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Atypical Antipsychotics in the Treatment of Affective Symptoms: A Review

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Atypical antipsychotics have demonstrated beneficial effects on affective symptoms, in addition to antipsychotic activity. Consequently, their role in the treatment of bipolar disorder and treatment-resistant or psychotic depression has been explored. Adjunctive atypical antipsychotic therapy appears to benefit patients experiencing manic episodes of bipolar disorder, and some studies suggest that monotherapy may also be efficacious. Clinical studies of patients with schizoaffective disorder and major depression support the use of atypical antipsychotics to treat depression. This review focuses on risperidone, olanzapine, quetiapine, and ziprasidone and provides evidence that these drugs demonstrate activity against manic episodes of bipolar disorder when used as adjunctive therapy and possibly as monotherapy and that depression in patients with schizoaffective disorder also responds to these agents.

Keywords Risperidone; Olanzapine; Quetiapine; Ziprasidone; Bipolar disorder; Mania; Depression.

INTRODUCTION

Atypical antipsychotic agents are commonly used to treat schizophrenia. Patients treated with these agents have demonstrated improvements in a wide range of symptoms, including anxiety and depression (1,2). An important attribute of the atypical antipsychotics is the reduced risk of extrapyramidal symptoms (EPS) and tardive dyskinesia. The favorable impact of the atypical antipsychotics on affective symptoms, combined with an acceptable tolerability profile, led to the study of these agents in conditions other than schizophrenia.

Bipolar disorder is an episodic illness with periods of euthymia alternating with periods of mania or depression (3). The management of bipolar disorder is complicated by several factors, including variable presentation and response to treatment. Treatment goals for bipolar disorder include short- and long-term mood stabilization with behavioral control for the patients' safety and that of those around them.

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Pharmacologic intervention for bipolar disorder has relied on lithium or divalproex monotherapy (4,5). Although these agents are efficacious in acute mania in some patients, lithium or divalproex monotherapy is often ineffective for prophylaxis against future episodes. Lithium is the only agent approved for treatment of both acute and chronic phases of bipolar disorder, despite having an inadequate response in patients with mixed episodes, rapid cycling, or comorbid substance abuse and an adverse effect profile that includes neurologic and psychiatric adverse events (such as tremor and cognitive slowing), decreased thyroid function, renal adverse effects (such as polydipsia and polyuria), edema, and acneiform eruptions. Although divalproex may be more effective for a broader range of symptoms, particularly dysphoric mania and rapid cycling, its response rates are not significantly better than those for lithium. Other treatments have been used to attempt to overcome the limitations of standard first-line therapy and to sustain the remission of bipolar disorder. Examples of such treatments include anticonvulsant agents, antidepressants, benzodiazepines, conventional and atypical antipsychotics, and bilateral electroconvulsive therapy (ECT) (3,5,6).

The Practice Guideline for the Treatment of Patients With Bipolar Disorder, published in 2002 by the American

Psychiatric Association, recommends the initiation of either lithium plus an antipsychotic or valproate plus an antipsychotic for the first-line pharmacological treatment of severe manic or mixed episodes (7). The guidelines recommend that less ill patients receive monotherapy with lithium, valproate, or an antipsychotic. For bipolar depression, the recommended first-line pharmacological treatment is lithium or lamotrigine. Adjunctive treatment with an antipsychotic or ECT is recommended for patients experiencing depressive episodes with psychotic features. When antipsychotics are used, the guidelines recommend the use of atypical rather than typical agents because of their more benign side effect profile.

The recognition in these guidelines that atypical antipsychotic therapy can play a major role in the treatment of bipolar disorder reflects the positive results of recent studies that have examined the role of atypical antipsychotics as monotherapy or adjunctive treatment for bipolar disorder (4). Substantial evidence suggests that the atypical antipsychotic agents may treat affective symptoms, independent of their antipsychotic efficacy (6,8–12). This characteristic may stem from their potent serotonin receptor antagonism (10,13). Randomized, controlled, double-blind clinical trials of atypical antipsychotics as adjunctive therapy to lithium or valproate have demonstrated improvements in acute mania of bipolar disorder that are superior to those with mood stabilizers alone (14). The atypical antipsychotic agents may also prove useful in the treatment of affective symptoms associated with other conditions, including obsessive-compulsive disorder, Tourette's syndrome, dementia, Lewy body disease, mental retardation, Parkinson's disease, idiopathic segmental dystonia, and organic catatonia (12).

Several reports have described the role of atypical antipsychotics in the treatment of affective symptoms. Ghaemi *et al*. have summarized and provided important insights into the results of randomized, controlled clinical trials of atypical antipsychotics for the treatment of affective symptoms of bipolar disorder and for the treatment of depression (8,9,15). The rapid evolution of this area necessitates an expansion on these reviews and an update of the role of atypical antipsychotics in the treatment of depression. This article focuses primarily on double-blind controlled trials of risperidone, olanzapine, quetiapine, and ziprasidone in bipolar disorder.

