Comparison of Treatment-Emergent Extrapyramidal Symptoms in Patients With Bipolar Mania or Schizophrenia During Olanzapine Clinical Trials

Patrizia A. Cavazzoni, M.D.; Paul H. Berg, M.S.; Ludmila A. Kryzhanovskaya, M.D., Ph.D.; Susan D. Briggs, Ph.D.; Tamra E. Roddy, M.S.; Mauricio Tohen, M.D., Dr.P.H.; and John M. Kane, M.D.

Background: Previous research on pharmacotherapy with conventional antipsychotics has suggested that patients with affective disorders have higher rates of treatment-emergent extrapyramidal symptoms (EPS) than patients with schizophrenia. It is not known whether this differential vulnerability holds true for treatment with atypical antipsychotics such as olanzapine. The present analysis retrospectively examined olanzapine clinical trial data for incidence of treatment-emergent EPS in patients with either schizophrenia or bipolar disorder.

Method: Study participants were 4417 patients meeting DSM-III or DSM-IV criteria for either schizophrenia or bipolar mania participating in olanzapine clinical trials through July 31, 2001. Data were pooled across haloperidol-controlled trials and separately across placebo-controlled trials. Measures of EPS included rates of treatment-emergent EPS adverse event by type (i.e., dystonic, parkinsonian, or residual), Simpson-Angus Scale score mean change, rates of treatment-emergent parkinsonism, and rates of anticholinergic use.

Results: Consistent with prior research, haloperidol-treated patients with bipolar disorder appeared to be more vulnerable to the development of EPS than those with schizophrenia. However, olanzapine-treated patients with bipolar disorder were no more likely to develop EPS than those with schizophrenia.

Conclusion: Results support previous research regarding conventional antipsychotics and suggest that olanzapine therapy does not increase the risk of EPS for patients with bipolar disorder.

(J Clin Psychiatry 2006;67:107–113)

Received September 10, 2004; accepted July 6, 2005. From Lilly Research Laboratories, Indianapolis, Ind. (Drs. Cavazzoni, Kryzhanovskaya, Briggs, and Tohen, Mr. Berg, and Ms. Roddy); the Department of Psychiatric Medicine, University of Virginia, Charlottesville (Dr. Kryzhanovskaya); the Department of Psychiatry, Harvard Medical School/McLean Hospital, Belmont, Mass. (Dr. Tohen); and the Department of Psychiatry, the Zucker Hillside Hospital and the Albert Einstein College of Medicine, Glen Oaks, N.Y. (Dr. Kane).

This work was supported by Eli Lilly and Company. Drs. Cavazzoni, Kryzhanovskaya, Briggs, and Tohen, Mr. Berg, and Ms. Roddy are employees of Eli Lilly and Company.

Portions of these data were presented at the 11th Congress of the Association of European Psychiatrists, May 4–8, 2002, Stockholm, Sweden; the 23rd Congress of the Collegium Internationale Neuropsychopharmacologicum, June 23–27, 2002, Montreal, Canada; and the 15th Congress of the European College of Neuropsychopharmacology, October 5–9, 2002, Barcelona, Spain.

Dr. Kane is a consultant to and has received honoraria from Abbott, Pfizer, Eli Lilly, Janssen, Bristol-Myers Squibb, and AstraZeneca. Drs. Cavazzoni, Kryzhanovskaya, Briggs, and Tohen, Mr. Berg, and Ms. Roddy report no additional financial or other relationships relevant to the subject of this article.

Data for the current analysis were obtained from a total of 18 olanzapine clinical trials conducted by Eli Lilly and Company. A complete list of study codes may be obtained by contacting the corresponding author. The authors wish to acknowledge Christopher Carlson, Ph.D., and Angela R. Evans, Ph.D., for their contribution to the development of this project, and Hank Wei, M.S., for statistical consultation.

Corresponding author and reprints: Patrizia Cavazzoni, M.D., Eli Lilly & Company, Lilly Corporate Center, Indianapolis, IN 46285 (e-mail: p_cavazzoni@lilly.com).

