Comparative Efficacy of Typical and Atypical Antipsychotics as Add-On Therapy to Mood Stabilizers in the Treatment of Acute Mania

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Background: Typical antipsychotics are commonly used in combination with mood stabilizers for acute mania. Although typical antipsychotics are effective, they have undesirable side effects such as induction of depressive symptoms and tardive dyskinesia. Atypical antipsychotics have more favorable side effect profiles, and recent evidence shows their efficacy in treating mania. Apart from a previous small study that compared risperidone with typical neuroleptics as add-on therapy to mood stabilizers, no studies to date have directly compared atypical antipsychotics with typical antipsychotics as add-on therapy to mood stabilizers in a clinically relevant, naturalistic setting.

Method: This study is a chart review of all patients with DSM-IV–defined bipolar disorder, current episode mania (N = 204), admitted to the University of British Columbia Hospital during a 30-month period. Patients were separated into 3 groups according to the medications used: (1) mood stabilizer and typical antipsychotic, (2) mood stabilizer and atypical antipsychotic, and (3) combination: mood stabilizer plus a typical antipsychotic, then switched to mood stabilizer plus risperidone or olanzapine within 1 week. The atypical group was further subdivided into risperidone and olanzapine subgroups. Outcome was measured using Clinical Global Impressions-Severity of Illness (CGI-S) and -Improvement (CGI-I) ratings generated by review of clinical information in the chart.

Results: Patients treated with typical antipsychotics were more severely ill at admission and at discharge than those treated with atypical antipsychotics. Patients in the atypical ($p < .005$) and combination ($p < .05$) groups showed significantly greater clinical improvement at discharge than patients treated with typical antipsychotics. This difference was also significant in the subset of patients with psychotic features ($p < .03$). Risperidone and olanzapine were associated with fewer extrapyramidal side effects than were typical antipsychotics (risperidone vs. typical antipsychotics, $\chi^2 = 8.72$, $p < .01$; olanzapine vs. typical antipsychotics, $\chi^2 = 16.9$, $p < .001$).

Conclusion: Due to their superior effectiveness and side effect profile when compared with typical antipsychotics, atypical antipsychotics are an excellent choice as add-on therapy to mood stabilizers for the treatment of patients with mania.

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Mood stabilizers such as lithium or valproic acid are used as first-line therapy for treatment of acute mania.[1,2] However, surveys of treatment practices for acute mania suggest that up to 90% of patients with acute mania are treated with a combination of both mood stabilizers and antipsychotics.[3–5] Often, typical antipsychotics are used. The advantages of using typical antipsychotics in the treatment of mania include the fact that they have proven antimanic properties[6] and are available in an intramuscular injectable form for behavioral control when needed in the acute emergency setting. However, typical antipsychotics have undesirable side effects, such as induction of depressive symptoms, extrapyramidal side effects (EPS), and a long-term risk of tardive dyskinesia (TD).[7,8] The risk of TD is particularly important to consider when treating mania, since studies suggest that the prevalence of TD is higher in patients with bipolar disorder compared with those with schizophrenia.[9–11]

Atypical antipsychotics, such as risperidone and olanzapine, may be better alternatives. Unlike the typical antipsychotics, they have a more favorable side effect profile with fewer EPS and less long-term risk of TD.[12–15] In addition, recent open studies and case series indicate that atypical antipsychotics not only do not induce depressive symptoms but in fact may be useful in treating depressive symptoms in bipolar patients.[16,17] Furthermore, recent double-blind, controlled studies[18–21] have shown risperidone (in combination with mood stabilizers) and olanzapine (both alone and in combination with mood stabilizers)

to be effective in the treatment of acute mania. However, as with all double-blind, randomized trials, these data may be subject to selection bias (volunteer bias, severity bias) and limitations due to exclusion criteria. For example, patients with severe illness are routinely excluded from double-blind clinical trials due to their inability to give informed consent. Also, patients with comorbid medical and psychiatric conditions, including substance abuse, are commonly seen in clinical practice, and such patients are often excluded from these trials. The result is that formal ascertainment of efficacy of medications is conducted in a very specific population, and this poses problems in generalizing the data to all patients seen in clinical practice.

The purpose of this study, therefore, was to compare the efficacy of atypical antipsychotics with that of typical antipsychotics as add-on therapy to mood stabilizers for treatment of mania in a "real-world" population. To achieve this objective, we reviewed the charts of all patients who were treated for a manic episode at a university teaching hospital during a 30-month period.