This review confirms that patients experiencing manic episodes of bipolar disorder benefit from adjunctive therapy and possibly from risperidone or olanzapine monotherapy and that depression in patients with schizoaffective disorder responds to these agents. The addition of atypical antipsychotics to the treatment of acute mania in bipolar disorder or depression associated with schizoaffective disorder may greatly improve patient outcome.

MANIA

Risperidone

Risperidone is efficacious in the treatment of both positive and negative symptoms of schizophrenia, with a low incidence of EPS and tardive dyskinesia, in multiple, randomized, controlled clinical trials (16–20). Unlike clozapine, risperidone is not associated with agranulocytosis or excessive sedation, and, unlike olanzapine, risperidone is not associated with substantial body weight gain or diabetes mellitus (21–23). Risperidone has demonstrated efficacy in the treatment of acute mania in patients with bipolar disorder when used either as monotherapy or as an adjunct to mood stabilizers (9,24,25).

Recently, Sachs *et al*. evaluated the efficacy and safety of risperidone as an adjunct to a mood stabilizer (lithium or divalproex) compared with haloperidol or placebo in 156 patients with bipolar disorder with a manic or mixed current episode (26). This was a randomized, double-blind, placebo-controlled, parallel-group study lasting up to 3 weeks and followed by a 10-week open-label maintenance phase. The primary efficacy variable was the change in Young Mania Rating Scale (YMRS) total score from baseline to endpoint. Endpoint was defined as the last available postbaseline assessment. Other variables included the Brief Psychiatric Rating Scale (BPRS), the Clinical Global Impressions (CGI) scale, and safety parameters.

During the 3-week double-blind phase of the study, the mean modal doses were 3.8 ± 1.8 mg/day of risperidone and 6.2 ± 2.9 mg/day of haloperidol. Time to premature discontinuation of study drug was significantly longer in patients treated with risperidone plus a mood stabilizer than in the placebo/mood stabilizer group ($p = 0.037$). At endpoint, a pairwise comparison found that patients in the risperidone/mood stabilizer and haloperidol/mood stabilizer groups experienced significantly greater improvements in YMRS total scores than did patients in the placebo/mood stabilizer group ($p = 0.009$ and $p = 0.021$; Figure 1). Mean BPRS total scores were significantly improved at week 1 in both the risperidone/mood stabilizer and haloperidol/mood stabilizer groups compared with placebo/mood stabilizer ($p = 0.029$ and $p = 0.016$, respectively). At endpoint, CGI-change scores were significantly improved in both the risperidone/mood stabilizer and haloperidol groups compared with placebo/mood stabilizer ($p = 0.002$ and $p = 0.003$, respectively). Patients continued to show improvement (reduction in YMRS scores) during the 10-week maintenance phase, during which they received risperidone and a mood stabilizer (26). No induction of mania was reported in any patient.

A comparative subanalysis found that patients with and without psychotic symptoms who received risperidone/

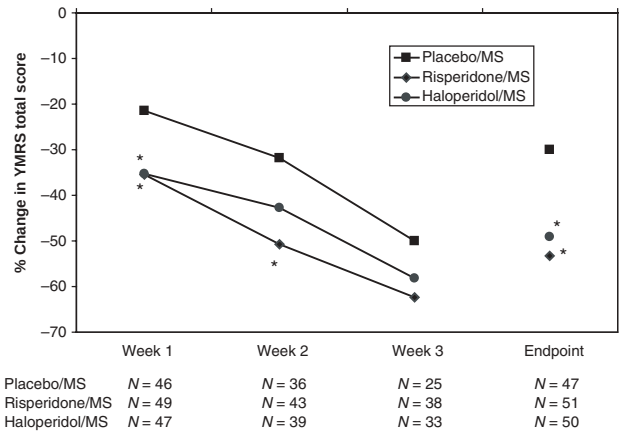

Figure 1 The addition of risperidone or haloperidol to a mood stabilizer induced significant improvements in YMRS total score in bipolar patients with current episode manic or mixed (26). $p = 0.009$ for risperidone/mood stabilizer versus placebo/mood stabilizer; $P = 0.021$ for haloperidol/mood stabilizer versus placebo/mood stabilizer. YMRS = Young Mania Rating Scale. Reprinted with permission from: Sachs GS, Grossman F, Ghaemi SN, Okamoto A, Bowden CL: Combination of a mood stabilizer with risperidone or haloperidol for treatment of acute mania: A double-blind, placebo-controlled comparison of efficacy and safety. *Am J Psychiatry* 2002; 159:1146–1154

mood stabilizer had improved YMRS total scores at endpoint compared with patients who received placebo/mood stabilizer (26). These findings suggest that risperidone has antimanic properties that are independent of its antipsychotic properties.