Extrapyramidal symptoms (EPS) are a common concern with antipsychotic treatment, particularly when conventional antipsychotics are used.[1] Acute EPS usually develop within hours after starting medication or increasing dose and include dystonia, parkinsonism, and akathisia. These symptoms are distressing to the patient and can decrease treatment adherence.[2,3] Acute EPS have also been identified as a significant risk factor for later development of tardive dyskinesia.[4] Antipsychotic-induced EPS are thought to occur via blockade of dopamine-2 (D_2) receptors in the striatum. Evidence for this mechanism includes the observation that patients treated with drugs with higher D_2 receptor occupancy have higher rates of treatment-emergent EPS.[5] Data from a single photon emission computed tomography (SPECT) study have also shown that the degree of striatal D_2 recep-

tor occupancy predicts the occurrence of EPS with both atypical antipsychotics and haloperidol.[6]

For patients with schizophrenia, rates of EPS have been lower with atypical antipsychotics than with conventional antipsychotics such as haloperidol. A recent meta-analysis[7] compared the efficacy and EPS profiles of haloperidol with those of olanzapine, quetiapine, risperidone, and sertindole. The 4 atypical antipsychotics were found to have more favorable EPS profiles than haloperidol, as indicated by concurrent use of antiparkinsonian medication.[7] A more recent qualitative review of schizophrenia trials concluded that clozapine, olanzapine, quetiapine, and sertindole had lower rates of EPS compared to conventional antipsychotics.[8] In 2001, Kane[9] provided data on antiparkinsonian medication use in schizophrenia clinical trials for the previously mentioned atypical antipsychotics as well as ziprasidone. The atypicals had similar rates of antiparkinsonian medication use (12%–28%), which were lower than those for haloperidol (42%–68%) and more similar to placebo (11%–18%).[9]

A few reports in the literature suggest that patients with bipolar disorder have a higher vulnerability to developing acute EPS and tardive dyskinesia than patients with schizophrenia.[10–13] Nasrallah et al.[12] were among the first to suggest this idea with data from a retrospective study of 181 patients. A 4-fold greater incidence of acute dystonia in patients with mania was reported. However, all the patients with mania received concomitant treatment with lithium, which is associated with an increased risk of dystonic reactions when combined with atypical antipsychotics. Khanna et al.[13] also reported a 1.5-fold greater incidence of dystonia in mania in a small prospective study of 83 patients. The difference in incidences was not significant, but there was a difference in the mean neuroleptic dose between groups. In fact, regression analysis revealed that neuroleptic dose and age were more strongly related to the occurrence of dystonia than illness. These studies demonstrate the lack of sufficient data to conclude whether EPS are more prevalent in patients taking typical antipsychotics for the treatment of mania versus schizophrenia. Furthermore, little information is available about relative rates of EPS produced by atypical antipsychotics, as their use in affective disorders is more recent.

In summary, data from schizophrenia trials suggest that atypical antipsychotics have significantly more favorable EPS profiles than conventional antipsychotics. This contributes to the increased use of atypicals as first-line agents in the treatment of schizophrenia. There is some suggestive evidence that patients with bipolar disorder are more vulnerable to EPS when treated with conventional antipsychotics. However, data on EPS for atypical agents in bipolar disorder are still limited. The present study examined olanzapine clinical trial data for rates of treatment-emergent EPS in schizophrenia and bipolar disorder patients. Due to the low overall incidence of EPS reported with olanzapine treatment,[14] it was hypothesized that there would be no differences in rates of treatment-emergent EPS between schizophrenia and bipolar disorder patients treated with olanzapine. It was also hypothesized that, based on previous literature, rates of treatment-emergent EPS for haloperidol-treated patients would be higher for bipolar disorder patients compared to schizophrenia patients.

METHOD

Patients

Study participants were 4417 patients meeting DSM-III or DSM-IV criteria for either schizophrenia or bipolar mania participating in all published[15–26] and unpublished olanzapine clinical trials conducted by Eli Lilly and Company through July 31, 2001. Eighteen studies were identified, including 13 comparing olanzapine and haloperidol in schizophrenia, 1 comparing olanzapine and haloperidol in mania, 3 comparing olanzapine and placebo in schizophrenia, and 2 comparing olanzapine and placebo in mania. One of the schizophrenia studies compared 3 therapies (olanzapine, haloperidol, and placebo) and for the purposes of this analysis was treated as 2 trials (i.e., 1 comparing olanzapine and haloperidol and 1 comparing olanzapine and placebo). Patients were inpatients or outpatients, ranging in age from 18 to 65 years, who had provided written informed consent after study designs and possible adverse events were described to them. Table 1 provides baseline demographic and severity of illness characteristics (see Procedure for description of the groups). There were no significant group differences (within illness) for the baseline subject characteristics. The following significant group differences (between illness) existed in the haloperidol-controlled database: the Barnes Akathisia Scale score was higher for schizophrenia ($p < .001$), the Simpson-Angus Scale score was higher for schizophrenia ($p < .001$), lithium use was higher for bipolar ($p < .001$), and bipolar patients were more likely to be female ($p < .001$), older ($p = .001$), and non-white ($p < .001$). The following significant group differences (between illness) existed in the placebo-controlled database: the Simpson-Angus Scale score was higher for schizophrenia ($p < .001$), lithium use was higher for bipolar ($p < .001$), the mean number of days in the study was higher for schizophrenia ($p < .001$), and bipolar patients were more likely to be female ($p < .001$) and older ($p = .003$).

