Antipsychotics in the Treatment of Mood Disorders and Risk of Tardive Dyskinesia

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Psychosis occurs commonly in patients with mood disorders and has traditionally been treated with typical antipsychotics. Exposure to typical antipsychotics poses a risk for the emergence of tardive dyskinesia. Atypical antipsychotics may have advantages over typical agents in the treatment of patients with mood disorders complicated by psychotic features. The studies of typical and atypical antipsychotics in the treatment of mood disorders were reviewed. Similarly, studies regarding the risk of tardive dyskinesia from typical and atypical agents in patients with mood disorders were surveyed. Typical and atypical antipsychotics appear to be comparably effective in the treatment of acute mania. Limited data regarding these medications in psychotic depression are available. Advantages of atypical antipsychotics include, for most agents, minimal extrapyramidal and prolactin effects, inherent thymoleptic activity, and lower rates of tardive dyskinesia. Atypical antipsychotics appear to have a number of advantages over typical agents in the treatment of patients with psychotic mood disorders.

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PSYCHOSIS IN MOOD DISORDERS

Psychosis is a common complication of manic, mixed, and depressive episodes in patients with bipolar disorder and of depressive episodes in patients with major depression.[1–4] Although mood-congruent or grandiose delusions may represent the most common manifestation of psychotic mania, mood-incongruent and bizarre delusions, including Schneiderian first-rank symptoms, also occur during manic episodes.[5–7] In addition to the frequent occurrence of delusions and hallucinations in mania, numerous studies have also found rates of thought disorder in mania comparable to those in schizophrenia.[1,8] The prevalence and characteristics of psychosis in bipolar depression have been less well studied.[1,2] The available studies suggest that although delusions, hallucinations, and thought disorder frequently occur in bipolar depression, psychosis occurs more commonly in mania than in depression.[1,2] Similarly, there are few data regarding the prevalence of psychotic depression among patients with major depressive disorder. However, in clinical populations, psychotic depression is common and may be underdiagnosed, accounting for approximately 25% of depressed patients.[9,10]

Given the high prevalence rates of psychosis in mood disorders, it is not surprising that antipsychotics have been commonly used in the pharmacologic treatment of these illnesses. In this article, we review the role of typical and atypical antipsychotic medications in the treatment of patients with bipolar disorder and major depressive disorder with psychotic features. We also discuss the risk of tardive dyskinesia associated with the use of these agents in the treatment of patients with mood disorders.

ANTIPSYCHOTICS IN THE TREATMENT OF MOOD DISORDER

Acute Mania

Typical antipsychotic medications (neuroleptics) were the first effective antimanic agents in the modern era of psychopharmacology. Prior to the availability of lithium, typical antipsychotics were also often used as maintenance treatment.[11] Typical antipsychotics have traditionally had 2 primary roles in the treatment of patients with bipolar disorder: first, as adjunctive medications combined with mood stabilizers (e.g., lithium, valproate, carbamazepine) for acute mania (with or without psychotic features) or acute psychotic bipolar depression; second, as adjunctive maintenance treatment in patients with symptoms refractory to mood stabilizers.[12–14] More recently, emerging data suggest that the atypical antipsychotics may have thymoleptic properties and fewer side effects compared with typical agents.[4] These data suggest that atypical antipsy-

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chotics may thus have specific advantages over typical agents in bipolar disorder.

In controlled studies of acute mania, both typical and atypical antipsychotics have been found to be effective in reducing manic symptoms. The only placebo-controlled, randomized trial of a typical antipsychotic found chlorpromazine to be superior to placebo in reducing manic symptoms.[15] In other controlled trials, typical antipsychotics were compared with lithium,[16–20] valproate,[21] or carbamazepine.[22,23] When typical antipsychotics were compared with lithium,[16–20] the overall rate of improvement was higher in patients receiving lithium by the third week of treatment. In a meta-analysis of the pooled results from many of these studies, the efficacy of lithium (89% responders) was superior to the efficacy of typical antipsychotics (54% responders; $\chi^2 = 13.1$, df = 1, $p < .001$).[24] However, antipsychotics were found to have greater efficacy than lithium in patients with prominent psychomotor agitation during the first week of treatment.[19,20] In studies comparing typical antipsychotics with valproate[21] or carbamazepine,[22,23] all agents exerted comparable efficacy in reducing manic and psychotic symptoms.