The most commonly reported adverse events were related to the central and peripheral nervous systems and occurred most often in the haloperidol/mood stabilizer group (66% of patients, compared with 41% of the placebo/mood stabilizer group and 42% of the risperidone/mood stabilizer group). The greatest between-group difference was in EPS: more than twice as many patients treated with haloperidol/mood stabilizer experienced EPS (28%) and received antiparkinsonian medications (38%), when compared with patients treated with risperidone/mood stabilizer (13% and 17%, respectively). Extrapyramidal symptoms were reported in 4% of patients who received placebo. Moderate weight gain in the risperidone group was significantly greater than in the placebo group (5.3 lb versus 1.1 lb; $p < 0.001$). No clinically significant changes in vital signs or laboratory values (such as glucose levels) were reported.

This study demonstrated that the addition of risperidone to a mood stabilizer was safe and efficacious in the treatment of acute bipolar mania. This regimen was superior to mood stabilizer alone and was associated with a substantially lower incidence of EPS and use of antiparkinsonian medications compared with haloperidol plus a mood stabilizer.

A similar study was conducted in 151 patients with bipolar mania (27). In addition to lithium and divalproex, carbamazepine was included as a mood stabilizer. This study did not include haloperidol. Patients were assessed using the YMRS, CGI scale, BPRS, and the Hamilton Depression Rating Scale (HAM-D). Substantially greater reductions in YMRS scores were seen with risperidone/mood stabilizer than placebo/mood stabilizer (mean risperidone modal dose, 3.9 mg/day). This difference, however, was not statistically significant, perhaps owing to a carbamazepine-induced enzymatic reduction of plasma risperidone. Significantly more risperidone/mood stabilizer-treated patients experienced at least a 50% reduction in YMRS ($p = 0.045$). Furthermore, improvements in CGI ratings and BPRS total scores were significantly greater in the risperidone/mood stabilizer-treated patients than in those who received placebo/mood stabilizer. There were no significant differences in HAM-D score between groups. Baseline HAM-D scores were 8.6 and 8.1 for the risperidone/mood stabilizer and placebo/mood stabilizer groups, respectively. The results of this study were consistent with those of Sachs et al (26) and suggest that the addition of risperidone to a mood stabilizer may improve symptom control in bipolar patients with acute mania.

In a longer study, Yatham *et al*. assessed the efficacy and safety of the addition of risperidone to mood stabilizers for 12 weeks in 108 patients with manic episodes of bipolar disorder (28). All patients were treated with 1 or 2 mood stabilizers at the initiation of risperidone therapy. The mean dose of risperidone was 2 mg/day and the mean last dose for study completers was 1.7 mg. Most patients received daily doses between 0.5 mg and 2 mg. The mean reduction in YMRS score was 17.7 ± 10.0 ($p < 0.0001$). A significant reduction from baseline in mean YMRS scores was noted as early as week 1 (−10.8 ± 9.0 [$p < 0.0001$]), and this trend ($p < 0.0001$) continued throughout the study period (Figure 2). No changes in EPS occurred between baseline and endpoint. Therefore, the addition of risperidone to a mood stabilizer continued to improve YMRS scores for up to 12 weeks of treatment, without inducing EPS.

Olanzapine

Olanzapine is approved for the treatment of acute manic episodes associated with bipolar-I disorder (29). Approval was based on two short-term (3 and 4 weeks), placebo-controlled clinical trials of patients with bipolar disorder who displayed acute manic or mixed episodes with or without psychotic features (30,31). A recent reanalysis using pooled data from those studies and stringent criteria for remission found that, compared with patients in the placebo group,

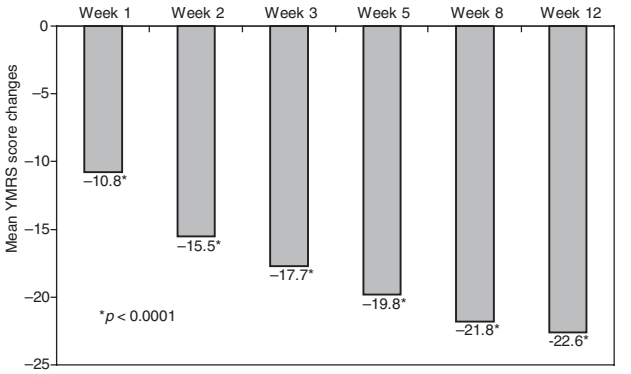

Figure 2 In a prospective open-label study of patients with bipolar mania, the addition of risperidone to one or two mood stabilizers continued to induce a significant mean decrease in YMRS score for up to 12 weeks of treatment ($n = 102$) (28). YMRS = Young Mania Rating Scale. Reprinted with permission from: Yatham LN, Binder C, Riccardelli R, Leblanc J, Connolly M, Kusumakar V: Risperidone in acute and continuation treatment of mania. RIS-CAN 25 Study Group. *Int Clin Psychopharmacol*. 2003; 18:227–235

those treated with olanzapine h ad significantly higher rates of clinical response (55% vs. 29.5% [$p = 0.001$]), euthymia (50% vs. 27% [$p = 0.001$]), and remission (18% vs. 7% [$p = 0.015$]) (32). A secondary analysis of those studies found that patients with acute dysphoric mania had a similar response to that of patients whose mania was not characterized by prominent depressive symptoms (33).