METHOD

A retrospective chart review was done, surveying charts of patients admitted to the University of British Columbia (UBC) Hospital with a DSM-IV–defined diagnosis of bipolar disorder, current episode mania, during a 30-month period (Nov. 1, 1997, to April 30, 2000). Since the focus of this study was to compare typical with atypical antipsychotics as add-on therapy to mood stabilizers, patients not treated with these medications were excluded.

The information contained in the UBC Hospital charts was quite detailed, since most patients were followed by psychiatry residents and/or senior medical students. A form was developed to summarize the pertinent information from each chart, including demographic data (age, gender), length of illness prior to admission, number of previous episodes, presence or absence of psychotic features, development of EPS, length of stay in hospital, and medications used at 3 points during treatment: week 1, week 2, and discharge. Data that were equivocal or unavailable were excluded on a case-by-case basis. Medication decisions were made independently by the treating psychiatrists. Patients were divided into 3 groups according to the medications used: (1) mood stabilizer plus typical antipsychotic, (2) mood stabilizer plus atypical antipsychotic (this group was further divided into 2 subgroups, mood stabilizer plus risperidone and mood stabilizer plus olanzapine), and (3) mood stabilizer plus a combination of typical and atypical antipsychotics. The combination group was composed of patients treated initially with a mood stabilizer plus a typical antipsychotic, then changed to a mood stabilizer plus risperidone or olanzapine within the first 7 days of treatment.

Outcome Measures

Patients were compared in terms of length of stay, development of EPS, Clinical Global Impressions-Severity of Illness (CGI-S)[22] score at admission and at discharge, and Clinical Global Impressions-Improvement (CGI-I)[22] score at week 1, week 2, and discharge. A subset analysis of CGI-I scores at week 1, week 2, and discharge was done using patients who had mania with psychotic features. Patients were considered to have psychotic features if it was noted in the clinical chart that they experienced delusion(s), hallucination(s), or both.

The CGI scores were obtained by reviewing the psychiatrists', residents', medical students', and nurses' notes. All ratings were done by a single investigator (D.S.M.). In rating the CGI-S scores, some objective measures were used. Patients who were admitted to the hospital voluntarily were given a rating of 4 (moderately ill) or less. Patients committed involuntarily were rated as 5 (markedly ill). Patients who required several days of confinement to a seclusion room were rated as 6 (severely ill), and patients referred to the tertiary psychiatric hospital intensive care unit (at Riverview Hospital, Coquitlan, British Columbia) received scores of 7 (most severely ill). At discharge, patients who were symptom free received a score of 1 (not mentally ill), those who had a few residual symptoms received a score of 2 (borderline mentally ill), and those who had several ongoing symptoms received a score of 3 (mildly ill) or 4 (moderately ill). The CGI-I ratings were done in comparison to the patients' own baseline severity of symptoms, ranging from scores of 1 (very much improved) to 7 (very much worse).

The presence or absence of EPS was also recorded. EPS were scored as either present (any mention of stiffness/rigidity/dystonia/parkinsonism in either nursing notes or physician notes) or absent in all charts reviewed. Since we found it difficult to ascertain the presence or absence of akathisia from chart notes, we did not include akathisia in our definition of EPS.

Data Analysis

Statistical analysis was conducted using the Statistical Package for the Social Sciences (SPSS) for Windows. Analysis of variance, the Friedman test (for within-subject CGI-I comparisons), the Kruskal-Wallis test (for between-group CGI-S and CGI-I comparisons), and the chi-square test were used for data analysis. Where significant results were obtained, appropriate post hoc tests such as t tests or Mann-Whitney U tests with Bonferroni corrections were used for comparing subgroups.

RESULTS

Between November 1, 1997, and April 30, 2000, 204 patients were admitted to the hospital with a diagnosis of bipolar disorder, current episode mania. Of these, 155

patients were included in the study. Patients treated with mood stabilizers alone (N = 17), benzodiazepines alone (N = 3), or antipsychotics alone (N = 5) were excluded from the study, as were patients whose medication regimen was too complex to fit into one of the categories described below (N = 15). Patients treated with new or experimental atypical antipsychotics (ziprasidone and quetiapine) were excluded as well, due to the very small number of subjects treated with these drugs (N = 5). Two patients were treated with electroconvulsive therapy and were excluded, and 2 patients were transferred to another facility within 2 days of admission.

