A Naturalistic Comparison of Clozapine, Risperidone, and Olanzapine in the Treatment of Bipolar Disorder

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Background: Our purpose was to evaluate the overall efficacy and tolerability of novel antipsychotic medications for patients with bipolar disorder type I.

Method: A retrospective study of the Massachusetts General Hospital Bipolar Clinic database was carried out to identify 50 consecutive treatment trials in patients with DSM-IV bipolar disorder type I who had received adjunctive treatment with risperidone, olanzapine, or clozapine, along with standard mood stabilizers. The treatment charts of those patients (N = 42) were reviewed for details of adverse effects, tolerability, and efficacy of medication.

Results: Overall results indicated equivalent efficacy in novel antipsychotic treatments according to change in Clinical Global Impressions scale score. Levels of extrapyramidal symptoms were similar in all groups and occurred in 12/42 patients (28.6%). Prolactin-related side effects were not observed in any patients. There were no cases of affective switch or worsening of mania. Substantial weight gain of more than 10 lb (4.5 kg) was significantly greater in patients treated with olanzapine.

Conclusion: These results suggest that the efficacy and tolerability of risperidone, olanzapine, and clozapine are similar in patients with bipolar disorder. One major differentiation factor of these drugs appears to be weight gain, particularly between olanzapine and risperidone. This may, in part, also be related to the need to use mood-stabilizing agents, like lithium or divalproex sodium, which may potentiate the weight-gain effect of novel antipsychotics.

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This naturalistic review is the first head-to-head comparison of the efficacy and tolerability of treatment with clozapine, risperidone, or olanzapine concomitant with mood stabilizers in bipolar disorder. Although antipsychotic medications appear to be beneficial for the treatment of manic episodes, the role of antipsychotic medication in the management of bipolar mood disorder has been limited largely by a concern about adverse effects, such as tardive dyskinesia and extrapyramidal symptoms (EPS). The high rates of antipsychotic use, however, suggest the perceived ongoing clinical need for this class of medication.[1] The new generation of antipsychotic agents, so-called novel antipsychotics, may offer at least equivalent efficacy with a substantially lower risk of tardive dyskinesia and EPS.[2] What remains unclear is whether there is any differential advantage of using one agent or another. This article reviews our experience with these agents and reports our findings on their efficacy and safety.

METHOD

The Massachusetts General Hospital (MGH) Bipolar Clinic database was searched to identify 50 consecutive treatment trials in which patients with bipolar disorder received at least one dose of clozapine (5 trials), risperidone (25 trials), or olanzapine (20 trials) in the absence of other antipsychotic medications. All patients were already taking standard mood stabilizers, with insufficiant response. These trials were identified in 42 patients with DSM-IV bipolar disorder type I, of whom 8 patients had multiple trials: 4 patients received risperidone and later switched to olanzapine; 2 patients received clozapine, followed by a trial of olanzapine; 2 patients received risperidone twice, and 1 of these patients had a subsequent trial of olanzapine. A chart review harvested clinical data from the systematic prospective clinical monitoring forms used routinely by clinicians in the MGH Bipolar Clinic. Data included body mass index (BMI), concomitant medications, EPS, and Clinical Global Impressions (CGI) assessment. EPS were systematically evaluated at each visit by the clinician on the basis of observation and patient self-report. The Abnormal Involuntary Movement Scale was not administered. In addition, data were collected on the

maximum novel antipsychotic dose, total duration of treatment, and maximum recorded weight during each treatment trial and at follow-up closest to week 4, week 8, and week 12. Patients were excluded from the sample if they had an unstable medical illness, abnormal thyroid-stimulating hormone level, diabetes, cancer, or surgery in the previous 6 months. Treatment outcomes were then determined on the basis of recorded changes in CGI, weight, and adverse effects. No patient was treated specifically for research purposes, and all rating scales were conducted as part of routine clinical treatment. The MGH institutional review board waived the need for informed consent since all treatment and rating scale assessments were part of routine clinical practice.