Olanzapine (10 mg/day) was compared with lithium (400 mg twice daily) as primary treatment for mania in a small, double-blind, randomized, controlled study of 30 patients treated for 4 weeks (34). Both groups showed improvement in symptoms from baseline to endpoint, and there were no significant differences between the two treatment groups in changes in BPRS scores, CGI-improvement scores, or the YMRS (Figure 3). Olanzapine was not associated with the induction of EPS. The results of this study are limited by the use of lithium levels at the lower end of the therapeutic range (mean, 0.74 mmol/L) and the absence of a placebo group, but the authors concluded that olanzapine exhibited similar efficacy to lithium in the treatment of mania.

Olanzapine has also been compared with divalproex as primary therapy for acute mania (35,36). In one randomized, double-blind study, patients with acute manic or mixed episodes of bipolar-I disorder were treated for 3 weeks (35). Doses of olanzapine ranged from 5 to 20 mg/day and divalproex from 500 to 2500 mg/day (no loading doses). Patients receiving olanzapine demonstrated significantly greater improvements in mean YMRS scores than did those treated with divalproex (–13.4 vs. –10.4; $p = 0.028$).

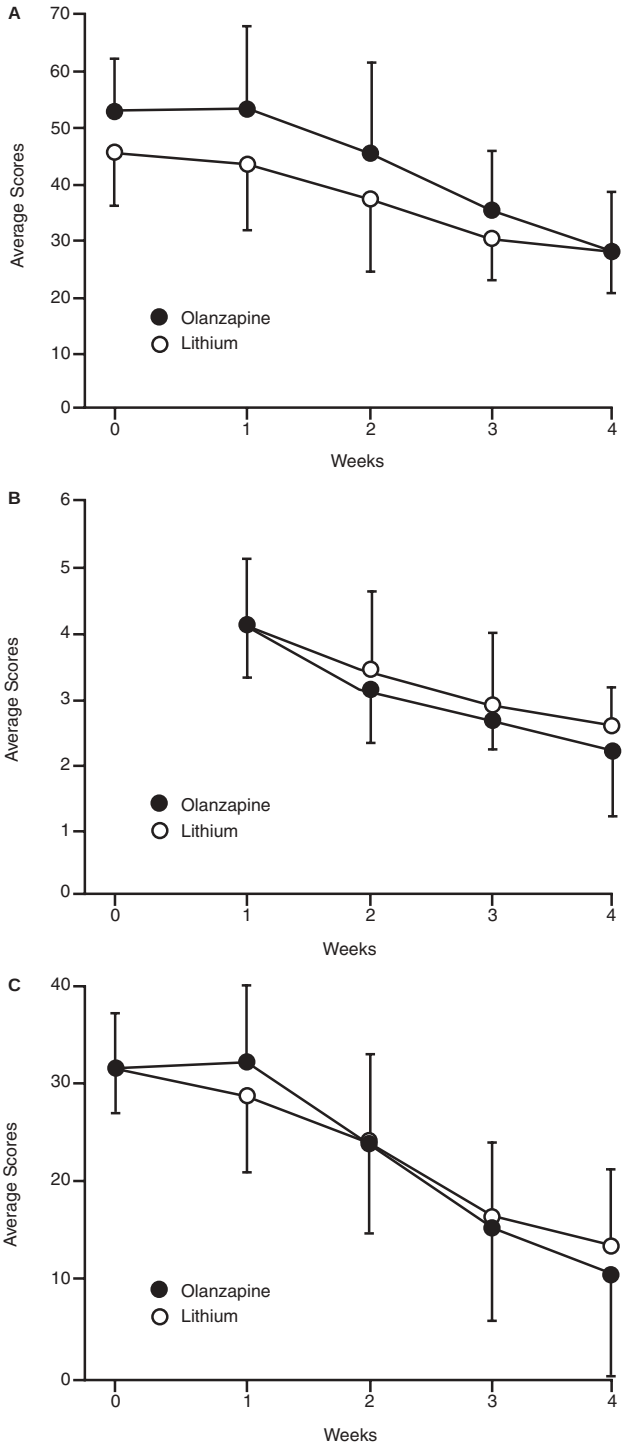

Figure 3 Similar improvements in symptoms were observed with olanzapine or lithium* in 30 patients with mania treated for 4 weeks (34). *The mean lithium level (0.74 mmol/L) was in the lower end of the therapeutic range. Reprinted with permission from: Berk M, Ichim L, Brook S: Olanzapine compared to lithium in mania: A double-blind randomized controlled trial. *Int Clin Psychopharmacol*. 1999; 14:339–343