Of the 155 patients included in the study, 69 (45%) were treated with a mood stabilizer plus a typical antipsychotic, 69 (45%) were treated with a mood stabilizer plus an atypical antipsychotic (44 [28%] with risperidone, 25 [16%] with olanzapine), and 17 (11%) were treated with a mood stabilizer plus a combination of antipsychotic medication (typical antipsychotic initially, then changed to atypical antipsychotic).

Demographic Data

There were no significant differences in gender ($\chi^2 = 0.866$, df = 3, p =. 83), presence of a comorbid Axis I diagnosis ($\chi^2 = 6.57$, df = 3, p = .09), or presence of a comorbid Axis II diagnosis ($\chi^2 = 3.34$, df = 3, p =. 34) between the groups. There was no significant difference in patient age (F = 0.181, p = .909) or number of previous episodes (F = 0.471, p = .703). A significant difference was found when the duration of illness prior to admission was compared (F = 2.726, p < .05). Post hoc analysis showed that the patients treated with risperidone had a longer duration of illness prior to admission than those treated with typical antipsychotics (p ≤ .05). No other significant differences were found. Table 1 shows further details.

Table 1. Demographics and Axis I and II Comorbidity Comparisons Between Groups[a]

Variable	MS + Atypical Antipsychotic (N = 69)	MS + Typical Antipsychotic (N = 69)	MS + Combination[b] (N = 17)
Age, mean (SD), y	39.72 (14.50)	40.86 (16.11)	41.06 (18.08)
Duration of illness prior to admission, mean (SD), wk	5.39 (5.65)	3.49 (3.07)	3.43 (2.71)
No. of previous episodes, mean (SD)	2.72 (2.80)	3.13 (1.51)	3.00 (1.46)
Duration of hospital stay, wk	27 (18)	31 (24)	29 (15)
Gender, N (%)			
Female	37 (53.62)	32 (46.38)	9 (52.94)
Male	32 (46.38)	37 (53.62)	8 (47.06)
Comorbid Axis I diagnosis, N (%)			
Present	21 (30.43)	30 (44)	8 (50)
Absent	48 (69.57)	39 (56)	8 (50)
Comorbid Axis II diagnosis, N (%)			
Present	13 (18.84)	21 (30)	5 (31)
Absent	56 (81.16)	48 (70)	11 (69)

[a]Abbreviation: MS = mood stabilizer.
[b]Patients treated with a typical antipsychotic, then switched to an atypical antipsychotic within 1 week of admission. For 1 patient receiving MS + combination therapy, it was not possible to establish with confidence whether Axis I or II comorbidity was present.

Comparison of Severity of Illness Between Groups

All groups of patients were less severely ill at discharge than at admission. The differences between groups in CGI-S score at admission and at discharge were significant ($\chi^2 = 23.17$, df = 2, p < .001 and $\chi^2 = 14.42$, df = 2, p < .001, respectively). Post hoc testing revealed that the patients treated with atypical antipsychotics were significantly less ill at admission than those treated with typical antipsychotics or a combination of typical and atypical antipsychotics (Mann-Whitney U = 1439, Z = –4.43, p < .001 and Mann-Whitney U = 321, Z = –3.25, p < .005, respectively). No other significant differences were found. When the subgroups were compared, no significant difference was found between the risperidone and olanzapine groups.

When differences in CGI-S score at discharge were compared, patients treated with atypical antipsychotics were significantly less ill than those treated with typical antipsychotics (Mann-Whitney U = 1401, Z = –3.84, p < .001). When the subgroups were examined, there was no significant difference between the risperidone, olanzapine, and combination groups. However, patients treated with risperidone were found to be significantly less ill at discharge than those treated with typical antipsychotics (Mann-Whitney U = 719, Z = –4.35, p < .005).

Since there were significant differences in CGI-S scores at baseline between patients who received typical antipsychotics and those who received atypical antipsychotics, we also computed changes in CGI-S scores from baseline to endpoint for each group. When changes in CGI-S scores were compared among the 3 groups, no significant differences were detected ($\chi^2 = 0.33$, df = 2, p = 0.84).

