Clinical Predictors of Acute Response With Olanzapine in Psychotic Mood Disorders

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Background: In controlled studies of patients with schizophrenia, the atypical antipsychotic olanzapine has been shown to be more effective in the treatment of positive and negative symptoms compared with haloperidol at doses of 10 mg/day. However, little is known about the efficacy of olanzapine in patients with psychotic mood disorders. The purpose of this study was to assess the efficacy of olanzapine in the treatment of these psychotic mood disorders in comparison with nonaffective psychotic disorders and to identify clinical factors associated with olanzapine response.

Method: In a naturalistic setting, by reviewing medical records, we assessed response to olanzapine and factors associated with response to olanzapine in 150 consecutive patients newly treated with the drug at a nonprofit academic psychiatric hospital.

Results: Patients displaying a moderate-to-marked response to olanzapine were more likely to be younger; be female; receive a diagnosis of bipolar disorder; and have a shorter duration of illness, shorter length of stay prior to olanzapine, and longer duration of trial.

Conclusion: Olanzapine may be a useful alternative or adjunctive treatment for patients with bipolar disorder.

(J Clin Psychiatry 1998;59:24–28)

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Supported in part by a National Alliance for Research on Schizophrenia and Depression (NARSAD) Young Investigator Award (Dr. Zarate) and by the McLean Pharmacoepidemiology Center Fund.

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Antipsychotic drugs have been utilized for the management of patients with bipolar disorder for several decades. A number of alternative somatic treatment approaches have been reported for patients with bipolar disorder who do not respond well to or who are intolerant to lithium treatment.[1,2] Somatic treatments other than lithium reported to have a role in the management of bipolar disorder include neuroleptics, anticonvulsant agents (carbamazepine, valproate, lamotrigine, gabapentin), calcium channel blockers, antidepressants, cholinergic agents, adrenergic blockers, thyroid hormones, phototherapy, and electroconvulsive therapy.[1,3] Still, in spite of all these alternatives, a proportion of patients with bipolar disorder continue to fail or are intolerant to these agents.

In the last several years, the search for new drugs for bipolar disorder has recently involved the serotonin-dopamine antagonist antipsychotic agents, clozapine and risperidone.[4–7] Unlike conventional antipsychotics, which have effects primarily on the acute psychotic or manic phases of the illness and a high risk for extrapyramidal side effects, new antipsychotics appear to have additional benefits (i.e., more mood-stabilizing and thymoleptic properties) and a lower risk of extrapyramidal symptoms. Clozapine was the first atypical antipsychotic agent that was reported to be effective not only in the treatment of patients with schizophrenia but also in patients with schizoaffective and bipolar disorder, including those with treatment-resistant conditions.[4,5,7,8] Because of the more favorable side effect profile of risperidone compared with clozapine and standard antipsychotics,[9] several investigators examined its tolerability and efficacy in the treatment of schizoaffective and bipolar disorders. Risperidone was reported to reduce mood as well as psychotic symptoms in patients who had the depressive type of schizoaffective disorder,[10,11] major depression with psychotic features,[10] and acute psychotic mania.[7] While risperidone, unlike clozapine,[12,13] appears to have antidepressant and antimanic properties, recent evidence suggests that risperidone treatment of patients with bipolar disorder may have to be combined with mood stabilizers. Keck and colleagues[14] found that risperidone-treated bipolar patients were more likely to respond to risperidone if they were also receiving mood stabilizers than if they were not.

Olanzapine is one of a new class of atypical antipsychotic drugs that combines potent dopamine-2 (D_2) and serotonin-2 ($5\text{-}HT_2$) receptor antagonists.[15] Olanzapine, in double-blind clinical trials at intermediate (7.5–12.5 mg/day) and high (12.5–17.5 mg/day) dosages, has been found to be superior to placebo and equivalent to haloperidol in the treatment of positive symptoms of schizophrenia and superior to both placebo and haloperidol in the treatment of negative symptoms.[15] Preliminary data on olanzapine in patients with schizophrenia, schizophreniform disorder, and schizoaffective disorder suggest that this drug may have antimanic and antidepressant properties in addition to antipsychotic effects.

