Olanzapine Therapy in Treatment-Resistant Psychotic Mood Disorders: A Long-Term Follow-Up Study

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Background: Recent studies suggest a role for the atypical antipsychotic olanzapine in the acute treatment of psychotic mood disorders, but long-term data are unavailable. The purpose of this naturalistic study was to determine the long-term effectiveness and tolerability of olanzapine as add-on therapy in psychotic mood disorders.

Method: Hospital records were reviewed for 125 inpatients at the state psychiatric hospital in Buffalo, N.Y., who received at least 6 weeks of add-on olanzapine treatment for psychotic mood disorders (schizoaffective disorders [bipolar and depressive type], bipolar disorders [I, II, and NOS], and major depressive disorder). A group of schizophrenic patients served as a control group (N = 50). Baseline measures, including age, gender, number of hospitalizations in the 2 years prior to olanzapine treatment, concomitant medications, the Clinical Global Impressions scale (CGI), and the Global Assessment of Functioning-Equivalent (GAF-EQ) and Kennedy Axis V psychological impairment, violence, social skills, and activities of daily living subscale scores, were obtained. Follow-up information was obtained from the patients at least 6 months after initiation of olanzapine or by chart review and discussion with the treating psychiatrist. Patients with a diagnosis of psychotic mood disorders were compared with patients with the non-affective psychotic disorder (schizophrenia) on a variety of outcome measures.

Results: Follow-up information was available on 102 patients (82%). Mean follow-up was 15 months; 50 (49%) of the 102 patients remained on olanzapine treatment at follow-up (32 psychotic mood disorder, 18 schizophrenic). The primary reason for discontinuation in both groups was lack of response. Both the psychotic mood disorder and schizophrenic groups had comparable outcomes on the CGI and GAF-EQ. Improvement on the Kennedy Axis V psychological impairment and social skills subscales was seen only in the psychotic mood disorders group ($p < .01$); both groups showed significant ($p < .02$) improvement in the violence subscale. Sustained mood-stabilizing effect was evident in only 7/27 (26%) of the psychotic mood disorders patients continuing on add-on olanzapine treatment at follow-up.

Conclusion: Lack of response was the primary reason for discontinuation of add-on olanzapine in both groups. Mood symptoms predicted a better response to add-on olanzapine in patients with psychotic mood disorders on selective outcome measures. However, only 26% of the patients with psychotic mood disorders sustained a clinically meaningful mood-stabilizing effect with add-on olanzapine treatment at follow-up.

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The potential role for atypical antipsychotic agents in the treatment of mood disorders has become a topic of considerable interest in the past decade. Review of published literature by several authors suggests that clozapine, the prototypical atypical antipsychotic, is effective in the treatment of primary mood disorders with and without psychotic features.[1–9] Olanzapine, a thienobenzodiazepine, is a psychotropic agent approved by the U.S. Food and Drug Administration (FDA) for the treatment of psychotic disorders and acute mania. Like clozapine, olanzapine has a broad receptor affinity profile that includes D_1, D_2, D_4, 5-HT_{2A}, 5-HT_{2C}, 5-HT_3, α_1-adrenergic, histamine H_1, and muscarinic M_1–M_5 receptors.[10] Its ratio of greater 5-HT_{2A}:D_2 receptor occupancy in binding studies and A10 (mesolimbic) dopamine neuron selectivity in electrophysiology studies are similar to that of clozapine.[11,12]

