Long–Term Observational Comparison of Risperidone and Olanzapine in Bipolar Disorder

S. NASSIR GHAEMI, M.D., DOUGLAS J. HSU, B.S., and KLARA J. ROSENQUIST, B.S.
Bipolar Disorder Research Program, Cambridge Health Alliance, Cambridge, Massachusetts and Department of Psychiatry, Harvard Medical School, Boston, Massachusetts, USA

JACOB J. KATZOW, M.D., and FREDERICK K. GOODWIN, M.D.
Department of Psychiatry, George Washington University School of Medicine, Washington, DC, USA

To compare long-term effectiveness and safety of risperidone versus olanzapine as adjunctive maintenance treatments of bipolar disorder. Retrospective observational chart review of 29 outpatients with bipolar or schizoaffective disorder (type I = 15, type II = 3, NOS = 5, schizoaffective = 6) who received risperidone or olanzapine added to lithium or valproate >3 months. Acute indications were depression (n = 8), manic/hypomanic/mixed states (n = 8), rapid cycling (n = 6), other indications (n = 6), and prophylaxis (n = 1). Logistic regression models adjusted for potential confounding factors (i.e., severity of illness, comorbid substance abuse, diagnostic subtype). Overall duration of follow-up was 65.9 ± 70.1 weeks. Mild to moderate response was similar in the risperidone and olanzapine groups after adjusting for potential confounders (OR = 0.91, 95% CI [0.05, 16.17]). Somewhat greater adjusted moderate to marked response (OR >3.60, 95% CI [0.31, >42.00]) and longer duration of treatment (HR = 0.52, 95% CI [0.22, 1.22]) occurred in the risperidone group, but were still compatible with the null hypothesis. Weight gain occurred more frequently with olanzapine (57%) than risperidone (13%). EPS was similar, and tardive dyskinesia did not occur. Risperidone and olanzapine appeared to have similar real-world maintenance effectiveness for bipolar disorder, but differed somewhat in side effects.

Keywords Bipolar disorder; Drug therapy; Risperidone; Olanzapine; Maintenance; Prophylaxis.

INTRODUCTION

Among atypical neuroleptics, risperidone and olanzapine are probably the most frequently used in bipolar disorder (1). However, most of the available data with these agents involve short-term acute mania studies.

We provide long-term observational data meant to augment the clinical trial data. As is well known in epidemiology (2,3), clinical trials provide evidence of validity; that is, whether or not an agent is effective pharmacologically. They do so, however, at the price of a small homogeneous sample (weed out by willingness to participate in randomized experiments as well as extensive clinical exclusion criteria). Based on clinical trials, we know that both risperidone and olanzapine are effective in acute mania, and that olanzapine may also have some long-term maintenance benefits in some patients. However, the generalizability of these clinical trial results to real-world samples of patients needs to occur with observational samples. In other words, once the validity of an agent is shown in clinical trials, the extent of that validity must be assessed in observational studies. The direct comparison of agents, in particular, must occur in the same sample. While clinicians often want to know about relative strengths and weaknesses when two agents, such as risperidone and olanzapine, are compared to each other, randomized studies of such comparisons rarely occur, partly because they are not required for FDA registration. Further, one cannot compare results from separate randomized trials (such as the side effect rates of olanzapine...
in one study versus the side effect rates of risperidone in another study) without committing the “apples and oranges” error: different samples will have different results because of differences between the samples.

In this study, we provide data about the generalizability of clinical trial data to real-world bipolar populations (with extension of those data to long-term outcomes), and we provide direct comparisons of these two agents in the same sample.

We further emphasize long-term outcomes because such data are especially relevant to the question of whether all or some of these agents are mood stabilizers (4,5). This debate in part rests on differences of opinion regarding the definition of a mood stabilizer (6,7). As one of us has suggested (6), a middle-of-the road definition would be that a mood stabilizer would have acute efficacy for at least one phase of bipolar disorder (mania or depression), as well as prophylactic efficacy for mood episodes (mania and depression). The inclusion of prophylactic efficacy is often recognized as an important feature of mood stabilization (7,8). To date, only lithium and lamotrigine have been demonstrated to show preventative benefits in bipolar disorder in controlled studies (8,9). Long-term data with atypical neuroleptics are suggestive and promising, but not definitive partly because those data are either uncontrolled or not placebo-controlled (10–13).