In the first study,[16] a random, double-blind, placebo-controlled study of 25 patients, the patients treated with 10 mg/day of olanzapine were noted to produce a significant reduction in Hamilton Rating Scale for Depression scores in comparison to 1 mg/day or placebo. In the second study,[3] a subanalysis of a larger database, olanzapine in a 6-week, double-blind study was as effective as haloperidol in decreasing the Brief Psychiatric Rating Scale (BPRS) mania score ($p = .251$) in the treatment of schizoaffective disorder, bipolar type. However, in patients with schizoaffective disorder, depressive type, olanzapine was superior to haloperidol in reducing BPRS depressed score ($p < .0001$). Tollefson et al.[17] recently examined the efficacy of olanzapine in depressive signs and symptoms associated with schizophrenia. The investigation was a 6-week, double-blind parallel study conducted in patients with DSM-III-R schizophrenia or a closely related condition. Individuals were randomly assigned to either olanzapine or haloperidol (5–20 mg/day) for 6 weeks. Subjects included in this subanalysis had a baseline Montgomery-Asberg Depression Rating Scale (MADRS) total score of ≥ 16. Olanzapine was found to be statistically superior to haloperidol in baseline to endpoint change in MADRS total score and BPRS depression subscale. Significant treatment differences favoring olanzapine were evident by Week 1.

Given the above preliminary data, we hypothesized that patients with psychotic mood disorders (bipolar disorder and major depression with psychotic features) would respond better to olanzapine than patients without these diagnoses. To test this hypothesis, we surveyed a consecutive series of patients receiving olanzapine at McLean Hospital, a private nonprofit psychiatric hospital.

METHOD

In a retrospective chart review, we identified all patients consecutively admitted to McLean Hospital over 5 months between October 1996 and February 1997. Patients included in this study were men or women aged 18 or older who were newly treated with olanzapine and received a discharge diagnosis of bipolar disorder (manic, mixed, or depressive type), major depression with psychotic features, schizophrenia, schizoaffective disorder (bipolar or depressive type), and psychosis not otherwise specified according to DSM-IV criteria.[18]

The following information was recorded from medical records: age; sex; race; marital status; psychiatric (DSM-IV) diagnosis; duration of illness; number of hospitalizations; concurrent medical illness; previous and concurrent medications, response, and side effects; olanzapine dose, duration of treatment, and response; and length of hospitalization prior and subsequent to olanzapine treatment.

Response to olanzapine was assessed according to a four-point scale used in other studies.[4,14] Response was defined as follows: 0 = no response; 1 = minimal improvement, with slight reduction in symptoms and mild improvement in social or vocational functioning; 2 = moderate improvement, with significant but incomplete reduction in symptoms allowing clearly improved social or vocational functioning; and 3 = marked improvement, with virtual or complete remission of symptoms allowing return to premorbid social or vocational functioning. Response on this scale was determined by review of hospital records. Raters of response were not blind to diagnosis. For the purposes of this report, responders were defined as patients displaying a moderate-to-marked response to treatment (score 2 or 3), and nonresponders were defined as patients displaying no-to-minimal response to treatment (score 0 or 1).

For statistical analyses, categorical variables were compared using the chi-square test or two-tailed Fisher's exact test when expected cell sizes were less than five. Continuous variables were compared using the Wilcoxon rank-sum test or Student's unpaired t test as appropriate.

RESULTS

From October 1996 to February 1997, there were 1467 admissions, of which 155 (10.6%) consecutive patients were newly treated with olanzapine. Five patients discontinued olanzapine because of intolerable side effects. These included sedation (N = 3), agitation (N = 1), and drug-induced fever (N = 1).