Preliminary data on olanzapine in patients with schizophrenia, schizophreniform disorder, and schizoaffective disorders suggested that this drug may possess acute antimanic and antidepressant properties in addition to its antipsychotic properties. Baker et al.[13] reported that patients with schizophrenia treated with 10 mg/day of olanzapine were noted to have a significant reduction in Hamilton Rating Scale for Depression scores in comparison with those receiving olanzapine, 1 mg/day, or placebo. Tollefson et al.[14] examined the efficacy of olanzapine in treating depressive signs and symptoms associated with schizophrenia and schizoaffective and schizophreniform disorders in a 6-week double-blind, placebo-controlled trial. Olanzapine was found to be statistically superior to haloperidol in baseline to endpoint change as measured by the Montgomery-Asberg Depression Rating Scale (MADRS) total score[14,15] (6-point decline compared with a 3-point decline with haloperidol, p = .001). The authors concluded that olanzapine had a direct therapeutic effect on the depressive signs and symptoms after covarying for indirect effects, including positive, negative, and extrapyramidal symptoms via a linear regression "path analysis."[15] For that trial, a recent subanalysis of schizoaffective disorder, bipolar type patients was reported.[16] In the schizoaffective patients who were currently depressed, olanzapine was noted to be superior to haloperidol in the reduction of the MADRS scores (p = .002). In the schizoaffective patients who were currently manic, olanzapine was as effective as haloperidol in decreasing the Brief Psychiatric Rating Scale (BPRS) mania score (p = .25). (The BPRS mania score was derived by adding the BPRS items assessing conceptual disorganization, grandiosity, hostility, excitement, and disorientation.[16]) In a retrospective naturalistic study of 150 consecutively admitted inpatients with a diagnosis of psychotic disorders treated with olanzapine, Zarate et al.[17] reported an overall response rate of 62% for all patients and a statistically significant better response rate of 83% for the bipolar disorder patients. In a blinded chart review study of the treatment of 30 inpatients with psychotic depression, Rothschild and colleagues[18] reported a response rate of 67% among patients treated with olanzapine compared with 27% in age- and sex-matched patients treated with typical antipsychotics.

These preliminary results have led to several controlled studies designed to test the acute efficacy of olanzapine as monotherapy and adjunctive therapy in acute mania and depression. In a double-blind, placebo-controlled parallel-group study of olanzapine in the treatment of acute mania (pure mania and mixed episodes), Tohen and colleagues[19] reported that more patients responded to olanzapine (based on a 50% reduction in the Young Mania Rating Scale [YMRS] score) than to placebo (olanzapine, 48.6%; placebo, 24.2%) at the end of the 3-week study period. Recently, a second 4-week double-blind, placebo-controlled parallel-group trial[20] of olanzapine in the treatment of acute mania conducted by the same group reported a significantly higher response rate of 64.8% with olanzapine versus 42.9% with placebo (based on a 50% reduction in YMRS score). These 2 studies resulted in FDA approval for the use of olanzapine in the short-term treatment of acute manic episodes associated with bipolar I disorder. In a prospective naturalistic study of 14 treatment-resistant bipolar disorder patients, olanzapine was added as an adjunct to mood-stabilizing agents. The authors[21] reported a response rate in 8/14 patients (57%) based on moderate to marked responses on the Clinical Global Impressions scale for bipolar disorder. A recent 8-week, double-blind parallel-group trial[22] randomly assigned 28 patients with a diagnosis of treatment-resistant major depressive disorder without psychotic features to 1 of the following 3 groups: fluoxetine and placebo, olanzapine and placebo, or fluoxetine and olanzapine. The olanzapine plus fluoxetine group demonstrated superior efficacy compared with both olanzapine and fluoxetine monotherapy in baseline to endpoint change in the total MADRS and CGI scores.

While data on the short-term efficacy of olanzapine as an antidepressant and antimanic agent are steadily increasing in the literature, very little is known regarding whether this mood-stabilizing effect is sustained. Tran et al.,[23] in analyzing their data on 110 schizoaffective patients from a 12-month blinded extension phase of a study of olanzapine versus haloperidol, reported the superiority of olanzapine over haloperidol treatment in the mean change from baseline to endpoint in MADRS total score. This antidepressant effect of olanzapine continuation beyond 6 weeks of acute treatment led the authors to speculate that olanzapine may behave as a mood stabilizer during long-term therapy.

The findings discussed above led us to consider 2 hypotheses:

1. Among psychotic patients, those with a mood component to their illness would have a better outcome when treated with add-on olanzapine compared with those without a mood component to their illness.
2. Treatment with add-on olanzapine would lead to a significant improvement in the pattern of illness (change in severity, duration, and frequency of manic and depressive episodes) over the long term in comparison to the 3-month period immediately preceding olanzapine intervention.