The results of these studies yielded several notable observations. First, typical antipsychotics appear to have a more rapid onset of action than lithium in acute mania and onset comparable with valproate and carbamazepine. Second, all 3 mood stabilizers produced reductions not only in manic symptoms but also in psychosis similar to comparison antipsychotics. Third, although typical antipsychotics are commonly used in combination with mood stabilizers in the treatment of acute mania, no study has assessed the response of acute mania to typical antipsychotics, mood stabilizers, or the combination based on the presence or absence of psychosis. These latter 2 observations are especially noteworthy, since the use of typical antipsychotics in the treatment of acute mania is associated with a number of drawbacks. These include extrapyramidal side effects (EPS), akathisia, hyperprolactinemia, possible propensity to exacerbate depressive symptoms, and obfuscation of the degree of response attributable to a mood stabilizer.[12,25]

There are relatively few controlled trials of atypical antipsychotics in the treatment of acute mania.[26–28] In the only controlled trial of clozapine, 38 patients with treatment-refractory bipolar disorder were randomly assigned to clozapine or treatment as usual (i.e., combinations of mood stabilizers and typical antipsychotics) and followed for up to 1 year.[26] Clozapine produced significantly greater improvement than treatment as usual, confirming earlier impressions of the mood-stabilizing properties of clozapine from open trials.[29,30] The results of a recent double-blind, randomized controlled trial comparing risperidone (6 mg/day), haloperidol (10 mg/day), and lithium (8000–1200 mg/day) in the treatment of 45 patients with acute mania provide the first controlled data to assess the effects of risperidone on manic symptoms.[27] In this 28-day trial, substantial and comparable reductions in manic symptoms were observed with all 3 agents. However, the results of this study must be interpreted with several methodological limitations in mind. First, a larger sample size was needed to detect possible differences in efficacy among the 3 agents. Second, adjunctive lorazepam was allowed throughout the 28-day study period, potentially contributing to improvement in certain manic symptoms across all 3 treatment groups (e.g., sleeplessness, psychomotor agitation, anxiety). Third, mean serum lithium concentrations were at the lower end of the therapeutic range. There was no difference in the occurrence of EPS between risperidone and haloperidol.

The preliminary results of a double-blind, placebo-controlled, multicenter study of olanzapine in the treatment of acute mania were recently presented.[28] In this study, only the second placebo-controlled trial of an antipsychotic in acute mania conducted, olanzapine (5–20 mg/day) was significantly superior to placebo in improvement in manic symptoms and psychosis and in number of responders over the 3-week study period. Approximately 49% of patients treated with olanzapine displayed ≥ 50% reduction in manic symptoms, a response rate very similar to those associated with divalproex sodium and lithium in 2 other recent placebo-controlled trials.[31,32] Furthermore, there was no significant difference in response rate according to presence or absence of psychosis, suggesting that olanzapine response was not a function of improvement in psychosis. Olanzapine was well tolerated, and the occurrence of EPS was not significantly different than with placebo. There are currently no data available regarding the efficacy of quetiapine and ziprasidone in the treatment of acute mania.