The remaining 150 patients were included for analysis. This group consisted of 47 patients (31%) with bipolar disorder with psychotic features (20 manic, 14 depressed, and 13 mixed type); 29 (19%) with schizophrenia; 23 (15%) with schizoaffective disorder bipolar type; 17 (11%) with schizoaffective disorder depressive type; 22 (15%) with major depression with psychotic features; and 12 (8%) with psychosis not otherwise specified (NOS). The proportion of patients newly treated with olanzapine during the 5-month period within each diagnostic group was as follows: 9.8% (47/482) with bipolar disorder with psychotic features (8.9% [20/225] manic, 12.2% [14/115] depressed, and 9.2% [13/142] mixed

Table 1. Demographic and Treatment Characteristics of Patients Responsive and Nonresponsive to Olanzapine*

Variable	Olanzapine Response: None-to-Minimal N	None-to-Minimal %	Moderate-to-Marked N	Moderate-to-Marked %	p Value	Odds Ratio	95% CI for Odds Ratio
Dichotomous measures[a]							
Total	44	29	106	71	…	…	…
Female	13	20	53	80	.02	0.42	0.20, 0.89
White	39	29	96	71	NS	1.23	0.39, 3.83
Married	2	18	9	82	NS	1.95	0.40, 9.41
Schizophrenia	7	24	22	76	NS	1.39	0.54, 3.52
Schizoaffective, bipolar	6	26	17	74	NS	1.21	0.44, 3.31
Schizoaffective, depressed	9	53	8	47	.02	0.31	0.11, 0.89
Schizoaffective disorder, all	15	37	25	62	NS	0.60	0.27, 1.29
Bipolar, manic	4	20	16	80	NS	1.78	0.56, 5.66
Bipolar, mixed	2	15	11	85	NS	2.43	0.52, 11.4
Bipolar, depressed	2	14	12	86	NS	2.68	0.57, 12.5
Bipolar, all	8	17	39	83	.03	2.61	1.11, 6.20
Major depression with psychotic features	7	32	15	68	NS	0.87	0.33, 2.31
Psychosis NOS	7	58	5	42	.02	0.26	0.078, 0.88
Substance abuse	12	24	38	76	NS	1.49	0.69, 3.23
Nonresponsive to standard antipsychotics	19	24	61	76	NS	1.78	0.88, 3.63
Severe EPS from standard antipsychotics	19	29	46	71	NS	1.01	0.50, 2.05
Nonresponsive to risperidone	12	27	32	73	NS	1.15	0.53, 2.52
Intolerance to risperidone	4	36	7	64	NS	0.71	0.19, 2.55
Nonresponsive to clozapine	9	43	12	57	NS	0.49	0.19, 1.28
Intolerance to clozapine	3	27	8	73	NS	1.12	0.28, 4.42

	Mean ± SD	Mean ± SD	Mean Difference	t[b]	p[b]
Nondichotomous measures					
Age, y	49.1 ± 19	41.5 ± 16	7.6	2.20	.03
Length of stay, d	23.9 ± 24	21.9 ± 18	2.0	0.45	NS
Duration of illness, y	16.8 ± 11	13.1 ± 9	3.7	1.54	NS
Number of hospitalizations	10.4 ± 9	8.6 ± 6	1.8	0.76	NS
Olanzapine dose, mg/d	11.8 ± 5	11.8 ± 4	0.0	–0.49	NS
Duration of olanzapine trial, d	12.2 ± 11	17.7 ± 16	–5.5	–2.43	.02
Olanzapine response[c]	0.91 ± 0.3	2.51 ± 0.50	…	–10.2	< .001
Length of stay prior to olanzapine, d	10.8 ± 19	4.8 ± 6	6.0	2.35	.02

*Abbreviations: ... = statistical tests not applicable, CI = confidence interval, EPS = extrapyramidal side effects, NOS = not otherwise specified, NS = not significant.
[a]Percentages are calculated on the total N of each subset.
[b]Based on log-linear analysis of variance, except for the categorical variable olanzapine response, for which the Wilcoxon rank-sum test was used.
[c]Response: 0 = no response, 1 = minimal improvement, 2 = moderate improvement, 3 = marked improvement.

type); 17.9% (29/162) with schizophrenia; 10.2% (40/392) with schizoaffective disorder (13.9% [23/166] bipolar and 7.5% [17/226] depressive type); 6.6% (22/335) with major depression with psychotic features; 12.5% (12/96) with psychosis NOS; total 10.6% (155/1467).

Fifty (33%) of the patients received olanzapine alone, while the remaining 100 (67%) received other psychoactive drugs—including typical antipsychotics, risperidone, antidepressants, lithium, valproate, or carbamazepine—in addition to olanzapine.