Comparison of Improvement Between Groups

As shown in Table 2, all groups improved during the course of the hospitalization. The differences in improvement (measured by the CGI-I) between groups were significant at week 1 ($\chi^2 = 6.53$, df = 2, p <. 05) and at discharge ($\chi^2 = 16.47$, df = 2, p <. 001). At discharge, patients treated with atypical antipsychotics (Mann-Whitney U = 1423, Z = –3.82, p < .005) or a combination of typical and atypical antipsychotics (Mann-Whitney U = 345, Z = –2.53, p < .05) showed significantly more improvement than those treated with typical antipsychotics. Analysis of the atypical antipsychotic subgroups showed no significant difference between patients treated with risperidone or olanzapine. Patients treated with ris-

Table 2. Clinical Global Impressions-Improvement and -Severity of Illness and Extrapyramidal Side Effects (EPS) Comparison Between Groups[a]

Value	MS + Atypical Antipsychotic (N = 69)[b]	MS + Typical Antipsychotic (N = 69)	MS + Combination[c] (N = 17)
Clinical Global Impressions-Severity of Illness score, mean (SD)			
Admission	4.70 (0.65)[d]	5.36 (0.89)	5.29 (0.59)
Discharge	1.79 (0.79)[e]	2.55 (1.34)	2.59 (2.37)
Clinical Global Impressions-Improvement score, mean (SD)			
Week 1	2.75 (0.90)	3.59 (3.79)	2.73 (0.70)
Week 2	2.39 (0.96)	2.79 (1.16)	2.23 (0.60)
Discharge	1.59 (0.58)	2.04 (0.73)	1.56 (0.63)[f]
Developed EPS, N (%)[g]			
Yes	15 (21.74)	40 (58)	...
No	52 (75.36)	29 (42)	...

[a]Abbreviation: MS = mood stabilizer.
[b]In 2 of 25 olanzapine-treated patients, it was unclear from the chart review whether they had EPS.
[c]Patients treated initially with a typical antipsychotic, then switched to an atypical antipsychotic within 1 week of admission. EPS data are not presented, because it would not be possible to determine if presence of EPS in this group is related to typical or atypical antipsychotics.
[d]The MS + atypical group was significantly less ill than the MS + typical and MS + combination groups ($p < .001$ and $p < .005$, respectively).
[e]The MS + atypical group was significantly less ill than the MS + typical group ($p < .001$).
[f]The MS + atypical and MS + combination groups were significantly more improved than the MS + typical group ($p < .005$ and $p < .05$, respectively).
[g]The MS + atypical group experienced significantly fewer EPS than the MS + typical group ($p < .001$).

peridone showed significantly greater improvement than those treated with typical antipsychotics (Mann-Whitney $U = 778$, $Z = -4.29$, $p < .005$). Although the olanzapine group had numerically greater improvement compared with those treated with typical antipsychotics, this difference was not significant.

Other Comparisons

There was no significant difference between groups in length of hospital stay. A comparison of outcome in the subset of patients with psychosis (28/44 patients treated with risperidone, 21/25 patients treated with olanzapine, 51/69 patients treated with typical antipsychotics, and 14/17 patients treated with a combination of typical and atypical antipsychotics had psychotic features associated with mania) demonstrated a significant difference in clinical improvement at the time of discharge between groups ($\chi^2 = 11.8$, $df = 2$, $p < .005$). Post hoc analysis revealed that both the atypical group (Mann-Whitney $U = 836$, $Z = -2.86$, $p < .01$) and the combination group (Mann-Whitney $U = 187$, $Z = -2.738$, $p < .03$) showed significantly more improvement at discharge when compared with the group treated with typical antipsychotics. When the subgroups of the atypical antipsychotics were compared, no significant difference was found.

Side Effects

Patients treated with typical antipsychotics developed more EPS than those treated with either risperidone (58.0% vs. 29.5%; $\chi^2 = 8.72$, $df = 1$, $p < .01$) or olanzapine (58.0% vs. 8.7%; $\chi^2 = 16.9$, $df = 1$, $p < .001$). Patients treated with olanzapine had fewer EPS than those treated with risperidone (8.7% vs. 29.5%; $\chi^2 = 3.78$, $df = 1$, $p = .052$). Patients who received a combination of typical and atypical antipsychotics were not included in the analysis, since it would be difficult to determine which medication caused the EPS.

DISCUSSION

This chart-review study compared the efficacy of atypical antipsychotics with that of typical antipsychotics as add-on therapy to mood stabilizers for the treatment of mania in a naturalistic environment. The strengths of this study are as follows: (1) it reports on a large number of patients, (2) medications were used in a naturalistic setting with treatment decisions made by treating clinicians, (3) the study included patients seen routinely in clinical practice, (4) the information obtained from the charts was quite detailed due to the contributions of residents and medical students, and (5) the improvement scores were obtained from a single rater. The limitations are as follows: (1) the study was retrospective; (2) the rater was not blind to the medications given; (3) the estimation of improvement was somewhat crude, using global clinical impressions rather than prospective, objective outcome measures; (4) benzodiazepine use in treatment was not monitored; (5) the choice of medication was determined by the individual psychiatrist, so systematic selection bias cannot be excluded; (6) different mood stabilizers were used; and (7) the study lacked a structured interview to confirm diagnoses.