Moreover, a greater percentage of patients treated with olanzapine experienced at least a 50% reduction in YMRS scores (54.4% vs. 42.3%; $p = 0.058$) and had a YMRS value ≤12 at endpoint (47.2% vs. 34.1%; $p = 0.039$). The most common treatment-emergent adverse events associated more often with olanzapine than with divalproex ($p \leq 0.05$) were dry mouth, increased appetite, and somnolence, while those occurring more frequently with divalproex ($p \leq 0.05$) were diarrhea and nausea. Weight gain was significantly greater in patients who received olanzapine than in those who received divalproex (2.49 kg vs. 0.92 kg, respectively; $p < 0.001$). The authors concluded that patients with acute manic or mixed episodes of bipolar-I disorder who received olanzapine experienced an improvement in symptoms superior to that of patients who received divalproex.

In a similar but longer study (12 weeks), patients with acute mania associated with bipolar disorder were treated with divalproex (loading dose) or olanzapine at initial doses of 20 mg/kg/day and 10 mg/day, respectively (36). Similar improvements from baseline to day 21 were noted on CGI scale scores, BPRS scores, and HAM-D scores in both treatment groups. Adverse events that occurred in significantly more olanzapine-treated patients included somnolence, weight gain, rhinitis, edema, and slurred speech. Mean increases in body weight over the 12-week study from baseline were significantly greater with olanzapine (8.8 lb) than with divalproex (5.5 lb; $p = 0.049$). This study demonstrated that olanzapine and divalproex had similar effects on mania of bipolar disorder, with some greater incidences of adverse events associated with olanzapine, particularly weight gain.

In the study reviewed above, one death, which was associated with olanzapine treatment and diabetic ketoacidosis, was reported (36). Accordingly, it should be cautioned that metabolic dysregulation is increasingly attributed to the atypical antipsychotics; however, it does not appear to be a class effect. Numerous published case reports suggest that olanzapine and clozapine may induce hyperglycemia and diabetic ketoacidosis in patients with schizophrenia, although reports of this specific association are rare among the other atypical antipsychotics (37–39). Even though these adverse events are reported infrequently, they are serious and have been reported in adolescents aged 13 to 18 treated with olanzapine (37,40) or clozapine (37) and in numerous adult patients treated with olanzapine or clozapine. Olanzapine is linked with at least one other case of treatment-related diabetic ketoacidosis that resulted in death (41).

Other treatment-emergent metabolic side effects such as increased concentrations of triglycerides, cholesterol, and glucose as well as newly reported cases of diabetes have been attributed to olanzapine. Meyer retrospectively found that during the first year of therapy with risperidone ($n = 47$) or olanzapine ($n = 47$), patients younger than 60 years old who received olanzapine ($n = 37$) had significant increases in triglycerides ($p = 0.037$), cholesterol ($p = 0.004$), and glucose ($p = 0.030$) at 1 year when compared with those who received risperidone ($n = 39$) (42). Concurrent use of lithium or divalproex resulted in significant increases in weight gain ($p = 0.009$) and body mass index ($p = 0.006$) that were limited to the olanzapine cohort. It is interesting to note that the adverse metabolic effects of risperidone and olanzapine were diminished in those patients age 60 years or older.

The onset or exacerbation of diabetes among patients with mood disorders who were treated with antipsychotics was measured in a managed care population (43). A total of 2644 untreated patients were compared with 2613 treated patients (risperidone, $n = 849$; olanzapine, $n = 656$, high-potency conventional antipsychotics, $n = 785$; and low-potency conventional antipsychotics, $n = 302$). With the exception of risperidone, all the antipsychotics were associated with diabetes in patients who were free of diabetes at 4 months before observation. Among all the antipsychotics evaluated, only olanzapine had a significant linear dose response related to diabetes. Other significant predictors of diabetes included age, observation period length, and use of other psychotropic medications.

Quetiapine

Existing data suggest that quetiapine is safe and well tolerated in patients with bipolar disorder. A double-blind placebo controlled trial of quetiapine (250 to 450 mg/day; mean dose, 432 mg/day) as an adjunct to divalproex in adolescents found that quetiapine plus divalproex was significantly more efficacious than divalproex monotherapy as measured by reductions of at least 50% in YMRS scores ($p = 0.05$) (44). The most frequently reported adverse events in patients who received quetiapine plus divalproex were headache (55%), nausea and vomiting (55%), and sedation (45%). Most adverse events were mild and none were serious. Additionally, no changes in thyroid function tests were reported.