To test these hypotheses, we collected data on a series of severely and persistently mentally ill inpatients started on olanzapine therapy while in treatment at a state psychiatric hospital.

METHOD

In a retrospective chart review, we identified all patients who (1) were consecutively admitted to the state hospital inpatient unit before January 1, 1999 (to be able to obtain at least 6 months of follow-up data); (2) had a DSM-IV discharge or most recent chart diagnosis of schizophrenia (bipolar depressed type), bipolar disorder (I, II, and NOS) with psychotic features, or major depressive disorder with psychotic features (the most recent chart diagnosis is determined biannually by the treating psychiatrist based on the clinical presentation of the patient in the past 6 months and corroborated with information from the past records and collateral information); (3) were started on olanzapine therapy during the hospitalization or within 3 months prior to admission; and (4) were older than 18 years of age. Patients on an active Criminal Procedure Law status were excluded from the study per New York State requirements. Records of 125 patients that met the inclusion criteria were reviewed, and a DSM-IV best-estimate diagnosis[24] was established by the investigators after discussion with treating clinicians.

Baseline Data Collection

Trained raters reviewed the hospital records for the following baseline information: age, sex, race, marital status, number of hospitalizations, concurrent medical illness, previous and concurrent treatment with antipsychotics/mood stabilizers (response and side effects), date of olanzapine initiation and length of hospitalization prior to olanzapine initiation, maximum olanzapine dosage, reasons for olanzapine trial, and total score on the Brief Psychiatric Rating Scale[25] obtained by the treating psychiatrist prior to the initiation of olanzapine, when available.

Follow-Up Data Collection

Follow-up data were collected by subject interview after obtaining informed consent or by review of the inpatient record. When follow-up data were obtained by chart review, information was corroborated with the treating psychiatrist. All subjects were contacted for a follow-up interview, excluding those whose account of their discontinuation of olanzapine was well documented in the inpatient record. When olanzapine was discontinued, the date, dosage, and reasons for discontinuation of olanzapine (ineffectiveness, side effects, and noncompliance) were obtained. Ineffectiveness was determined from the progress notes by the treating psychiatrist on the worsening of the clinical status of the patient. Information on concomitant medications, side effects, and hospitalization status was collected.

Outcome Measures

Clinical outcome for all patients was measured using the Clinical Global Impressions scale[26] and the Kennedy Axis V (K Axis V).[27] The CGI is a 7-point scale in which 1 indicates no mental illness and 7 indicates severe mental illness. The K Axis V is a clinician-scored instrument designed to measure the patient's functioning on 7 subscales that include (1) psychological impairment, (2) social skills, (3) violence, (4) activities of daily living/occupational skills, (5) substance use, (6) medical impairment, and (7) ancillary impairment. Ratings can range from a low of 5 (dysfunctional) to a high of 100 (no symptoms). Only the first 4 subscales were performed and utilized in the analysis for this study. Scores on the first 4 subscales were added and divided by 4 to generate a score that is roughly equivalent to the Global Assessment of Functioning score [GAF-EQ].[28] Information about social, residential, and vocational functioning was obtained with the use of the Modified Location Code Index (MLCI) and Modified Vocation Status Index (MVSI).[29] Assessments were performed at baseline and at follow-up. Baseline ratings for the outcome scales were performed on all patients retrospectively for the week prior to initiation of olanzapine based on chart review. Follow-up ratings for the week prior to the interview were performed only for the patients who continued on olanzapine treatment.

We were interested in determining if the mood-stabilizing effect of olanzapine was sustained in psychotic mood disorders. We therefore retrospectively administered the CGI bipolar version change from preceding phase (prophylactic assessment) scale (CGI-BP)[30] to the group with psychotic mood disorders continuing on add-on olanzapine therapy. The CGI-BP compared the change in the patient's pattern of illness (severity, duration, and frequency of manic and depressive episodes) during the add-on olanzapine treatment phase with the phase immediately preceding the addition of olanzapine. We had at least 3 months of progress notes in the charts documenting the clinical status of all the patients with psychotic mood disorders prior to the initiation of olanzapine treatment. Therefore, we decided to compare this 3-month period with the first 3-month period on olanzapine treatment (in a mirror design) and with the patient's last available evaluation.