Measures

Outcome variables were the incidence of EPS as measured by treatment-emergent adverse event data, mean baseline-to-endpoint change in Simpson-Angus Scale score, rates of treatment-emergent parkinsonism, and use of anticholinergic medications (incidence, dose, and duration of treatment). Treatment-emergent adverse events

Table 1. Baseline Demographics and Severity of Illness

Characteristic	Haloperidol-Controlled Database				Placebo-Controlled Database			
	Schizophrenia		Bipolar Disorder		Schizophrenia		Bipolar Disorder	
	Olanzapine (N = 2110)	Haloperidol (N = 1059)	Olanzapine (N = 234)	Haloperidol (N = 219)	Olanzapine (N = 388)	Placebo (N = 153)	Olanzapine (N = 125)	Placebo (N = 129)
No. of clinical trials[a]	13		1		3		2	
Age, mean ± SD, y[b,c]	37.9 ± 11.1	37.6 ± 10.6	40.7 ± 13.1	39.1 ± 13.3	37.0 ± 10.2	36.2 ± 8.5	39.4 ± 11.2	38.8 ± 10.2
Gender, %[b,c]								
Male	67.4	66.4	36.8	42.9	77.6	77.1	49.6	51.9
Female	32.6	33.6	63.2	57.1	22.4	22.9	50.4	48.1
Origin, %[b]								
White	77.0	71.6	51.3	51.6	79.6	73.9	74.4	77.5
Other	23.0	28.4	48.7	48.4	20.4	26.1	25.6	22.5
Taking lithium, %[b,c]	0.8	1.1	4.3	11.0	0.0	0.0	16.8	16.3
Recruited from US site, %[b,c]	52.0	52.1	3.9	3.7	61.3	74.5	100	100
Days in study, mean ± SD[c]	37.0 ± 12.9	33.8 ± 13.8	37.3 ± 11.0	35.6 ± 12.7	33.5 ± 13.6	28.4 ± 13.9	20.0 ± 8.8	15.7 ± 8.8
YMRS score, mean ± SD[b,c]	NA	NA	31.1 ± 7.6	30.1 ± 7.7	NA	NA	28.7 ± 6.7	28.7 ± 6.9
HAM-D-21 score, mean ± SD[b,c]	NA	NA	8.0 ± 6.3	8.1 ± 6.4	NA	NA	14.7 ± 8.4	15.1 ± 8.1
Simpson-Angus Scale score, mean ± SD[b,c]	2.5 ± 3.9	2.8 ± 4.2	1.4 ± 3.5	1.6 ± 3.8	1.8 ± 3.0	2.0 ± 3.3	0.9 ± 1.5	0.5 ± 1.2
Barnes Akathisia Scale score, mean ± SD[b]	1.6 ± 2.5	1.8 ± 2.6	0.9 ± 2.1	0.8 ± 2.2	1.7 ± 2.5	1.4 ± 2.3	2.1 ± 2.7	1.8 ± 2.4

[a]Eighteen studies were identified; one of the schizophrenia studies compared olanzapine, haloperidol, and placebo and was treated as 2 trials (i.e., 1 comparing olanzapine and haloperidol and 1 comparing olanzapine and placebo) for the purposes of this analysis.
[b]Significant bipolar vs. schizophrenia between-group difference for the haloperidol-controlled database ($p < .05$).
[c]Significant bipolar vs. schizophrenia between-group difference for the placebo-controlled database ($p < .05$).
Abbreviations: HAM-D-21 = 21-item Hamilton Rating Scale for Depression, NA = not administered, YMRS = Young Mania Rating Scale.

were unsolicited (i.e., were signs or symptoms spontaneously reported by subjects in response to general inquiry or noted by an examiner).

Treatment-emergent EPS events were classified into 3 descriptive categories: dystonic (dystonia, oculogyric crisis, opisthotonos, and torticollis), parkinsonian (akinesia, cogwheel rigidity, extrapyramidal syndrome, hypertonia, hypokinesia, masked facies, and tremor), or residual (movement disorder, myoclonus, and twitching). Treatment-emergent parkinsonism was defined as a Simpson-Angus Scale total score of ≤ 3 at baseline and > 3 at any time thereafter.