These data are supported by studies in difficult-to-treat patients, including a retrospective analysis in which treatment-refractory bipolar disorder patients responded to quetiapine add-on therapy (45). This small study ($n = 19$) assessed quetiapine responses during a treatment period of 2 weeks to 6 months with dosages that ranged from 25 to 600 mg/day. Treatment decreased depressive symptoms and mania in most patients. Sedation was the most commonly reported adverse event.

Another study focused on rapid-cycling patients with bipolar disorder. In this prospective open-label trial, quetiapine was shown to improve rapid-cycling symptoms, including those associated with depression (46). A total of

40 rapid-cycling bipolar-I patients treated with quetiapine with and without concomitant mood stabilizers were followed up for up to 1 year. The mean dose of quetiapine was 141 mg/day. Patients improved significantly on the HAM-D assessment ($p = 0.03$) and showed clinical improvement on YMRS and GCI-BP measures. Once again, sedation was the most commonly reported adverse event.

In a smaller prospective open-label study, 14 treatment-resistant rapid-cycling patients received add-on quetiapine therapy for 112 ± 33 days at a mean final dose of 268 ± 190 mg/day (47). Patients showed significant improvement on the general CGI-BP ($p = 0.013$), the CGI-BP mania subscale ($p = 0.016$), and the YMRS ($p = 0.025$), but not on the CGI-BP depression subscale or the HAM-D. The most frequently reported adverse event was again sedation.

Ziprasidone

In a short-term study of patients with schizoaffective disorder, ziprasidone demonstrated efficacy and tolerability in the treatment of both affective and psychotic symptoms (48). Ziprasidone was also evaluated in a 3-week, double-blind, randomized study in bipolar patients with acute mania (49). This study compared ziprasidone 80 to 160 mg/day (140 patients) with placebo (70 patients). Ziprasidone induced a significantly greater improvement in the SADS-C Mania Rating Scale compared with placebo from baseline to endpoint ($p < 0.005$), and this improvement was evident by day 2. Ziprasidone was well tolerated and effective in reducing overall psychopathology.

Relative Efficacy and Safety of Atypical Antipsychotics in Bipolar Disorder

Guille *et al*. conducted a retrospective, naturalistic analysis of the use of atypical antipsychotics as adjunctive therapy to mood stabilizers to treat manic episodes of bipolar-I disorder in 50 consecutive treatment trials (50). The treatment charts of 42 patients were reviewed for adverse effects, tolerability, and efficacy. This analysis demonstrated similar efficacy (such as the change in CGI scale score) for risperidone, olanzapine, and clozapine. Of the 42 patients, 34 (68%) experienced at least a 1-point improvement in CGI rating. Improvements in CGI rating from baseline were significant for each drug (risperidone, –1.3 points, $p < 0.0001$; olanzapine, –1.0 points, $p < 0.05$; clozapine, –1.2 points, $p < 0.01$). Treatment was generally well tolerated, and safety variables were similar among the agents, except for substantial and significant weight gain with olanzapine (>10 lb; Figure 4) For patients treated for more than 12 weeks, mean weight gain was 23.5 lb in olanzapine-treated patients compared with 3.7 lb in risperidone-treated patients ($p < 0.05$). The incidence of EPS was similar in all groups, and was seen in 29% of patients (12/42). Double-blind, randomized clinical trials are needed to further investigate the relative efficacy and safety of these drugs for the treatment of acute mania in bipolar disorder.

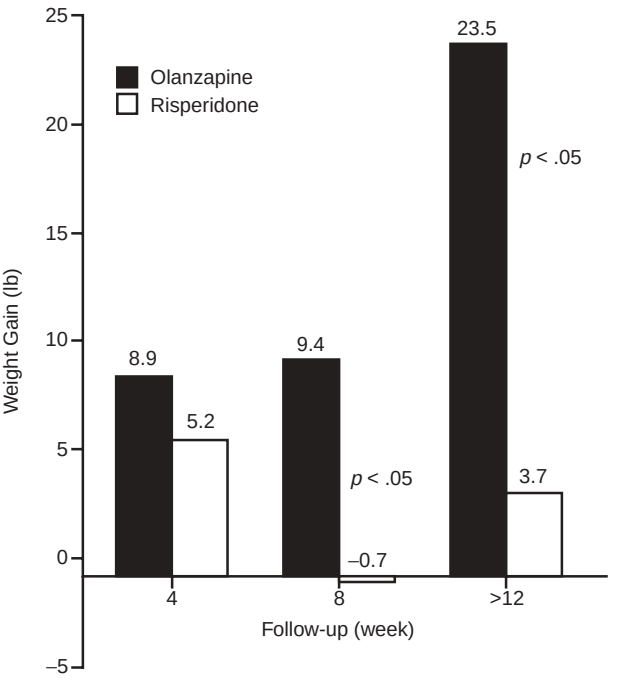

Figure 4 The use of atypical antipsychotics to treat mania of bipolar disorder: olanzapine induced substantial and significantly greater weight gain than did risperidone (50). Reprinted with permission from: Guille C, Sachs GS, Ghaemi SN: A naturalistic comparison of clozapine, risperidone, and olanzapine in the treatment of bipolar disorder. *J Clin Psychiatry* 2000; 61:638–642