Demographic and clinical characteristics of these patients, compared by olanzapine response, are presented in Table 1. Compared with patients displaying no-to-minimal response, patients displaying a moderate-to-marked response to olanzapine were more likely to be younger; female; receive a diagnosis of bipolar disorder; have a shorter duration of illness; have a longer olanzapine trial; and have a shorter length of stay prior to olanzapine treatment (Table 1). Compared with patients displaying moderate-to-marked response, patients displaying no-to-minimal response were more likely to have a diagnosis of schizoaffective disorder, depressive type and psychosis not otherwise specified (Table 1). No other demographic and treatment characteristics that were compared predicted response to olanzapine.

Of the 150 patients treated with olanzapine, 37% had previously discontinued risperidone, and 21% had previously discontinued clozapine because of either non-

Table 2. Response to Olanzapine Alone and in Combination With Thymoleptics According to DSM-IV Diagnosis

	None-to-Minimal		Moderate-to-Marked	
Diagnosis	N	%	N	%
Olanzapine alone				
Schizophrenia	4	14	11	38
Schizoaffective disorder, all	4	10	8	20
Schizoaffective disorder, bipolar type	0	0	4	17
Schizoaffective disorder, depressive type	4	24	4	24
Bipolar disorder, all	2	4	7	15
Bipolar disorder, manic type	2	10	4	20
Bipolar disorder, mixed type	0	0	1	8
Bipolar disorder, depressed type	0	0	2	14
Major depression with psychotic features	2	9	4	18
Psychosis NOS	4	33	4	33
Subtotal	*16*		*34*	
Olanzapine and thymoleptics				
Schizophrenia	3	10	11	38
Schizoaffective disorder, all	10	25	18	45
Schizoaffective disorder, bipolar type	5	22	14	61
Schizoaffective disorder, depressive type	5	29	4	24
Bipolar disorder, all	6	13	32	68
Bipolar disorder, manic type	2	10	12	60
Bipolar disorder, mixed type	2	15	10	77
Bipolar disorder, depressed type	2	14	10	71
Major depression with psychotic features	5	23	11	50
Psychosis NOS	3	25	1	8
Subtotal	*27*		*73*	
Overall total	*43*	*29*	*107*	*71*

response or intolerance (Table 1). A history of either intolerance or failure to respond to risperidone or clozapine failed to predict response or lack of response to olanzapine; still, 68% (59/87) of these patients subsequently responded to olanzapine (Table 1).

Response to olanzapine by diagnosis and concomitant thymoleptics is presented in Table 2. Patients with schizoaffective disorder and psychotic mood disorders were more likely to receive concomitant thymoleptics than those with schizophrenia ($p < .05$). However, responders in these former groups were no more likely than nonresponders to receive thymoleptics. Patients with schizoaffective or bipolar disorder who responded to treatment were no more likely to receive a thymoleptic than those who did not respond.

DISCUSSION

In this retrospective study, olanzapine was more likely to exert substantial therapeutic effects in younger, female, and less chronically ill patients. The response rate in our patients with schizophrenia was 76%, higher than the 66% rate reported by Beasley and colleagues.[15] More importantly, the response rate to olanzapine for the majority of psychiatric diagnoses studied (bipolar disorder, schizoaffective disorder-bipolar type, major depression with psychotic features) was above 65%, but only statistically significant for bipolar disorder. Given the severity, chronicity, and treatment-refractory nature of some of these diagnoses (many patients were either intolerant or refractory to neuroleptics, 53%; risperidone, 37%; or clozapine, 21%), these response rates are quite high.

Our initial hypothesis that patients with a diagnosis of bipolar disorder would have a positive response to olanzapine was confirmed. All but 8 bipolar patients responded to olanzapine. Second, we speculated that patients with a diagnosis of major depression with psychotic features would be associated with a high rate of response. However, we found no significant difference in the number of patients with major depression between responder and nonresponder groups. We also found that a diagnosis of schizoaffective disorder, depressive type or psychosis not otherwise specified treated with olanzapine was associated with poor response.

Another interesting finding was that moderate-to-marked response to olanzapine was associated with a shorter length of stay prior to olanzapine and a longer duration of trial. On the basis of this finding, it appears that some patients will require an earlier implementation of olanzapine treatment and a longer period of time on the drug to obtain a significant response. Similar clinical predictors of acute risperidone response have been reported. In the survey reported by Keck et al. in 1995,[14] patients displaying moderate-to-marked response to risperidone were more likely to be younger, receive a diagnosis of bipolar disorder, and have a shorter duration of illness and shorter length of stay prior to risperidone treatment.