Procedure

Acute phase data (up to 8 weeks) from 19 randomized, double-blind olanzapine clinical trials investigating the treatment of bipolar disorder or schizophrenia were pooled. For studies with acute phase duration of 6 weeks rather than 8 weeks, only 6 weeks of data were included. The pooled database was then divided into 2 clinical trial databases: a placebo-controlled database and a haloperidol-controlled database. The placebo-controlled database contained placebo- and olanzapine-treated patients from studies in which an olanzapine group was directly compared to a placebo group. Similarly, the haloperidol-controlled database contained haloperidol- and olanzapine-treated patients from studies in which an olanzapine group was directly compared to a haloperidol group. Within each of these 2 databases, EPS data from schizophrenia patients were analyzed by therapy (olanzapine, haloperidol, or placebo) and then compared to EPS data from bipolar disorder patients analyzed by therapy (olanzapine, haloperidol, or placebo).

Specifically, for each of the 2 databases, the percentages of patients with dystonic, parkinsonian, residual, or any type of EPS event were compared across therapies for schizophrenia and bipolar studies. Similarly, the percentages of patients who met the criteria for treatment-emergent parkinsonism and who were administered concomitant anticholinergic medications to treat EPS were compared across therapies for schizophrenia and bipolar disorder studies. Additionally, among the patients who required anticholinergic medications, the mean doses (converted to benztropine equivalents) and the mean days of exposure were examined. Mean changes on the Simpson-Angus Scale were also compared across therapies for schizophrenia and bipolar studies.

Statistical Analyses

Comparisons of incidence rates of EPS between bipolar and schizophrenia studies and between treatments were analyzed using the Fisher exact test. Because comparing crude incidence rates of EPS events for a given drug between diagnoses is vulnerable to confounding (i.e., due to design differences between studies), comparisons between studies were also analyzed using the Breslow-Day test for homogeneity of odds ratios. The Breslow-Day test has a χ^2 distribution and tests for differences between odds ratios across strata. Furthermore, incidence of any EPS event per patient year of exposure was calculated, and comparisons between diagnostic groups within each therapy group were made via exact

Table 2. Treatment-Emergent Adverse Events in the Haloperidol-Controlled Database

	Olanzapine Patients			Haloperidol Patients		
Event	Schizophrenia (N = 2110)	Bipolar (N = 234)	p Value[a]	Schizophrenia (N = 1059)	Bipolar (N = 219)	p Value[a]
Dystonic, N (%)	11 (0.5)	4 (1.7)	.055	59 (5.6)	14 (6.4)	.632
Parkinsonian, N (%)	197 (9.3)	20 (8.5)	.812	300 (28.3)	95 (43.4)	< .001
Residual, N (%)	34 (1.6)	1 (0.4)	.250	24 (2.3)	2 (0.9)	.292
Any EPS event, N (%)	230 (10.9)	25 (10.7)	1.00	346 (32.7)	102 (46.6)	< .001
Incidence rate of any EPS event per patient year	1.08	1.05	.999	3.53	4.78	.010

[a]p Values for percentages are from the Fisher exact test, and p values for events per patient year are from the exact binomial test.
Abbreviation: EPS = extrapyramidal symptoms.

Table 3. Treatment-Emergent Adverse Events in the Placebo-Controlled Database

	Olanzapine Patients			Placebo Patients		
Event	Schizophrenia (N = 388)	Bipolar (N = 125)	p Value[a]	Schizophrenia (N = 153)	Bipolar (N = 129)	p Value[a]
Dystonic, N (%)	1 (0.3)	0 (0.0)	1.00	0 (0.0)	1 (0.8)	.457
Parkinsonian, N (%)	37 (9.5)	13 (10.4)	.732	10 (6.5)	7 (5.4)	.804
Residual, N (%)	9 (2.3)	2 (1.6)	1.00	2 (1.3)	1 (0.8)	1.00
Any EPS event, N (%)	44 (11.3)	15 (12.0)	.872	11 (7.2)	8 (6.2)	.815
Incidence rate of any EPS event per patient year	1.24	2.19	.089	0.92	1.44	.464

[a]p Values for percentages are from the Fisher exact test, and p values for events per patient year are from the exact binomial test.
Abbreviation: EPS = extrapyramidal symptoms.

binomial tests. Comparisons of mean change in Simpson-Angus Scale scores, mean modal doses of study drug, and mean dose and duration of anticholinergic treatment between bipolar and schizophrenia studies were analyzed using the Student t test. All tests of hypothesis were done at a 2-sided .05 level of significance and Statistical Analysis System (SAS) versions 6.09 and 8 (SAS Institute, Cary, N.C.) were used to perform all analyses. No adjustments were made to the p values to account for multiple comparisons because there was no need to maintain an overall type I error rate of .05 for this analysis.