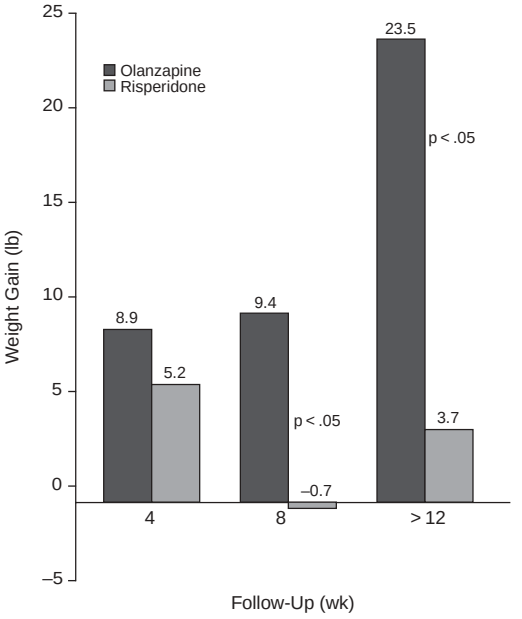
RESULTS

The mean ± standard deviation (SD) dosage was 1.7 ± 0.9 mg/day for risperidone, 11.7 ± 6.2 mg/day for olanzapine, and 210.0 ± 119.4 mg/day for clozapine. Age and gender did not differ between the groups: mean ± SD age in the risperidone group was 40.3 ± 12.2 years versus 39.8 ± 11.7 years for the olanzapine group versus 38.4 ± 14.2 years for the clozapine group; 76% (N = 19) of the risperidone group were women versus 75% (N = 15) of the olanzapine group versus 80% (N = 14) of the clozapine group. Mean baseline BMI was 26.7 ± 5.5 for risperidone, 25.5 ± 5.9 for olanzapine, and 23.3 ± 2.7 for clozapine, and baseline weight was 159.0 ± 35.4 lb (71.6 ± 15.9 kg) versus 155.9 ± 33.0 lb (70.2 ± 14.8 kg) versus 141.0 ± 26.9 lb (63.4 ± 12.1 kg) for the risperidone, olanzapine, and clozapine groups, respectively; neither measure was significantly different between the groups. No differences concerning concomitant medication were found between groups except for statistically nonsignificant increased selective serotonin reuptake inhibitor (SSRI) use in the risperidone group (12/25 vs. 4/20 vs. 2/5 in the risperidone, olanzapine, and clozapine groups, respectively; $\chi^2 = 3.82$, df = 2, p = .15).

No differences in efficacy were noted between treatment groups based on change in CGI score. During treatment trials with risperidone, olanzapine, or clozapine, 34 (68%) of the CGI ratings improved by at least 1 point. In 7 cases (14%), CGI scores stayed the same, and in 1 case (2%), CGI score increased by 1 point. Similar improvements in CGI scores from baseline visit to last visit were noted in all treatment groups (for risperidone, mean ± SD score = 4.1 ± 0.7 at baseline vs. 2.8 ± 0.9 at last visit, p < .0001; for olanzapine, mean ± SD score = 3.9 ± 0.9 at baseline visit vs. 2.9 ± 0.6 at final visit, p < .05; for clozapine, mean ± SD score = 4.6 ± 0.5 at baseline visit vs. 3.4 ± 0.5 at final visit, p < .01; all comparisons were paired t tests).

Treatment was generally well tolerated. The only severe adverse effect was one seizure in a patient taking clozapine. Six patients were unable to tolerate treatment during the first week, 4 (16%) with risperidone (sedation = 1, acute dystonia = 1, and parkinsonism = 2), and 2 (10%) with olanzapine (sedation = 1, akathisia = 1). There were no observed cases of switching to hypomania or mania.

Figure 1. Comparison of Weight Gain in Patients Taking Risperidone or Olanzapine



At any follow-up visit, EPS were reported in 12 (28.6%) of 42 subjects. Parkinsonism was noted in 4 of 25 risperidone-treated patients, 1 of 20 olanzapine-treated patients, and 1 of 5 clozapine-treated patients. Akathisia occurred in 2 of 25, 3 of 20, and 1 of 5 in the 3 groups, respectively. Only 2 patients discontinued treatment because of EPS: akathisia in 1 olanzapine-treated patient and dystonia in 1 risperidone-treated patient. Prolactin-related side effects were observed in none of the groups.