Statistical Analysis

Differences between the psychotic mood disorders and schizophrenic groups in baseline variables were compared by means of independent t tests (continuous variables) and the chi-square test or 2-tailed Fisher exact test (categorical variables) as deemed appropriate. Within-group comparisons of the various scales between baseline and follow-up were made using paired t tests. The Bonferroni correction, a multiple-comparison correction, was applied to the comparison of the schizophrenic and psychotic mood disorders groups on the individual subscale scores of the K Axis V before and after treatment with olanzapine.

Table 1. Sociodemographics, Baseline Psychopathology, and Neuroleptic Treatment of Sample

		Age, y	Duration of Illness, y	Men	Baseline BPRS[a]	Failed Antipsychotic (%)	
Diagnostic Group	N	Mean (SD)	Mean (SD)	N (%)	Mean (SD)	Risperidone	Clozapine
Psychotic mood disorders	61	48.1 (16.6)	26.1 (13.5)	29 (47.5)	54.7 (11.8)	46.0	11.1
Schizophrenia	41	47.9 (14.1)	26.2 (12.6)	29 (70.7)	48.0 (12.7)	54.4	23.8
Total	102	48.0 (15.3)	26.2 (13.1)	58 (56.9)	51.3 (12.2)	50.2	17.4

[a]Abbreviation: BPRS = Brief Psychiatric Rating Scale.

RESULTS

The mean age for the entire study sample of 125 patients was 49.9 ± 16.4 years (range, 19–86 years). There were 71 men (57%) and 54 women (43%). The schizoaffective disorders (N = 56), bipolar disorders (N = 16), and major depressive disorders (N = 3) groups were combined (hereafter referred to as psychotic mood disorders group) for comparison with schizophrenic disorders (N = 50) on the baseline and outcome measures to test our hypothesis. Follow-up information was available from 102 (82%) of the 125 potential patients; this group then constituted the study sample. Patient interviews conducted in person (N = 17) or by telephone (N = 4) were performed with 21% of the 102 subjects. Medical record reviews and interviews with the treating psychiatrist were performed for all of the remaining 79% of the subjects. No follow-up information was available for 23 patients due to one of the following: our inability to locate them (N = 18), their refusal to participate (N = 4), or their death for reasons unrelated to olanzapine (N = 1). No significant difference was evident between the follow-up group and the group that was lost in terms of baseline demographics (age, race, duration of illness, and history of prior risperidone or clozapine trial) and severity of psychopathology.

Of the 102 patients for whom follow-up data were available, baseline demographic and clinical data are presented by group as seen in Table 1. There were 61 patients diagnosed with psychotic mood disorders (comprising bipolar manic [N = 4], bipolar depressed [N = 2], bipolar mixed [N = 5], bipolar not otherwise specified [N = 1], schizoaffective bipolar [N = 41], schizoaffective depressed [N = 6], and major depressive disorder [N = 2]) and 41 patients in the schizophrenic group. There were no statistically significant differences between these groups in demographics. The mean length of olanzapine treatment was 15.5 ± 8.0 months (range, 1–33 months).

Olanzapine Discontinuation

The olanzapine discontinuation rate for the entire study population was 51% (52/102). Discontinuation for those with psychotic mood disorders was 48% (29/61) and for those with schizophrenia, 56% (23/41). Eighty-one percent (42/52) of discontinuations were due to ineffectiveness as determined by the patient's psychiatrist after a minimum trial of at least 1 month's duration, 13% (7/52) were due to side effects, and 6% (3/52) were due to noncompliance. Side effects that led to discontinuation of the drug included weight gain (3/7), orthostatic hypotension (2/7), intolerable anticholinergic side effects (1/7), and refractory seizures (1/7). Both the psychotic mood disorders group and the schizophrenic group had the same (41%) discontinuation rate for ineffectiveness. The mean dosage of olanzapine for those patients in whom the drug was discontinued for ineffectiveness was 21.96 ± 8.06 mg/day.