DEPRESSION

Risperidone

In controlled clinical trials, risperidone improved measures of depression in patients with schizophrenia (19,51,52). An analysis of pooled data from six double-blind trials demonstrated that risperidone was more efficacious than haloperidol or placebo in alleviating affective symptoms, including each measure of symptoms indicative of mania and anxiety/depression, in 1254 patients with chronic schizophrenia (1). More specifically, improvements in the Positive and Negative Syndrome Scale (PANSS) anxious/depressive cluster (somatic concern, anxiety, guilt feelings, and depression) for all patients and for anxious/depressed patients were significantly greater at study endpoints for

Table I A Pooled Analysis of Six Controlled Studies of Risperidone Demonstrated Significant Improvements in Affective Symptoms of Schizophrenia, Including Anxiety/Depression

	All Patients		Anxious/Depressed Patients[a]	
PANSS measure: Anxiety/depression cluster (mean ± standard deviation)	Baseline	Change	Baseline	Change
Risperidone	10.0 ± 3.8	−2.1 ± 3.8	13.6 ± 2.4	−4.1 ± 4.0
Haloperidol	10.3 ± 4.0	−1.5 ± 3.7[b]	13.7 ± 2.6	−3.2 ± 3.9[c]
Placebo	11.0 ± 4.1	−0.4 ± 4.0[b]	14.0 ± 2.5	−1.7 ± 3.8[c]

PANSS = Positive and Negative Syndrome Scale.

[a]*PANSS anxiety/depression cluster score at least the median (11); risperidone, n = 304; haloperidol, n = 224; placebo, n = 48.*

[b]*$p < 0.001$ versus risperidone.*

[c]*$p < 0.01$ versus risperidone.*

Source: Peuskens J, Van Baelen B, De Smedt C, Lemmens P: Effects of risperidone on affective symptoms in patients with schizophrenia. Int Clin Psychopharmacol 2000; 15:343–349

risperidone-treated patients than for haloperidol-treated patients or patients receiving placebo (Table 1).

The long-term impact of risperidone compared with haloperidol on affective symptoms of patients with schizophrenia and schizoaffective disorder has been assessed (53). In a randomized, double-blind, multicenter trial, 365 patients were treated with risperidone ($n = 177$; mean modal dose, 4.9 ± 1.9 mg/day) or haloperidol ($n = 188$; mean modal dose, 11.7 ± 5.0 mg/day) for at least 1 year. Patients treated with risperidone experienced significantly greater improvements in the PANSS anxiety/depression cluster ($p < 0.01$) and on individual symptoms, including guilt ($p = 0.05$), anxiety ($p = 0.003$), and depressed mood ($p = 0.004$), compared with those treated with haloperidol. Interestingly, a relationship was identified between greater improvement in depression and reduced risk of relapse in risperidone-treated patients (odds ratio, 1.380; $p = 0.081$), although this link was not statistically significant. These findings support the benefit of risperidone in ameliorating symptoms of depression in schizophrenia patients treated for at least 1 year.

To assess the relative contribution of risperidone to the treatment of mood symptoms in patients with schizophrenia and schizoaffective disorder, Myers *et al*. conducted a retrospective post hoc analysis of data from an 8-week, randomized, double-blind, multicenter, prospective comparison of risperidone ($n = 188$) and olanzapine ($n = 189$) (24). Patients treated with either agent experienced clinical improvement in all measures of mood symptoms. Risperidone led to significantly greater improvements at week 8 in the PANSS anxiety/depression cluster ($p = 0.04$), individual symptoms of depression ($p = 0.025$), and grandiosity ($p = 0.037$) compared with olanzapine. Patients treated with olanzapine experienced significantly greater mean weight gain (8.6 lb) than did those treated with risperidone (4.4 lb; $p < 0.001$). Thus, risperidone may better improve affective symptoms of schizophrenia, with less weight gain, compared with olanzapine. These findings are in contrast with a post hoc analysis by Tollefson *et al*., who reported that olanzapine induced a significantly greater mean improvement in the depression cluster of the PANSS (59%) compared with risperidone (45%; $p < 0.05$) (54). Prospective, randomized, controlled clinical trials are needed to determine the true relative impact of these agents on depression in schizophrenia.

Evidence that risperidone is useful in treatment-resistant major depression was found in a small clinical trial that examined the use of risperidone to augment selective serotonin reuptake inhibitor (SSRI) antidepressants (55). Eight patients with major depressive disorder without psychotic symptoms who did not respond to an SSRI had low dosages of risperidone (0.5 to 1.0 mg) added to their SSRI regimen. Depression in all eight patients remitted within 1 week of adding risperidone. Beneficial effects on sleep disturbance and sexual dysfunction were noted as well.