Comparing change in baseline weight with the highest weight during antipsychotic treatment, there was a mean ± SD overall weight gain of 11.2 ± 15.2 lb (5.0 ± 6.8 kg; paired t test = –5.2, p < .0001). Excluding 2 patients who received only one dose of antipsychotic, more weight gain occurred in patients treated with olanzapine (16.1 ± 13.7 lb [7.2 ± 6.2 kg]) than risperidone (7.8 ± 11.2 lb [3.5 ± 5.0 kg]; unpaired t test = –2.1, p = .03). Among the sample receiving olanzapine (N = 7) or risperidone (N = 9) for 12 weeks, olanzapine treatment resulted in even greater weight gain (23.5 ± 17.2 lb [10.6 ± 7.7 kg] with olanzapine vs. 3.7 ± 13.6 lb [1.7 ± 6.1 kg] with risperidone; unpaired t test = –2.56, p = .02) (Figure 1). Clozapine-treated patients experienced weight gain of a similar magnitude to those receiving olanzapine, but the

small sample size precluded meaningful statistical analysis. For patients' recorded last weight, 63% of the olanzapine group (12/19), compared with 33% (8/24) of the risperidone group, gained 10 lb [4.5 kg] or more (Fisher exact test, p = .069). A trend toward less weight gain among patients receiving a novel antipsychotic with lithium than those receiving other agents was observed, mainly divalproex sodium (mean ± SD = 8.4 ± 10.3 lb [3.8 ± 4.6 kg] with lithium vs. 16.5 ± 19.7 lb [7.4 ± 8.9 kg] with other mood stabilizers; unpaired t test = –1.89, p = .06).

DISCUSSION

We found that the novel antipsychotics appeared equally effective in the treatment of bipolar disorder and that there were no notable differences in EPS. Worsening of mania was not observed. Although all 3 drugs were associated with weight gain, olanzapine and clozapine were associated with substantial increase in weight compared with risperidone; no differences were noted between the groups for other side effects.

Since clozapine use is limited by the risk of aplastic anemia, seizures, sedation, and weight gain, risperidone and olanzapine have become foci of clinical interest. Over 10 early naturalistic uncontrolled studies of risperidone in bipolar disorder reported a mean weighted average antimanic/mixed response of about 60%.[2–9] All these reports reflected acute treatment. A recent large, open, 6-month outcome study[10] confirmed the earlier reports, finding risperidone (mean dose = 4.3 mg/day) to be effective in adjunctive treatment with mood stabilizers for 305 patients with bipolar and schizoaffective disorders. All patients experienced acute mania, mixed, or hypomanic episodes, and Young Mania Rating Scale (YMRS) scores improved from 24.8 at baseline to 5.2 at endpoint (p < .001), while Hamilton Rating Scale for Depression (HAM-D) scores also improved from 12.7 at baseline to 5.6 at endpoint (p < .0001). EPS were uncommon, and only 7% of the sample dropped out. Weight gain was not assessed or reported in that study.

Olanzapine, while in use for somewhat less time, also was reported to be effective in 3 separate retrospective uncontrolled reports.[11–13] A recent open, prospective, long-term study[14] also confirmed these early findings: in a 49-week open-label extension of a clinical trial of olanzapine for acute mania, 113 bipolar type I patients were followed for an average of 6.7 months while taking a mean dose of 13.8 mg/day of olanzapine. YMRS scores improved from 25.5 at baseline to 7.5 on follow-up (p < .001), and HAM-D scores improved from 12.2 to 6.5 (p < .001). Few EPS were noted. Adjunctive lithium was allowed, although the available abstract is unclear about how many patients received lithium.