Outcome of Patients Continuing on Olanzapine Therapy at Follow-Up

The mean length of treatment for those patients still taking olanzapine at follow-up (N = 50) was 20.2 ± 6.2 months. The mean dosage of olanzapine for those patients still taking olanzapine at follow-up was 22.4 ± 6.5 mg/day. The results of the clinical data for the patients continuing on olanzapine therapy at follow-up are presented in Table 2.

Clinical Outcome

Both the psychotic mood disorders patients (N = 32) and the schizophrenic patients (N = 18) who continued to be treated with olanzapine showed a statistically significant change toward improvement on the CGI and GAF-EQ during the course of this study (Table 3). Although the psychotic mood disorders cohort exhibited a greater change from baseline to follow-up on the CGI compared with the schizophrenic cohort, this difference between groups failed to reach statistical significance. Seventy-five percent (24/32) of the psychotic mood disorders patient group and 100% (18/18) of the schizophrenic patients taking olanzapine remained hospitalized at follow-up.

A subanalysis was performed on the individual subscale scores of the K Axis V before and after treatment with olanzapine after lowering the a value of significance utilizing the Bonferroni correction (Table 4). The psychotic mood disorders group revealed a statistically significant change from baseline to follow-up scores in the psychological impairment, violence, and social skills subscales in contrast to the schizophrenic group, which revealed a significant change in score only on the violence subscale.

Table 2. Clinical Data for 50 Patients With Psychotic Mood Disorders Continuing Treatment With Olanzapine at Follow-Up[a]

	Subjects Continuing Olanzapine[b]		Dose at Follow-Up		Duration of Olanzapine			Change in GAF-EQ			Change in CGI			Change in MVSI			Change in MLCI		
Diagnosis	N	(%)	Mean	(SD)	N	Mean	(SD)	N	Mean	(SD)	N	Mean	(SD)	N	Mean	(SD)	N	Mean	(SD)
Psychotic mood disorders																			
Schizoaffective bipolar	25/41	(61)	22.80	(5.97)	25	17.4	(5.36)	23	–11.04	(11.53)	24	0.79	(1.10)	24	0.00	(0.00)	24	–0.04	(2.53)
Schizoaffective depressed	1/6	(17)	20.00	(…)	1	29.00	(…)	1	–1.25	(…)	1	0.00	(…)	1	0.00	(…)	1	3.00	(…)
Bipolar depressed	1/2	(50)	20.00	(…)	1	12.00	(…)	1	–5.25	(…)	1	1.00	(…)	1	0.00	(…)	1	0.00	(…)
Bipolar manic	1/4	(25)	20.00	(…)	1	30.00	(…)	1	15.00	(…)	1	–1.00	(…)	1	0.00	(…)	1	0.00	(…)
Bipolar mixed	2/5	(40)	17.50	(3.34)	2	23.50	(0.70)	2	–11.62	(16.44)	2	0.50	(0.70)	2	0.00	(0.00)	2	0.00	(…)
Major depression	2/2	(100)	15.00	(7.07)	2	19.00	(1.41)	2	–12.50	(22.98)	2	1.00	(2.82)	2	2.00	(2.82)	2	3.00	(4.24)
Total																			
Affective disorders	32/61	(52)	21.72	(5.90)	32	18.46	(5.84)	30	–9.79	(12.44)	31	0.71	(1.16)	31	0.13	(0.72)	31	0.25	(2.51)
Schizophrenia	18/41	(44)	23.75	(7.78)	18	23.44	(5.92)	18	–7.14	(9.60)	18	0.53	(1.06)	18	0.00	(0.00)	18	0.00	(0.00)

[a]Abbreviations: CGI = Clinical Global Impressions scale, GAF-EQ = Global Assessment of Functioning-Equivalent, MLCI = Modified Location Code Index, MVSI = Modified Vocation Status Index.
[b]Broken down by subgroup from the 102 patients for whom follow-up data were available.

