to hasten and maximize response or an antipsychotic alone when patients refuse mood-stabilizing medications. Accumulating clinical data suggest that clozapine, administered alone or adjunctively with mood stabilizers, may have acute antimanic and long-term stabilizing effects in patients with bipolar and schizoaffective disorders[27]; this includes those patients who have pure mania, mixed mania, and rapid cycling with psychotic features resistant to mood stabilizers, electroconvulsive therapy, and conventional antipsychotics. Risperidone is less well studied than clozapine and reports of its efficacy in patients with mania are more mixed than those for clozapine.

Psychotic Depression

The presence of delusions or hallucinations in major depressive disorder indicates a severe form of the disorder. The short- and long-term outcomes for such patients are poor. Monotherapy with antidepressants is usually ineffective. Treatment is more rapid when antidepressants are combined with antipsychotics. The advent of newer antipsychotic agents has proved to be effective for alleviating psychotic symptoms in many patients. However, most controlled trials have assessed schizophrenic patients, and the

potential for clinical benefits in patients with psychotic depression deserves further investigation. Olanzapine may prove to be an effective treatment modality for psychotic depression. Debattista and colleagues[28] presented a case report of a 59-year old man with a 6-year history of untreated depression who developed severe paranoid delusions. Four weeks after treatment with olanzapine, the patient questioned whether his delusions were real and was less motorically retarded. By week 6, his HAM-D score had dropped from 33 to 13 and his BPRS score fell from 73 to 38.

CONCLUSION

Depression in schizophrenia may contribute to the high suicide rate that occurs in patients with this disorder. Conventional antipsychotics may induce dysphoria and heighten the depression. By contrast, novel antipsychotics may produce an antidepressant effect in schizophrenia, thereby promoting a reduction in patient hospital days and mortality rates.

The role of atypical antipsychotic agents may also be enhanced in affective disorders, either as an alternative or adjunct to mood-stabilizing agents. Controlled studies are in order to determine the nature and extent of each atypical compound as an antimanic, antidepressant, antipsychotic, and mood-stabilizing agent.

Drug names: clozapine (Clozaril), haloperidol (Haldol and generic brands), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal).

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DISCLOSURE OF OFF-LABEL USAGE

The following off-label uses of the atypical antipsychotics clozapine, risperidone, olanzapine, and quetiapine were discussed: depression, bipolar disorder, and mania.