Acute Bipolar Depression

There are no published controlled trials of typical or atypical antipsychotics in the treatment of acute bipolar depression (with or without psychotic features). Nevertheless, atypical antipsychotics could have an important role in the treatment of this phase of the illness. In particular, there are various pharmacologic mechanisms associated with these different agents that may produce antidepressant effects. These include 5-HT_{2A} receptor antagonism (clozapine, risperidone, olanzapine, quetiapine, ziprasidone), α_2 antagonism (clozapine, risperidone), serotonin and norepinephrine reuptake inhibition (ziprasidone), and potent 5-HT_{1A} and 5-HT_{2D} affinity (ziprasidone).[33] Preliminary data from open trials support predictions, based on these pharmacologic mechanisms, that clozapine, risperidone, and olanzapine possess antidepressant as well as antipsychotic activity.[34–37]

Maintenance Treatment of Bipolar Disorder

Typical antipsychotics are commonly used in both the acute[11,38] and maintenance treatment of bipolar disorder.[39–42] However, there are several concerns regarding the

use of typical antipsychotics in this phase of illness management. First, there are no compelling data from controlled trials indicating that these agents are effective as maintenance treatments.[43–49] Second, maintenance treatment with typical antipsychotics may exacerbate or precipitate depressive symptoms.[43,50,51] Third, as discussed in greater detail below, patients with bipolar disorder may be at higher risk for developing tardive dyskinesia and other neurologic side effects from typical antipsychotics than patients with schizophrenia.[52–54]

In contrast, atypical antipsychotics have a number of potential advantages over typical agents as possible maintenance treatment alternatives in patients with bipolar disorder who have incomplete responses to or intolerance of mood stabilizers. Atypical agents have substantially lower risks of neurologic side effects.[33] Second, preliminary data suggest that clozapine[26,29,30] and olanzapine[55] may have long-term efficacy in preventing mood episodes. As previously described, 1 controlled[26] and a number of open long-term trials[29,30] have found marked reductions in manic and depressive episodes in patients with treatment-refractory bipolar disorder treated with clozapine. Recently, in a 1-year, open-label extension trial, olanzapine was found to maintain improvement in manic symptoms in patients who responded in the acute-phase, placebo-controlled trial.[55] To our knowledge, there are no long-term (e.g., 1-year) maintenance data to date regarding risperidone, quetiapine, or ziprasidone in patients with bipolar disorder.

Third, atypical antipsychotics appear to have a lower risk of tardive dyskinesia.[55–59] In addition, a number of reports suggest that clozapine,[56] risperidone,[58] and olanzapine[59] may have therapeutic effects on tardive dyskinesia. To our knowledge, specific data regarding the risk of tardive dyskinesia associated with atypical antipsychotics in patients with bipolar disorder are limited to 1 open-label, 1-year trial of olanzapine.[55] In this study, of 98 patients at risk over the 1-year interval, none developed tardive dyskinesia. In summary, atypical antipsychotics appear to have important advantages over typical agents in the maintenance treatment of patients with bipolar disorder.

Psychotic Depression

There are few randomized, controlled trials examining typical or atypical antipsychotics in the treatment of psychotic unipolar depression. The available data indicate that the combination of a typical antipsychotic and an antidepressant is superior to either agent alone.[60–62]

As described earlier, there are a number of pharmacologic mechanisms by which different atypical antipsychotics could potentially produce antidepressant effects. There are, however, no randomized, controlled trials of atypical antipsychotics in the treatment of psychotic depression published to date.

Remarkably little is known about the optimal duration of antipsychotic treatment in psychotic depression.[10] The available reports suggest that the risk of psychotic or depressive relapse may be high if typical antipsychotics are discontinued before 1 year of remission.[63,64] Since patients with psychotic depression appear to commonly require maintenance antipsychotic treatment beyond recovery from an acute episode, the relative risks of tardive dyskinesia between typical and atypical antipsychotics are important considerations in treatment choice.