Table 3. Outcome Measure Scores Before and After Olanzapine Treatment[a]

	Before		After		Paired Sample t Tests		
Measure	Mean	(SD)	Mean	(SD)	t	df	p
CGI							
Psychotic mood disorders	4.97	(0.71)	4.26	(0.86)	3.41	30	< .01
Schizophrenia	4.69	(0.67)	4.17	(0.92)	2.11	17	.05
GAF-EQ							
Psychotic mood disorders	35.36	(10.13)	45.15	(8.38)	–4.31	29	< .01
Schizophrenia	37.67	(9.83)	44.81	(7.34)	–3.16	17	< .01

[a]Abbreviations: CGI = Clinical Global Impressions scale, GAF-EQ = Global Assessment of Functioning-Equivalent.

Residential and Vocational Outcome

There was no statistically significant difference in the change from baseline to follow-up in residential and vocational index scores between the psychotic mood disorders (MVSI: z = 0.13 ± 0.72, MLCI: z = 0.25 ± 2.51) and the schizophrenic patients (MVSI: z = 0 ± 0, MLCI: z = 0 ± 0).

Dose and Concomitant Medications

There was no significant difference in the mean olanzapine dose at follow-up for the psychotic mood disorders group (21.72 ± 5.90 mg) compared with the schizophrenic group (23.75 ± 7.78 mg). An evaluation of concomitant mood stabilizers and antidepressants for the psychotic mood disorders subjects showed that lithium was used by 72% (23/32) at baseline and 75% (24/32) at follow-up. Valproate was used by 50% (16/32) of these patients both at baseline and at follow-up. Antidepressants were used by 62% (20/32) of these patients at baseline and 75% (24/32) at follow-up. No significant difference between the baseline and follow-up use of mood stabilizers or antidepressants was evident.

Clinical Global Impressions-Bipolar Version

A retrospective analysis of the 27 psychotic mood disorders patients continuing on olanzapine treatment at follow-up was performed to assess their improvement in affective morbidity. Eight patients (30%) at 3 months and 7 patients (26%) at final evaluation (last available observation was a mean 15 months postinitiation of treatment) were rated as much or very much improved in terms of their affective symptoms at follow-up. Detailed results are summarized in Table 5.

DISCUSSION

This study offers a naturalistic, long-term evaluation of olanzapine treatment in a cohort of subjects with psychotic mood disorders (major depressive, bipolar, and schizoaffective disorders). Naturalistic studies can provide valuable data through the representation of typical clinical conditions.[31,32] The study compared the long-term outcome of treatment-resistant subjects with psychotic mood disorders with a group of treatment-resistant schizophrenia subjects. The psychotic mood disorders group and the schizophrenic group had comparable clinical, residential, and vocational outcomes with olanzapine treatment. Subjects with psychotic mood disorders demonstrated a significant improvement on the K Axis V psychological impairment, social skills, and violence subscales compared with a significant improvement only on the violence subscale in the schizophrenic subjects. The score on the K Axis V psychological impairment subscale reflects the

Table 4. Kennedy Axis V Subscale Scores Before and After Olanzapine Treatment

	Before		After		Paired Sample t Tests	
Diagnostic Subtype	Mean	(SD)	Mean	(SD)	t	df
Psychological impairment						
Psychotic mood disorders	30.00	(7.99)	38.67	(11.37)	–3.99*	29
Schizophrenia	34.72	(12.42)	37.50	(10.88)	–0.95	17
Social skills						
Psychotic mood disorders	37.83	(12.78)	45.67	(10.14)	–3.19*	29
Schizophrenia	36.11	(9.78)	44.17	(11.27)	–2.43	17
Violence						
Psychotic mood disorders	41.83	(19.19)	59.17	(18.34)	–4.07*	29
Schizophrenia	50.00	(18.78)	63.61	(14.83)	–3.24*	17
Activities of daily living						
Psychotic mood disorders	32.00	(8.23)	37.50	(9.97)	–2.21	29
Schizophrenia	30.61	(5.65)	34.17	(6.00)	–2.15	17

*$p < .0125$.