RESULTS

Olanzapine and Haloperidol Use

Mean modal dose (mg/day) of olanzapine in the haloperidol-controlled database was 12.3 (SD = 5.5) for schizophrenia and 16.3 (SD = 4.3) for bipolar disorder. Mean modal dose of haloperidol was 11.6 (SD = 5.6) for schizophrenia and 8.9 (SD = 4.3) for bipolar disorder. In the placebo-controlled database, mean modal dose of olanzapine was 11.6 (SD = 5.5) for schizophrenia and 15.6 (SD = 4.7) for bipolar disorder. Mean modal dose of olanzapine was significantly higher in bipolar studies than in schizophrenia studies in both the haloperidol-controlled database ($p < .001$) and the placebo-controlled database ($p < .001$). Mean modal dose of haloperidol was significantly higher in schizophrenia studies ($p < .001$) than in bipolar studies.

Treatment-Emergent Adverse Events Data

Tables 2 and 3 show treatment-emergent adverse events data for the haloperidol-controlled and placebo-controlled databases. In schizophrenia studies, the rate of parkinsonian events in haloperidol-treated patients relative to the rate in olanzapine-treated patients yielded an odds ratio of 3.84 (95% CI = 3.15 to 4.68). In bipolar studies, the rate of parkinsonian events in haloperidol-treated patients relative to the rate in olanzapine-treated patients yielded an odds ratio of 8.20 (95% CI = 4.82 to 13.93). The bipolar odds ratio was significantly larger than the schizophrenia odds ratio (Breslow-Day $\chi^2 = 7.06$, $p = .008$), indicating that the differential effect of haloperidol versus olanzapine was greater in the bipolar population. Similar results were seen with the analysis for any EPS event (Breslow-Day $\chi^2 = 6.09$, $p = .014$). Dystonic and residual events odds ratios were not significantly different between studies. The odds ratios for olanzapine versus placebo in bipolar and schizophrenia studies were either nonsignificant or incalculable due to low overall numbers of EPS events. In addition, none of the Breslow-Day tests were significant for olanzapine versus placebo.

During the schizophrenia studies, compared to olanzapine patients, haloperidol patients had significantly higher rates of dystonic (5.6% vs. 0.5%, $p < .001$) and parkinsonian (28.3% vs. 9.3%, $p < .001$) but not residual (2.3% vs. 1.6%, $p = .207$) events. Similarly, for the bipolar studies, haloperidol patients had significantly