The long-term treatment of bipolar disorder also introduces a different set of concerns regarding side effects with atypical neuroleptics (14). Most extrapyramidal symptoms are by definition acute, with tardive dyskinesia being the main long-term risk (15). Weight gain appears to be more of a problem in up to one year of follow-up in the same studies, as opposed to in the first weeks (16). Sedation and cognitive side effects may also pose subtle but notable difficulties in long-term occupational functioning.

METHODS

A waiver of consent was obtained from the Cambridge Health Alliance IRB for this chart review. Charts of all patients treated by SNG and IJK in two university-affiliated outpatient psychopharmacology clinics were reviewed to identify all patients receiving adjunctive risperidone (RIS) or olanzapine (OLZ) treatment for greater than 3 months between May 1994 and July 2001. 29 outpatients met DSM-IV criteria for bipolar or schizoaffective disorder (15 received risperidone, and 14 received olanzapine) and were treated for depression (n = 8), manic/mixed/hypomanic states (n = 8), rapid cycling (n = 6), other indications (n = 6), and prophylaxis (n = 1). Diagnoses were as follows: 15 bipolar type I, 3 bipolar type II, 5 bipolar NOS, and 6 schizoaffective disorder, bipolar type. Patients received open adjunctive treatment of either risperidone or olanzapine for at least 3 months, added to their maintenance mood-stabilizing medications (lithium, valproic acid, and/or carbamazepine). All patients were treatment refractory since they had failed to respond to at least one mood-stabilizing agent, alone or in combination with other mood-stabilizing agents.

Charts were reviewed for the following clinical and demographic variables: age, sex, bipolar diagnostic subtype, concurrent medications, mood stabilizer use and dosage, previous use of risperidone or olanzapine, evidence regarding whether mania was induced, adverse events, weight gain, current substance abuse, risperidone/olanzapine dose and duration of treatment, indications for treatment with risperidone/olanzapine, discontinuation of risperidone/olanzapine and reason for discontinuation. Weight gain was recorded based on patient report, and subjects were identified as having gained weight if they gained ≥5 pounds at last assessment and this weight gain was considered clinically likely to be related to the neuroleptic.

Clinical response was based on chart review using the Clinical Global Impression of Improvement scale (CGI-I), which rates improvement as follows: 1 = marked improvement, 2 = moderate improvement, 3 = mild improvement, 4 = no change, 5 = mild worsening, 6 = moderate worsening, and 7 = marked worsening. Clinical response was rated retrospectively at date of chart review.

Statistical analyses for discrete variables including effect estimates are reported as proportional response rates with 95% confidence intervals (CI). Risk ratios (RR) are reported for comparison of clinical and demographic characteristics. Using a logistic regression model in order to control for potential confounders, odds ratios and 95% confidence intervals are reported. We adjusted for covariates which either appeared imbalanced (see Table I) or based on a priori judgment of potential confounding impact. We assessed different regression models for evidence of confounding effects, but limited our final model to 3 covariates due to the limited sample size. Our final model adjusted for severity of illness (based on the Clinical Global Impression–Severity Overall (CGI-S) scale), diagnostic subtype, and substance abuse. Cox regression analysis was used to assess length of risperidone or olanzapine treatment, again adjusted for the above covariates.

All statistical analyses were carried out with Intercooled-Stata 7.0 (2001) software (Stata Corp., College Station, TX).

RESULTS

Baseline clinical and demographic characteristics are reported in Table I. Potential imbalances in the two treatment groups appeared to exist in severity of illness (somewhat less overall in the RIS group), substance abuse (more in the RIS group), and diagnostic subtype (somewhat more bipolar type I illness in the RIS group). These potential confounding covariates were included in regression models.
The mean age of the study sample was 42.3 ± 12.0 (range 23–66) years, with 15 males and 14 females. The mean maintenance dose of risperidone was 2.0 ± 1.8 mg/day for a mean duration of 87.5 ± 87.5 (range 13–300) weeks. The mean maintenance dose of olanzapine was 8.0 ± 4.4 mg/day for a mean duration of 42.9 ± 35.0 (range 12–130) weeks. Overall duration of follow-up was 65.9 ± 70.1 (range 12–300) weeks.