Table 5. Improvement in Manic and Depressive Episodes for the Patients Continuing on Olanzapine Treatment at Follow-Up[a]

		Much or Very Much Improved		Minimal or No change		Much or Very Much Worsened, N	
		At 3 Months	At Last Evaluation	At 3 Months	At Last Evaluation	At 3 Months	At Last Evaluation
Affective State[b]	N	N (%)	N (%)	N (%)	N (%)		
Manic or Mixed	23	6 (26)	4 (17)	17 (74)	19 (83)	0	0
Depressed	4	2 (50)	3 (75)	2 (50)	1 (25)	0	0
Total	27	8 (30)	7 (26)	19 (70)	20 (74)	0	0

[a]Excluded from the analysis are the 4 patients who entered the study in a euthymic state and remain unchanged.
[b]At the time of olanzapine administration.

degree and impact of both the psychotic and mood symptoms on the patient's functioning. The K Axis V social skills subscale reflects the degree of impairment in the social and communication skills of the patient. One might speculate that olanzapine improved both mood symptoms and psychotic symptoms, leading to the better outcome evidenced on the K Axis V psychological impairment and social skills subscales for the psychotic mood disorders group. Further, at follow-up, fewer patients in the psychotic mood disorders group (75%) remained hospitalized compared with the schizophrenic group (100%). These high rates of hospitalization are difficult to interpret and may in part reflect the myriad impairments associated with severe and persistent mental illness rather than a simple treatment effect. In spite of the fact that both the psychotic mood disorders group and schizophrenic group had a high olanzapine discontinuation rate for ineffectiveness, our first hypothesis appears true in that mood symptoms predicted a better response to add-on olanzapine in patients with psychotic disorders over long-term follow-up on selective outcome measures.

Nearly three quarters of the subjects with psychotic mood disorders, however, failed to display a substantial improvement in their affective symptoms at follow-up. Their discontinuation rate for ineffectiveness was high at 41%, and only 26% (7/27) of those continuing on olanzapine treatment showed a clinically meaningful improvement in the refractory affective symptoms in a follow-up averaging more than 15 months. These results are in sharp contrast to the Banov et al.[33] study of clozapine therapy in refractory affective disorders, which reported a relatively low 15% discontinuation rate for ineffectiveness and an overall response (rated as good or very good on the CGI-Improvement scale) rate of 64% (83/129) for the refractory affective disorders in a mean follow-up of 18 months. Further, Banov et al. reported a reduction in the use of concurrent mood stabilizers such as lithium and valproate at follow-up in their affective cohort. Such a reduction in the use of concurrent mood stabilizers, which would render further support for independent mood-stabilizing effects, was not evident with olanzapine in our study. The Banov et al. sample was a treatment-resistant private hospital sample, which may not be comparable to the treatment-resistant state psychiatric hospital sample of this study. Such low discontinuation rates for ineffectiveness and high responder rates have been consistently reported with clozapine in the treatment of psychotic mood disorders.

In a 26-month, retrospective study[1] of clozapine in patients with refractory schizophrenia and psychotic mood disorders, McElroy and colleagues reported a 4% (4/98) discontinuation rate for ineffectiveness. Calabrese et al.[5] reported a similar 4% (1/25) discontinuation rate for ineffectiveness in a prospective 13-week trial of clozapine monotherapy in the treatment of refractory bipolar manic and schizoaffective disorder.[5] In a meta-analysis of the published studies of clozapine in the treatment of severe mood disorders, Zarate et al.[6] reported an overall response rate of 70% in manic-psychotic bipolar disorder and schizoaffective disorder patients. In contrast to that with clozapine, the benefit on long-term mood stabilization appears to be limited for olanzapine in the treatment of resistant psychotic mood disorders. Nevertheless, the results of our study fail to support our second hypothesis; add-on olanzapine treatment did not lead to a clinically meaningful improvement in the pattern of illness (severity, duration, and frequency of manic and mixed episodes) compared with the period immediately preceding olanzapine intervention. There was not evidence for a sustained, prophylactic mood-stabilizing (antidepressive and antimanic) effect in treatment-resistant subjects with psychotic mood disorders.