The results of our survey are naturalistic and are affected by several important methodological limitations. Most importantly, patients received olanzapine under nonblinded, uncontrolled conditions. Ratings of response were not blinded to psychiatric diagnosis. DSM-IV diagnoses were not determined by a single investigator or by structured diagnostic interview, but by a number of treating clinicians, thereby introducing a source of variance. Finally, the majority of patients also received other psychotropic agents, and as a result, caution should be used when interpreting these findings.

Despite these limitations, the findings, though preliminary, suggest that olanzapine may be a useful alternative or adjunctive treatment for patients with bipolar disorder when used as monotherapy or in conjunction with mood stabilizers. Controlled studies of olanzapine in bipolar disorders are needed to determine the exact nature and extent of this agent as an antimanic and mood-stabilizing agent.

Drug names: carbamazepine (Tegretol and others), clozapine (Clozaril), gabapentin (Neurontin), haloperidol (Haldol and others), lamotrigine (Lamictal), olanzapine (Zyprexa), risperidone (Risperdal).

REFERENCES

1. Baldessarini RJ, Tondo L, Suppes T, et al. Pharmacological treatment of bipolar disorder across the life cycle. In: Shulman KI, Tohen M, Kutcher SP, eds. Mood Disorders Across the Life Span. New York, NY: John Wiley & Sons; 1996:299–338
2. Keck PE Jr, McElroy SL, Nemeroff CB. Anticonvulsants in the treatment of bipolar disorder. J Neuropsychiatry Clin Neurosci 1992;4:395–405
3. Tohen M, Zarate CA Jr. Antipsychotic agents and bipolar disorder. J Clin Psychiatry 1998;59(suppl 1):38–48
4. McElroy SL, Dessain EC, Pope HG Jr, et al. Clozapine in the treatment of psychotic mood disorders, schizoaffective disorder, and schizophrenia. J Clin Psychiatry 1991;52:411–414
5. Zarate CA Jr, Tohen M, Baldessarini RJ. Clozapine in severe mood disorders. J Clin Psychiatry 1995;56:411–417
6. Calabrese JR, Kimmel SE, Woyshville MJ, et al. Clozapine for treatment-refractory mania. Am J Psychiatry 1996;153:759–764
7. Tohen M, Zarate CA Jr, Centorrino F, et al. Risperidone in the treatment of mania. J Clin Psychiatry 1996;57:249–253
8. Banov MD, Zarate CA Jr, Tohen M, et al. Clozapine therapy in refractory affective disorders: polarity predicts response in long-term follow-up. J Clin Psychiatry 1994;55:295–300
9. Marder SR, Meibach RC. Risperidone in the treatment of schizophrenia. Am J Psychiatry 1994;151:825–835
10. Hillert A, Maier W, Wetzel H, et al. Risperidone in the treatment of affective disorders with a combined psychotic and depressive syndrome: a functional approach. Pharmacopsychiatry 1992;25:213–217
11. Dwight MM, Keck PE Jr, Stanton SP, et al. Antidepressant activity and mania associated with risperidone treatment of schizoaffective disorder. Lancet 1994;344:554–555
12. Suppes T, McElroy S, Gilbert J, et al. Clozapine in the treatment of dysphoric mania. Biol Psychiatry 1992;32:270–280
13. Zarate CA Jr, Tohen M, Banov MD, et al. Is clozapine a mood stabilizer? J Clin Psychiatry 1995;56:108–112
14. Keck PE Jr, Wilson DR, Strakowski SM, et al. Clinical predictors of acute risperidone response in schizophrenia, schizoaffective disorder, and psychotic mood disorders. J Clin Psychiatry 1995;56:466–470
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. Baker R, Ames D, Umbricht D, et al. Olanzapine's impact on depressive and obsessive-compulsive symptoms in schizophrenia. Psychopharmacol Bull 1995;31:549
17. Tollefson GD, Beasley CM Jr, 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. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Association; 1994