Mild to moderate response was similar in both the risperidone (73.3%, 11/15) and olanzapine (71.4%, 10/14) groups (OR = 1.1, 95% CI [0.22, 5.61]), and remained so after adjustment for potential confounders (OR = 0.91, 95% CI [0.05, 16.12]).

In the full regression model, the main predictor of response was severity of illness (OR = 0.065, 95% CI [0.005, 0.81], which is interpretable as meaning for every point increase in severity of illness in the CGI-S scale, there is markedly decreased likelihood, with an odds ratio of 0.06, of mild or better treatment response).

Moderate to marked response was greater in the risperidone (26.7%, 4/15) than olanzapine (0/14) groups (OR > 4.73, 95% CI [0.46, >48.77]), though the variability of the data are still compatible with the null hypothesis. Adjustment for potential confounders did not alter these results notably (OR > 3.60, 95% CI [0.31, 42.00]).

Cox regression analysis of duration of treatment suggests longer treatment in the risperidone than the olanzapine group (HR = 0.50 ± 0.20, 95% CI [0.23, 1.09]) and remained so after adjustment for potential confounders (HR = 0.52 ± 0.23, 95% CI [0.22, 1.22]), but again the variability of these data do not rule out the null hypothesis.

Medication was stopped in 67% (19/29) of patients. Side effects were cited as the major cause of medication termination in the olanzapine group (8/10, 80% of the patients that discontinued olanzapine) while lack of efficacy was the major cause of medication termination in those patients in the risperidone group (5/9, 56% of the patients that discontinued risperidone). Seven patients had received prior treatment with either olanzapine (n = 3) or risperidone (n = 4) but had discontinued due to inefficacy or side effects. Of risperidone non-responders, 3/4 experienced mild improvement and 0/4 marked improvement with olanzapine. Of olanzapine non-responders, all 3 experienced at least mild improvement, and 2/3 moderate to marked improvement with risperidone. 5/29 (20%) reported no adverse effects (4/15, 27%, with risperidone and 1/14, 7%, with olanzapine; RR = 3.73, 95% CI [0.47, 29.49]). The most commonly reported side effect was sedation, occurring somewhat more in the risperidone

### Table I  Comparison of Baseline Clinical and Demographic Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Risperidone (n = 15)</th>
<th>Olanzapine (n = 14)</th>
<th>Mean differencea</th>
<th>95% Confidence intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>41.9 ± 13.3 (range 23–66) years</td>
<td>42.9 ± 11.0 (range 25–60) years</td>
<td>0.99</td>
<td>−8.33, 10.31</td>
</tr>
<tr>
<td>CGI-Severity overall</td>
<td>4.6 ± 0.63 (range 4–6)</td>
<td>4.38 ± 1.19 (range 3–7)</td>
<td>−0.22</td>
<td>−0.94, 0.51</td>
</tr>
<tr>
<td>CGI-Severity mania</td>
<td>4.13 ± 0.92 (range 3–6)</td>
<td>3.54 ± 1.13 (range 2–6)</td>
<td>−0.59</td>
<td>−1.39, 0.20</td>
</tr>
<tr>
<td>CGI-Severity depression</td>
<td>3.67 ± 0.90 (range 2–5)</td>
<td>3.92 ± 1.13 (range 2–7)</td>
<td>0.26</td>
<td>−0.61, 1.12</td>
</tr>
<tr>
<td>Sex</td>
<td>8 female</td>
<td>6 female</td>
<td>Risk Ratioa</td>
<td>1.24b</td>
</tr>
<tr>
<td>Diagnostic subtype</td>
<td>7 male</td>
<td>8 male</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BP I</td>
<td>9 BP I</td>
<td>6 BP I</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BP II</td>
<td>1 BP II</td>
<td>2 BP II</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BP NOS</td>
<td>2 BP NOS</td>
<td>3 BP NOS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S/A</td>
<td>3 S/A</td>
<td>3 S/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute indication</td>
<td>4 depression</td>
<td>4 depression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mania</td>
<td>5 mania/mixed/hypomania</td>
<td>3 mania/mixed/hypomania</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rapid Cycling</td>
<td>2 rapid cycling</td>
<td>4 rapid cycling</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>3 Other</td>
<td>3 Other</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current substance abuse</td>
<td>20.0%</td>
<td>7.1%</td>
<td>2.80</td>
<td>0.33, 23.86</td>
</tr>
<tr>
<td>Concurrent mood stabilizer use</td>
<td>100%</td>
<td>100%</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Concurrent antidepressant use</td>
<td>73.3%</td>
<td>64.3%</td>
<td>1.14</td>
<td>0.69, 1.87</td>
</tr>
<tr>
<td>Concurrent other anticonvulsant use</td>
<td>46.7%</td>
<td>50.0%</td>
<td>0.93</td>
<td>0.44, 1.98</td>
</tr>
</tbody>
</table>