Table 1. Studies Finding Elevated Rates of Tardive Dyskinesia in Antipsychotic-Treated Patients With Mood Disorders

	Prevalence	
Study	Mood Disorder	Schizophrenia
Davis et al, 1976[65]	…	…
Kane and Smith, 1982[67]	26%	18%
Mukherjee et al, 1986[71]	35%	…
Rush et al, 1982[68]	64%	…
Yassa et al, 1984[70]	42%	25%

RISK OF TARDIVE DYSKINESIA IN MOOD DISORDERS

Two reports in the mid-1970s were the first to observe unexpectedly high prevalence rates of tardive dyskinesia in patients with mood disorders who had received long-term treatment with typical antipsychotics.[65,66] Since then, numerous studies have examined the prevalence of tardive dyskinesia in patients with mood disorders, especially patients with bipolar disorder (Table 1).[65–76] These prevalence rates range from 9% to 64%, but only 1 study[70] provided comparison data for patients with schizophrenia. In this study,[70] the prevalence of tardive dyskinesia was higher in patients with bipolar disorder (42%) compared with patients with schizophrenia (25%). All of these surveys attempted to delineate risk factors for those patients with bipolar disorder who developed tardive dyskinesia compared with those who did not. Not surprisingly, the majority of studies found an association between older age and risk of tardive dyskinesia.[69,73–76] Curiously, only 2 studies found a significant association between duration of typical antipsychotic treatment and risk for tardive dyskinesia.[71,76] Five studies did not find such an association.[69,70,72–74] Similarly, duration of lithium treatment has been found to be associated with an increased[74–76] and decreased[71–73] risk of tardive dyskinesia. Two studies found an association between greater severity of illness[73] or number of hospitalizations[74] and risk for tardive dyskinesia.

For some patients with bipolar disorder, mood-dependent fluctuations in the appearance and severity of tardive dyskinesia have been reported.[77–85] In the majority of these reports, patients had rapid-cycling episodes.[86] During manic episodes, tardive dyskinesia was either improved or abated entirely, whereas, with the exception of 1 report,[82] dyskinesias worsened during depressive epi-

sodes. One important implication of this observation is that an as-yet undetermined change in CNS neurophysiologic activity associated with mania also contributes to a reduction in dyskinesias. Conversely, neurophysiologic changes associated with depression seem to contribute to exacerbation of dyskinesias.[85,86]

A positive family history of mood disorders in patients with schizophrenia also appears to increase the risk of developing tardive dyskinesia in this patient population.[87–89] This observation is particularly relevant to antipsychotic treatment of patients with schizophrenia and co-occurring depression as well as patients with schizoaffective disorder, patient groups that frequently have elevated rates of mood disorder in first-degree relatives.[90] These patients often require long-term antipsychotic treatment. Fortunately, recent data suggest that risperidone[91,92] and olanzapine[93] have low risks of tardive dyskinesia in the long-term treatment of patients with schizophrenia and schizoaffective disorder. Although long-term treatment data bearing on the risk of tardive dyskinesia associated with quetiapine and ziprasidone are not available, to our knowledge, this risk should also be lower than with typical antipsychotics.

CONCLUSION

Psychosis is a common complication of mood disorders. Typical antipsychotics have traditionally been used adjunctively in the treatment of acute mania and acute psychotic bipolar and unipolar depression. However, these medications have a number of limitations including EPS, hyperprolactinemia, induction of dysphoria and/or depressed mood, and obfuscation of the degree of response to the principal thymoleptic agents. In addition, patients with mood disorders, especially bipolar disorder, appear to be at greater risk for developing tardive dyskinesia from typical antipsychotics compared with patients with schizophrenia.

The atypical antipsychotics offer a number of advantages over typical agents in the treatment of patients with psychotic mood disorders. These advantages include minimal risk of EPS, lack of sustained prolactin elevations (except for risperidone), inherent thymoleptic properties in addition to their antipsychotic activity, and substantially lower rates of tardive dyskinesia.

Drug names: carbamazepine (Tegretol and others), chlorpromazine (Thorazine and others), clozapine (Clozaril and others), divalproex sodium (Depakote), haloperidol (Haldol and others), lorazepam (Ativan and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal).

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, the following agents are not approved by the U.S. Food and Drug Administration for use in psychotic mood disorders: carbamazepine, chlorpromazine, clozapine, divalproex sodium, haloperidol, lithium, lorazepam, olanzapine, quetiapine, and risperidone. Ziprasidone is not approved for use in the United States.

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