Figure 1. Mean Change in Simpson-Angus Scale Score for the 8 Groups

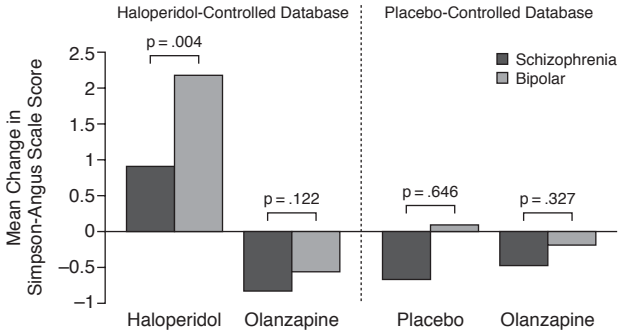

Figure 2. Rates of Treatment-Emergent Parkinsonism for the 8 Groups

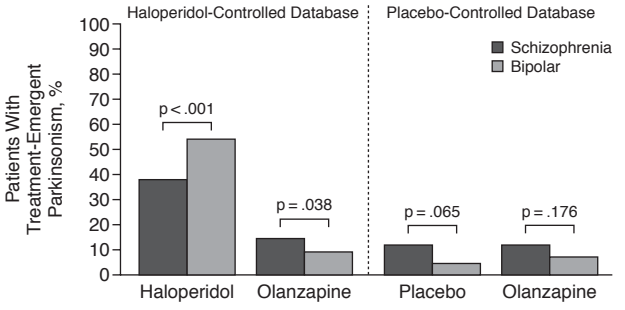

Table 4. Use of Anticholinergic Medication in Schizophrenia and Bipolar Patients

	Schizophrenia Studies			Bipolar Studies			Schizophrenia vs Bipolar Between-Group Difference		
Study Group	Incidence, N (%)	Dose, mean, mg/d	Duration, mean, d	Incidence, N (%)	Dose, mean, mg/d	Duration, mean, d	Incidence p Value	Dose p Value	Duration p Value
Haloperidol-controlled database									
Olanzapine	248 (11.8)	2.50	40.7	32 (13.7)	3.66	32.9	.396	.052	.200
Haloperidol	347 (32.9)	3.04	48.1	103 (47.2)	4.87	58.2	< .001	.103	.004
Placebo-controlled database									
Olanzapine	41 (10.6)	2.11	29.8	11 (8.8)	1.08	26.6	.733	< .001	.750
Placebo	15 (9.9)	1.91	37.7	9 (7.0)	1.49	26.1	.521	.342	.354

higher rates of dystonic (6.4% vs. 1.7%, p = .014) and parkinsonian (43.4% vs. 8.5%, p < .001) but not residual (0.9% vs. 0.4%, p = .612) events.

Simpson-Angus Scale Data

Figure 1 depicts mean baseline-to-endpoint change for the Simpson-Angus Scale. Means and standard deviations for schizophrenia versus bipolar patients were as follows for the haloperidol-controlled database: olanzapine, –0.84 (SD = 3.30) versus –0.58 (SD = 3.09); haloperidol, 0.91 (SD = 4.83) versus 2.16 (SD = 5.35). For the placebo-controlled database, they were olanzapine, –0.47 (SD = 2.16) versus –0.20 (SD = 1.76); placebo, –0.68 (SD = 2.30) versus 0.08 (SD = 1.75). Figure 2 shows treatment-emergent parkinsonism rates for all patient groups.

Anticholinergic Medication Use

Rates of anticholinergic medication use were examined for diagnostic group differences and are reported in Table 4. There was a significantly higher incidence of anticholinergic use among bipolar patients taking haloperidol than among schizophrenia patients taking haloperidol. Bipolar patients taking haloperidol also had significantly longer duration of anticholinergic use than schizophrenia patients taking haloperidol. Bipolar patients taking olanzapine took significantly lower doses of anticholinergics than schizophrenia patients taking olanzapine in the placebo-controlled database. There were no other significant schizophrenia versus bipolar differences in either database.

DISCUSSION

The occurrence of EPS during pharmacotherapy with antipsychotics is of great concern to both physicians and patients. Although the pathophysiology is unknown, previous research has suggested that patients with affective disorders are more vulnerable to antipsychotic-related EPS than patients with schizophrenia. Our results suggest that this may be true for patients treated with conventional antipsychotics such as haloperidol but not necessarily for those treated with olanzapine. Contrary to previous publications, we found no meaningful increases in the incidence of EPS in bipolar patients treated with olanzapine relative to schizophrenia patients treated with olanzapine.

Haloperidol treatment was associated with a significantly greater incidence of treatment-emergent parkinsonian events in patients with bipolar disorder versus schizophrenia. This occurred despite a significantly lower mean modal dose of haloperidol in the bipolar studies. Moreover, when the incidence of EPS events was adjusted for patient exposure time, haloperidol-treated bipolar patients still experienced a greater number of these

events than their schizophrenia counterparts, with no other statistically significant differences. This increased vulnerability to parkinsonian-like EPS in the bipolar patient population was further supported by the mean change and categorical analysis of the Simpson-Angus Scale. In contrast, olanzapine was not associated with greater rates of EPS in the bipolar group even though the mean modal dose of olanzapine was significantly higher in the bipolar studies. In the haloperidol-controlled studies, a significantly lower incidence of treatment-emergent parkinsonism was observed in the bipolar patients taking olanzapine compared to the schizophrenia patients taking olanzapine. The incidence of EPS in the olanzapine-treated groups was similar to that of placebo-treated patients.

The rates of treatment-emergent dystonic and parkinsonian EPS events were significantly higher for haloperidol than for olanzapine. This was true for both schizophrenic and bipolar patients, confirming earlier research showing that atypicals have a more favorable EPS profile overall than haloperidol. When bipolar patients were compared to schizophrenic patients, statistically significant differences in EPS were generally seen only with haloperidol therapy. These included significantly higher rates of treatment-emergent EPS events, significantly higher rates of treatment-emergent parkinsonism, and a significantly greater mean increase on the Simpson-Angus Scale for bipolar patients. One exception for olanzapine was a significantly greater incidence of treatment-emergent parkinsonism for schizophrenia patients relative to bipolar patients.