aAll mean differences and risk ratios describe the risperidone group as the reference group.
bDescribes reference as female.
group (9/15, 60%) than the olanzapine group (5/14, 36%; RR = 1.68, 95% CI [0.74, 3.80]). Weight gain also occurred with both medications although it was over four times more frequent with olanzapine than with risperidone (8/14, 57%, vs. 2/15, 13%, respectively; RR = 4.29, 95% CI [1.09, 16.83]). Mean weight gain for olanzapine patients was 11.5 ± 13.3 lbs. Amount of weight gain was not recorded for risperidone patients. Both medications had similar rates of extrapyramidal symptoms (3/15, 20%, with risperidone vs. 2/14, 14%, with olanzapine; RR = 1.07, 95% CI [0.17, 6.61]). Tardive dyskinesia was not observed in any patient.

**DISCUSSION**

In general, we found risperidone and olanzapine to have similar modest adjunctive mood-stabilizing benefits in the long-term preventative treatment of bipolar disorder when added to mood stabilizer. There was a suggestion that the risperidone group stayed in treatment somewhat longer. The two agents differed in side effects, with olanzapine leading to more weight gain and risperidone to more sedation. They did not differ notably in extrapyramidal symptoms.

Our data are adjusted for potential confounding factors, particularly severity of illness, comorbid substance abuse, and diagnostic subtype. Of these, severity of illness was the main independent predictor of outcome. After adjusting for these factors, risperidone and olanzapine did not differentiate in their impact on outcome.

In the only other long-term comparison of risperidone and olanzapine, there were similar outcomes with the two agents, although that observation did not adjust for potential confounders such as severity of illness (17).

Differences in side effects were noted. Weight gain was a problem, more so with olanzapine, while, somewhat surprisingly, sedation was more of a problem with risperidone. Such side effect rates are notable especially given the relatively low doses of these agents used. The doses of risperidone and olanzapine used are consistent with naturalistic studies of adjunctive therapy as well as current pharmacy data (18), though lower than monotherapy clinical trials (1,19).

Interestingly, EPS rates did not differ between the groups. The absence of tardive dyskinesia is reassuring and agrees with clinical trial data in schizophrenia (20,21).

**Limitations of the Current Study**

The main limitation of any observational report is confounding bias. We adjusted for those potential confounders which we could identify in a multivariable logistic regression model. However, other confounding factors which were not identified, or for which we did not have data, cannot be ruled out. In general, such observational data augment, rather than replace, the more rigorous data obtained from randomized clinical trials. The goal of this study was primarily to assess the generalizability of clinical trial data, not to directly prove the validity of any hypotheses. Further, this retrospective chart review is also limited by the small sample size, which provides for the potential of type II error when employing multiple p-value cut-off comparisons. We thus did not analyze the data with hypothesis testing techniques, but simply provide the results descriptively, with effect sizes and confidence intervals, so that readers can interpret the results on their own, and so that these data might serve as pilot evidence for larger projects.

Treatment discontinuation did not occur due to recovery on the atypical neuroleptic with a clinical decision to stop treatment after recovery. It was our practice to continue atypical neuroleptics as putative mood-stabilizing agents unless lack of response or intolerable side effects necessitated discontinuation. Treatment response was assessed retrospectively by chart review, and was limited to available recorded data. However, these patients were well known to the investigators (SNG and JJK) and had been followed clinically by them for a long time. Further, weight gain was only assessed by patient report and amount of weight change was not recorded in all patients, especially in the risperidone group. Future studies should objectively assess weight gain.

**CONCLUSIONS**

Both risperidone and olanzapine appeared largely similar in observational long-term effectiveness in bipolar disorder, after adjusting for severity of illness and other confounding factors. They differed in side effects, with more sedation with risperidone and more weight gain with olanzapine, but they did not differ in extrapyramidal symptoms.

**REFERENCES**