Given these limitations, the study yields interesting results. First, the patients treated with typical antipsychotics were more severely ill than those treated with atypical antipsychotics, both at admission and at discharge. This makes intuitive sense, since severely ill patients often need intramuscular medications for behavioral control, and there was no intramuscular atypical antipsychotic available in Canada at the time of the study. Given that the patients treated with typical antipsychotics were more severely ill than those treated with atypical antipsychotics, the fact that they were also more ill at discharge is difficult to interpret in a meaningful way. However, the clinical improvement (measured by the CGI-I) in patients treated with atypical antipsychotics or a combination of typical and atypical antipsychotics was significantly greater than that of those treated with typical antipsychotics alone. Among patients with psychosis, the risperidone and combination groups were associated with significantly greater clinical improvement at discharge than the typical antipsychotic group. This suggests that using atypical antipsychotics, or using a typi-

cal antipsychotic for 1 week and then switching to an atypical antipsychotic, may be superior to using typical antipsychotics alone as add-on therapy to mood stabilizers in the treatment of moderately to markedly ill patients with mania, with or without psychotic features, in a real-world clinical population.

When the atypical antipsychotics were compared separately, the risperidone subgroup showed greater improvement than the typical antipsychotic group. This finding is consistent with a previous study that reported a higher response rate in patients receiving a combination of risperidone and a mood stabilizer compared with those receiving a typical neuroleptic and mood stabilizer combination (90% vs. 43%).[23] The improvement at discharge for patients treated with olanzapine was greater than the improvement in patients treated with typical antipsychotics, although this difference was not significant. It is possible that this difference represented a true difference in outcome that may not have been significant due to type II error related to the small sample size in the olanzapine group (N = 25). Also, there was no significant difference in improvement between the risperidone and olanzapine groups. Again, the implications of this result are unclear, as type II error may be involved in this comparison.

When side effects were compared, this study showed that risperidone and olanzapine have a lower incidence of EPS than typical antipsychotics, and other studies[12–21] have demonstrated a lower risk of TD with these drugs than with typical antipsychotics. Furthermore, recent data suggest that atypical antipsychotics may improve depression, whereas typical antipsychotics can worsen depression.[17,19,20] Thus, the atypical antipsychotics may be a better choice than the typical antipsychotics in the treatment of moderate-to-marked mania, with or without psychotic features, due to their superior effectiveness and better side effect profile compared with the typical antipsychotics.

Given this information, how should patients with severe illness who refuse oral medication (thus requiring intramuscular medication) be treated? Currently, intramuscular typical antipsychotics are the only option for treating such patients. The data above suggest that patients who require typical antipsychotics during the first week of hospitalization may have a better outcome (with greater improvement at time of discharge) if switched to an atypical antipsychotic for the remainder of their hospital stay. In addition, since injectable forms of the atypical antipsychotics are being developed, clinicians may soon have the opportunity to use these medications in acute settings with severely ill patients.

In the future, prospective trials should be done comparing patients treated with intramuscular forms of typical versus atypical antipsychotics as add-on therapy to mood stabilizers in the treatment of mania. Also, the newer atypical antipsychotics, such as ziprasidone and quetiapine, should be compared in similar trials or chart reviews.

In summary, this chart review demonstrates that atypical antipsychotics may be more effective than typical antipsychotics when used with mood stabilizers to treat manic episodes. Risperidone in particular may be more effective than the typical antipsychotics. If patients require initial treatment with typical antipsychotics, they may have better short-term outcome with greater improvement at the time of discharge if they are switched to an atypical antipsychotic after the first week of hospitalization. Long-term outcome may also be better with the atypical antipsychotics, due to decreased risk of EPS, TD, and possibly depression, making atypical antipsychotics an excellent choice as add-on therapy to mood stabilizers for the treatment of patients with mania.

Drug names: olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), valproic acid (Depakene and others), ziprasidone (Geodon).

Disclosure of off-label usage: The authors of this article have determined that, to the best of their knowledge, quetiapine, risperidone, and ziprasidone are not approved by the U.S. Food and Drug Administration for the treatment of bipolar disorder and acute mania.

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