Another index of treatment-emergent EPS, rate of anticholinergic use, provided a similar pattern of results. Haloperidol treatment was associated with a higher incidence and duration of anticholinergic use among patients with bipolar disorder versus schizophrenia. It should be noted that the incidence of antiparkinsonian medication use for haloperidol was 47%, suggesting that treatment-emergent EPS or physicians' concerns about EPS were extremely common for patients taking haloperidol. The incidence of antiparkinsonian medication use for olanzapine was under 15% for both databases and similar for schizophrenia and bipolar patients.

Because of concerns that population differences among the different types of studies included might have impacted our results, we conducted logistic regressions examining the effects of various baseline characteristics (therapy assignment, gender, age, race, and baseline lithium use) on treatment-emergent EPS. In the placebo-controlled bipolar studies, only gender significantly predicted treatment-emergent EPS. Females had a lower risk of treatment-emergent EPS than males (odds ratio = 0.37, 95% CI = 0.15 to 0.97). In the placebo-controlled schizophrenia studies, none of the baseline characteristics predicted EPS. In the haloperidol-controlled bipolar studies, only therapy assignment significantly predicted treatment-emergent EPS. Patients assigned to haloperidol had more than 7 times the risk of treatment-emergent EPS as olanzapine patients (odds ratio = 7.71, 95% CI = 4.66 to 12.76). In the haloperidol-controlled schizophrenia studies, both therapy assignment and age predicted treatment-emergent EPS. Patients assigned to haloperidol had nearly a 4-fold increase in risk of treatment-emergent EPS over olanzapine patients (odds ratio = 3.97, 95% CI = 3.29 to 4.79). Also, patients' risk of EPS decreased with age (odds ratio = 0.98, 95% CI = 0.97 to 0.99). Taken together, these results do not suggest that population differences significantly influenced our results. Rather, the fact that the bipolar population tended to be older and more female further emphasizes the significance of finding no increased risk of EPS in bipolar patients treated with olanzapine.

Limitations of the current analyses include the relatively small number of bipolar trials in the database compared to schizophrenia trials. These results should be replicated after other studies of olanzapine, haloperidol, and placebo in bipolar disorder are completed. Other limitations involve the methodological issues regarding pooling data from noncontemporaneous trials with different study designs and the lack of data on hospitalization status, which prevented assessing its impact on the results. It should also be noted that these analyses did not distinguish EPS occurring early in the trial (which could have been due to carryover from prior treatment) and EPS occurring later on in the trial. This limitation would include the possibility that bipolar patients were more vulnerable to new treatment-emergent EPS due to being antipsychotic-naive, which could partly explain the greater incidence of EPS in bipolar patients treated with haloperidol. We also did not incorporate data on prior antipsychotic treatment, as information on prior treatment was not consistently collected in the trials included in these analyses. The effect of prior antipsychotic exposure on the emergence of new EPS is an important area for future research. Finally, for all trials, only the first 8 weeks of acute treatment data were examined. No conclusions can be made about rates of treatment-emergent EPS after 8 weeks of treatment.

In summary, we examined the incidence of treatment-emergent EPS for olanzapine, haloperidol, and placebo groups in clinical trials of olanzapine for bipolar disorder or schizophrenia. Although patients with bipolar disorder appeared to be more vulnerable to the development of EPS when treated with haloperidol, this was not true for the olanzapine-treated bipolar patients. These results confirm earlier research regarding conventional antipsychotics and suggest that olanzapine therapy does not increase the risk of EPS for patients with bipolar disorder. However, the extent to which this finding applies to other atypical agents requires further study.

Drug names: clozapine (Clozaril, FazaClo, and others), haloperidol (Haldol and others), lithium (Eskalith, Lithobid, and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), ziprasidone (Geodon).