Double-blind data with risperidone and olanzapine are only now becoming available. One double-blind study[15] found risperidone to be equally effective as lithium or haloperidol in the treatment of acute mania, with significant improvements in all groups. Another double-blind study[16] found olanzapine to be superior to placebo in the treatment of acute mania over 3 weeks. It is likely that both of these agents are effective in treating mania.

Both risperidone and olanzapine have been implicated in inducing mania, although this is rare and almost always associated with inadequate concomitant mood-stabilizer use or a potentiating effect from concomitant antidepressant use.[2] Neither of the large prospective 6-month outcome studies described above noted any significant risk of mania induction with these agents.

Besides improved efficacy, another benefit of using these agents in bipolar disorder may be in minimizing side effects, since novel antipsychotics have been found to be associated with fewer EPS than conventional neuroleptics in double-blind clinical trials.[17,18] However, some naturalistic reports describe continued risk of EPS. For instance, in a sample of patients treated with clozapine (N = 19), risperidone (N = 9), or conventional neuroleptics (N = 22), the incidence of akathisia was 10.5%, 11.1%, and 22.7%, respectively. Parkinsonian symptoms were reported to be 0% with clozapine, 11.1% with risperidone, and 22.7% with the conventional agents.[19] In another study, similar rates of EPS were found between patients receiving treatment with risperidone (49%) and haloperidol (48%).[20] It appears that the tendency of risperidone and olanzapine to cause EPS is dose dependent.[17,18,21,22] Thus, novel antipsychotics can still produce EPS, although typically at a lower rate than conventional neuroleptics.

As is often stated, EPS are reportedly more common and more severe in patients with affective disorders than in patients with schizophrenia. The evidence for this finding is mostly related to tardive dyskinesia.[23] The increased risk of parkinsonism or akathisia, although clinically common in patients with bipolar disorder, may need to be better established in empirical comparisons to patients with schizophrenia. In the present study, the EPS rates observed were not dissimilar to those in naturalistic studies of atypical antipsychotics in schizophrenia, although the doses we used were much lower than are commonly used in schizophrenia. The clinical finding that atypical antipsychotic dosing in bipolar disorder is about half that in schizophrenia[2] may be indirect evidence of greater susceptibility to EPS on the part of patients with bipolar disorder.

Novel antipsychotics seem to have a very low rate of tardive dyskinesia. Morgenstern and Glazer[24] reported that in the first year of treatment, about 5% of patients develop tardive dyskinesia while taking traditional neuroleptics. In the first year of treatment with atypical neuroleptic agents, much lower tardive dyskinesia rates are observed. With risperidone, 0.3% of patients developed tardive dyskinesia after 1 year of double-blind treatment

in schizophrenia clinical trials.[25] With olanzapine, a double-blind clinical trial, which included a haloperidol comparison arm, produced a 1-year tardive dyskinesia rate of 1.0% with olanzapine (N = 707) versus 4.6% with haloperidol (N = 197).[26]

Besides EPS and tardive dyskinesia, one of the major side effects of the newer antipsychotics is weight gain. Significant weight gain can increase the long-term risk for cardiovascular morbidity and mortality.[27] Patient compliance is also an important issue for clinicians when choosing an antipsychotic medication, especially for a patient who is concerned about weight gain. Although clozapine has the highest propensity for weight gain (average = 9–27 lb [4–12 kg]), this problem is also found among patients taking risperidone or olanzapine. The literature suggests that patients who experience weight gain as a side effect will do so during the first 12 weeks of treatment. On average, patients gain 2–8 lb (0.9–3.6 kg) over the first 6 to 8 weeks of treatment.[28] A recent study[29] found more weight gain with clozapine and olanzapine compared with other atypical antipsychotics in patients with schizophrenia.