Risperidone was also found to induce a rapid and sustained mood change in patients with bipolar disorder, depressed type (56). In this 12-week study, 22 patients were randomized to risperidone or risperidone plus paroxetine. Risperidone monotherapy and combination therapy resulted in rapid improvements in Montgomery-Asberg Depression Rating Scale (MADRS) scores; however, a sustained response was only reported on the Beck Depression Inventory subscale in patients who received risperidone plus paroxetine.

Olanzapine

Treatment with olanzapine has been shown to ameliorate depressive symptoms in patients with schizophrenia, schizophreniform disorder, or schizoaffective disorder (52,54,57,58). The impact of olanzapine on depressive symptoms has also been described in patients with psychotic depression and treatment-refractory depression (59,60). Recently, Shelton *et al*. examined the effect of adding olanzapine to the selective serotonin reuptake inhibitor fluoxetine in patients with treatment-resistant major depression

(60). This was an 8-week, randomized, double-blind study of 28 patients diagnosed with recurrent, nonbipolar, treatment-resistant depression without psychotic features. Patients were treated with olanzapine (range, 5 to 20 mg/day) plus placebo, fluoxetine plus placebo, or olanzapine plus fluoxetine (combination therapy). Patients entered a 6-week open-label screening phase, during which they were treated with fluoxetine in escalating doses (range, 20 to 60 mg/day), and then entered the 8-week double-blind phase. During the double-blind phase, the mean modal dose of fluoxetine was 52.0 mg/day for both fluoxetine treatment groups. The mean modal dose of olanzapine was 12.5 mg/day for the monotherapy group and 13.5 mg/day for the combination group. Combination therapy resulted in significantly greater improvements in the MADRS than did monotherapy with either agent (versus olanzapine, $p = 0.03$; versus fluoxetine, $p = 0.006$), and in significantly greater improvements in the HAM-D and CGI severity of depression subscale compared with olanzapine monotherapy ($p = 0.03$ and $p = 0.01$, respectively). Both drugs were well tolerated alone or in combination. Increased appetite and weight gain were significantly greater with olanzapine (13.35 lb for olanzapine monotherapy, $p = 0.008$ versus baseline; 14.67 lb for combination therapy, $p = 0.002$ versus baseline) than with fluoxetine monotherapy (1.94 lb).

Quetiapine

In an analysis of data from double-blind clinical trials of patients with schizophrenia, quetiapine was superior to placebo in improving negative symptoms (61,62). Although no randomized, controlled clinical trials have been published, several case studies and a naturalistic chart review (63) suggest that quetiapine may be efficacious for the treatment of depression.

Ziprasidone

Ziprasidone may improve depressive symptoms in patients with schizophrenia and schizoaffective disorder, although the doses required to elicit this effect have been associated with adverse effects, including EPS (48,64). A study of 302 patients with schizophrenia or schizoaffective disorder evaluated the impact of 80 mg/day ($n = 106$) or 160 mg/day ($n = 104$) of ziprasidone compared with placebo ($n = 92$) (65). In patients with clinically significant depression at baseline, ziprasidone 160 mg/day was associated with a significant improvement in depressive symptoms (MADRS score) compared with placebo ($p < 0.05$). However, this effect was not maintained when all treated patients were included in the analysis. The most common adverse events associated with ziprasidone were somnolence, dizziness, dyspepsia, and nausea. Extrapyramidal symptoms were reported in 7% of patients treated with 160 mg/day, but in only 1% of patients in the placebo group and in 2% of those in the 80 mg/day ziprasidone group. A more recent double-blind, placebo-controlled study of various doses of ziprasidone failed to confirm the findings of the previously described study (48). Patients received ziprasidone at 40 mg/day ($n = 16$), 80 mg/day ($n = 18$), 120 mg/day ($n = 22$), 160 mg/day ($n = 25$), or placebo ($n = 34$). Mean scores for improvement in the BPRS depressive items and the MADRS scores (for both the total cohort and patients with MADRS baseline scores of at least 14) suggested a trend toward better outcome, but were not significantly better than those observed with placebo.

CONCLUSIONS

The treatment of affective symptoms attributable to bipolar disorder and schizophrenia continues to improve with the advent of novel therapies and exploration of innovative applications of existing drugs. The atypical antipsychotics have shown activity in the treatment of affective symptoms with acceptable tolerability; however, patients who receive clozapine or olanzapine potentially should be monitored for such metabolic complications as hyperglycemia on a regular basis, particularly if they are younger than 60 years old. Future research, including controlled comparative clinical trials, will continue to define the role of these agents for these debilitating disorders. The addition of risperidone or olanzapine to treatment regimens for bipolar mania or depression associated with schizoaffective disorder may greatly improve patient outcome.

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