REFERENCES

1. Casey DE. Effects of clozapine therapy in schizophrenic individuals at risk for tardive dyskinesia. J Clin Psychiatry 1998;59(suppl 3):31–37
2. Buchanan A. A two-year prospective study of treatment compliance in patients with schizophrenia. Psychol Med 1992;22:787–797
3. Gerlach J. Improving outcome in schizophrenia: the potential importance of EPS and neuroleptic dysphoria. Ann Clin Psychiatry 2002;14:47–57
4. Kane JM, Woerner M, Borenstein M, et al. Integrating incidence and prevalence of tardive dyskinesia. Psychopharmacol Bull 1986;22: 254–258
5. Balestrieri M, Vampini C, Bellantuono C. Efficacy and safety of novel antipsychotics: a critical review. Hum Psychopharmacol 2000;15: 499–512
6. Tauscher J, Kufferle B, Asenbaum S, et al. Striatal dopamine-2 receptor occupancy as measured with [123I]iodobenzamide and SPECT predicted the occurrence of EPS in patients treated with atypical antipsychotics and haloperidol. Psychopharmacology (Berl) 2002;162:42–49
7. Leucht S, Pitschel-Walz G, Abraham D, et al. Efficacy and extrapyramidal side-effects of the new antipsychotics olanzapine, quetiapine, risperidone, and sertindole compared to conventional antipsychotics and placebo: a meta-analysis of randomized controlled trials. Schizophr Res 1999;35: 51–68
8. Remington G, Kapur S. Atypical antipsychotics: are some more atypical than others? Psychopharmacology (Berl) 2000;148:3–15
9. Kane JM. Extrapyramidal side effects are unacceptable. Eur Neuropsychopharmacol 2001;11(suppl 4):S397–S403
10. Hunt N, Silverstone T. Tardive dyskinesia in bipolar affective disorder: a catchment area study. Int Clin Psychopharmacol 1991;6:45–50
11. Brotman MA, Fergus EL, Post RM, et al. High exposure to neuroleptics in bipolar patients: a retrospective review. J Clin Psychiatry 2000;61: 68–72
12. Nasrallah HA, Churchill CM, Hamdan-Allan GA. Higher frequency of neuroleptic-induced dystonia in mania than in schizophrenia. Am J Psychiatry 1988;145:1455–1456
13. Khanna R, Das A, Damodaran SS. Prospective study of neuroleptic-induced dystonia in mania and schizophrenia. Am J Psychiatry 1992;149:511–513
14. Bhana N, Foster RH, Olney R, et al. Olanzapine: an updated review of its use in the management of schizophrenia. Drugs 2001;61:111–161
15. Beasley CM, Tollefson G, Tran P, et al. Olanzapine versus placebo and haloperidol: acute phase results of the North American double-blind olanzapine trial. Neuropsychopharmacology 1996;14:111–123
16. Beasley CM, Hamilton SH, Crawford AM, et al. Olanzapine versus haloperidol: acute phase results of the international double-blind olanzapine trial. Eur Neuropsychopharmacol 1997;7:125–137
17. Tollefson GD, Beasley CM, Tran PV, et al. Olanzapine versus haloperidol in the treatment of schizophrenia and schizoaffective and schizophreniform disorders: results of an international collaborative trial. Am J Psychiatry 1997;154:457–465
18. Altamura AC, Velonà I, Curreli R, et al. Is olanzapine better than haloperidol in resistant schizophrenia? a double-blind study in partial responders. Int J Psych Clin Prac 2002;6:107–111
19. Bernardo M, Parellada E, Lomena F, et al. Double-blind olanzapine vs haloperidol D2 dopamine receptor blockade in schizophrenic patients: a baseline-endpoint [123I]IBZM SPECT study. Psychiatry Res 2001;107: 87–97
20. Keefe RSE, Young CA, Rock SL, et al. One-year double-blind study of the neurocognitive efficacy of olanzapine, risperidone, and haloperidol in schizophrenia. Schizophr Res. In press
21. Kinon BJ, Ahl J, Rotelli MD, et al. Efficacy of accelerated dose titration of olanzapine with adjunctive lorazepam to treat acute agitation in schizophrenia. Am J Emerg Med 2004;22:181–186
22. Purdon SE, Jones BD, Stip E, et al. Neuropsychological change in early phase schizophrenia during 12 months of treatment with olanzapine, risperidone, or haloperidol. The Canadian Collaborative Group for research in schizophrenia. Arch Gen Psychiatry 2000;57:249–258
23. Beasley CM, Sanger T, Satterlee W, et al. Olanzapine versus placebo: results of a double-blind, fixed-dose olanzapine trial. Psychopharmacology (Berl) 1996;124:159–167
24. Tohen M, Sanger TM, McElroy SL, et al. Olanzapine versus placebo in the treatment of acute mania. Olanzapine HGEH Study Group. Am J Psychiatry 1999;156:702–709
25. Tohen M, Jacobs TG, Grundy SL, et al. Efficacy of olanzapine in acute bipolar mania: a double-blind, placebo-controlled study. The Olanzapine HGGW Study Group. Arch Gen Psychiatry 2000;57: 841–849. Correction 2002;59:91
26. Tohen M, Goldberg JF, Gonzalez-Pinto Arrillaga AM, et al. A 12-week double-blind comparison of olanzapine versus haloperidol in the treatment of acute mania. Arch Gen Psychiatry 2003;60:1218–1226