The mechanism of weight gain with atypical antipsychotics has been discussed mainly in terms of blockade of histamine-1 (H_1) antagonism rather than serotonin-2C ($5\text{-}HT_{2C}$) receptors. H_1 blockade has a long-known association with weight gain, and clozapine and olanzapine have significant H_1 blockade, while risperidone does not.[30] Recent interest in an association with $5\text{-}HT_{2C}$ receptors and weight gain derives from findings that mutant mice genetically engineered to "knockout" $5\text{-}HT_{2c}$ receptors are obese.[31] Olanzapine has more $5\text{-}HT_{2C}$ blockade than clozapine and much more than risperidone.[30] β_3-Adrenergic receptors have also been associated with weight; a genetic variant of this receptor is associated with hereditary obesity in Pima Indians.[31] Thus, the biochemical basis for weight gain is complex. Interestingly, in the Wirshing et al. study,[29] atypical antipsychotic weight gain was related more to H_1 blockade than to $5\text{-}HT_{2C}$ blockade.

The relationship between concomitant medication and weight gain with atypical antipsychotics is also raised by the present study. We found that the combination of divalproex and atypical antipsychotics caused more weight gain than did the combination with lithium. Stanton[32] reported that concomitant medication did not predict weight gain in bipolar disorder, however. The specific mechanisms of interaction between mood stabilizers and atypical antipsychotics relating to weight gain are unclear, especially given the limited synaptic activity of mood stabilizers. This is an area of research that needs further investigation.

Another concern in using novel antipsychotics is increased prolactin levels. However, no prolactin side effects were observed in any of the groups in this study.

Our side effect data are consistent with observations of these drugs in samples of patients with schizophrenia. The observed incidence of EPS was low, and prolactin-related side effects were not observed. While parkinsonian EPS were somewhat more common with risperidone than with the other agents, SSRI use was also greater in the risperidone-treated group. Since SSRIs have been found to be associated with EPS,[33] and risperidone is metabolized by the hepatic cytochrome P450 enzymes,[34] which could explain interactions with SSRIs, their concomitant use may have influenced the observed EPS rates in this study. However, weight gain appeared to be a substantial problem, with a mean weight gain of 11.2 lb (5.0 kg). This appears to be a greater burden than the average gain of 2 to 8 lb reported for patients with schizophrenia[28] and may reflect the interaction between novel antipsychotics and other medications known to promote weight gain. The trend for less weight gain in patients already maintained with lithium raises the possibility that the weight gain produced by the other agents may have a common mechanism. Notably, weight gain was significantly greater in patients treated with olanzapine than in those taking risperidone.

While this sample consisted of adult patients with type I bipolar disorder, it might be asked what evidence exists for the effectiveness and safety of atypical antipsychotics in type II bipolar disorder. In our experience, since those patients suffer from severe depression, atypical antipsychotics are less useful than in patients with type I bipolar disorder. Although there is some evidence for antidepressant effects with atypical antipsychotics, their antimanic effects appear more prominent.[2] However, in adolescents with bipolar disorder (type I or type II), the use of standard mood stabilizers is often compromised by increased toxicity risks (e.g., valproate-related hepatotoxicity) and decreased lithium response (due to early age at onset, presence of mixed episodes, comorbid substance abuse). In these patients, atypical antipsychotics may be better tolerated and provide antimanic benefits.[35] Empirical research is needed to increase our awareness in these populations.

Limitations

This study poses a number of limitations. First, it was limited by the small sample size; therefore, comparisons of EPS and prolactin-related side effects may reflect type II error. Second, this study relied on patients' self-report of weight and prolactin-related side effects, both of which are not always reported accurately. Third, the use of concurrent medication may have obscured the actual amount of weight gain caused by the antipsychotic medication. Fourth, treatment choice was nonrandomized and unblinded.

CONCLUSION

Novel antipsychotics appeared equally effective in treating patients with bipolar disorder. They produced similar rates of EPS and other side effects, with the excep-

tion of weight gain, which was more prominent with olanzapine. Since patients with bipolar disorder require mood stabilizers that often produce weight gain, the addition of novel antipsychotics with this side effect can exacerbate this problem. Future studies would benefit by having a larger sample with prospective controlled data.

Drug names: clozapine (Clozaril and others), divalproex sodium (Depakote), haloperidol (Haldol and others), olanzapine (Zyprexa), risperidone (Risperdal).

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