Several contrasts and parallels are highlighted between our naturalistic follow-up study and a 12-month double-blind extension phase study by Tran and colleagues[23] of

schizoaffective patients randomly assigned to either olanzapine or haloperidol monotherapy. Tran and colleagues reported on the 85 patients receiving olanzapine treatment in the extension phase. The olanzapine discontinuation rate for ineffectiveness in our affective disorders groups was 41% (25/61) over a mean follow-up of 15 months, while Tran and colleagues reported a 34% (66/196) olanzapine discontinuation rate for ineffectiveness (acute and maintenance phase) at 12 months. Several factors could have contributed to the higher discontinuation rate seen in our study. These include greater baseline severity in psychopathology, as evidenced by an inpatient state psychiatric hospital sample, a higher mean BPRS score of 51 versus 32 in the Tran et al. study, the treatment-resistant nature of the cohort (all of the patients had failed at least 1 to 2 typical antipsychotics, 50% had failed a risperidone trial, and 17% had failed a clozapine trial), as well as the retrospective nature of the data collection regarding discontinuation. Among the patients continuing on olanzapine therapy at follow-up in our study, more depressed patients (75%) had substantial improvement in affective morbidity compared with the manic and mixed patients (17%). A similar sustained improvement was reported by Tran et al. for the depressive signs and symptoms in the schizoaffective patients (mean change from baseline to follow-up in MADRS score was –8.26). Both of these studies suggest that the antidepressant properties of olanzapine may be sustained over the long term.

An unexpected finding is the robust improvement in scores on the K Axis V violence subscale in both the schizophrenic and affective disorders populations. The K Axis V violence subscale measures dangerousness, namely, intentional attempts to hurt self or others. Scores on this subscale are rated on the basis of violent behaviors independent of the diagnosis and severity of the psychopathology. Studies have suggested that the prototypical atypical antipsychotic agent clozapine has specific antiaggressive effects in addition to its antipsychotic effect.[34] A primary indication for continued olanzapine treatment in the control of aggressive behavior warrants further exploration in future studies.

The strengths of our study include the high follow-up rate (82%), the long length of follow-up (mean = 15.5 months), the adequacy of the trial dose, and the monitoring of medication adherence in an inpatient setting. However, because of the naturalistic design, there are several important methodological limitations. The patients received olanzapine under nonblinded, uncontrolled conditions. DSM-IV diagnoses were not determined by a single investigator or by structured diagnostic interviews but rather by a best-estimate method. The psychotic mood disorders cohort had an overrepresentation of patients with schizoaffective bipolar disorder. Collection of baseline data was done retrospectively,[35] outcome ratings were not blinded to psychiatric diagnosis, and the study lacked a comparison group treated without olanzapine. The majority of patients received concomitant psychotropic agents. In addition, the decision to discontinue olanzapine among psychiatrists may not have been consistent.

The FDA approval for olanzapine is for the short-term use as an antimanic agent in the treatment of bipolar I disorder. Our findings, though preliminary, suggest that add-on olanzapine has limited effectiveness in the long-term treatment of refractory psychotic mood disorders. Further studies need to address the long-term role of olanzapine monotherapy in the treatment of psychotic depression. In addition, future studies should focus on the prophylactic effectiveness of olanzapine in preventing manic, mixed, and depressive relapses in specific disorders such as bipolar and schizoaffective disorders. Such studies will lead to a better understanding into the prophylactic effect of this agent in preventing different mood episodes.

Drug names: clozapine (Clozaril and others), fluoxetine (Prozac), haloperidol (Haldol and others), olanzapine (Zyprexa), risperidone (Risperdal).

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