Clinical Predictors of Acute Response With Quetiapine in Psychotic Mood Disorders

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Background: In controlled studies of patients with schizophrenia, the atypical antipsychotic quetiapine, 300 mg/day, has been shown to be as effective in the treatment of positive and negative symptoms as haloperidol. However, little is known about the efficacy of quetiapine in patients with psychotic mood disorders. The purpose of this study was to assess the efficacy of quetiapine in the treatment of psychotic mood disorders in comparison with nonaffective psychotic disorders and identify clinical factors associated with quetiapine response.

Method: In a naturalistic setting, by reviewing medical records, we assessed response to quetiapine and factors associated with response to quetiapine in 145 consecutive patients newly treated with the drug at a nonprofit academic psychiatric hospital. These patients had received a discharge diagnosis of bipolar disorder (manic, mixed, or depressive type), major depression with psychotic features, schizophrenia, schizoaffective disorder (bipolar or depressive type), delusional disorder, or psychosis not otherwise specified (NOS) according to DSM-IV criteria.

Results: Patients with a diagnosis of bipolar disorder, manic, mixed, or depressed and schizoaffective disorder, bipolar type displayed higher response rates (> 74%) compared with patients with schizophrenia. However, this finding did not achieve statistical significance. A diagnosis of major depression with psychotic features ($p = .02$) and longer duration of illness ($p = .03$) were associated with less chance of responding.

Conclusion: Quetiapine may be a useful alternative or adjunctive treatment for patients with bipolar and schizoaffective disorders.

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The last several years have seen an increased interest in the role of atypical antipsychotic agents in bipolar disorder.[1] Clozapine was the first atypical antipsychotic agent introduced and has, in case series and open-label studies, been shown to be efficacious in patients with severe mood disorders.[2–6] Similarly, in many case series and open-label studies[7–9] and one small double-blind study,[10] risperidone has been suggested to have thymoleptic properties in patients with schizoaffective and bipolar disorder. More recently, it has been suggested that olanzapine may be efficacious in patients with psychotic mood disorders.[11–13] Zarate and colleagues[12] recently conducted a retrospective review of 150 patients treated with olanzapine at a private psychiatric hospital. They found treatment response rates in bipolar disorder (83%, N = 47) and schizoaffective disorder (74% for bipolar type, N = 23; 47% for depressed type, N = 17) to be similar to that in schizophrenia (76%, N = 29).

Quetiapine is the third of the atypical antipsychotic drugs to be released into the market after clozapine. Quetiapine exhibits affinity for brain serotonin 5-HT_{1A} and 5-HT_2 receptors and dopamine D_1 and D_2 receptors.[14,15] These receptor properties have been shown to be characteristic of atypicality, i.e., antipsychotic action with minimal extrapyramidal symptoms (EPS).[16] Quetiapine has, in 2 double-blind clinical trials[14,15] at doses ranging from 75 to 750 mg/day, been found to be superior to placebo and equivalent to haloperidol in the treatment of positive and negative symptoms of schizophrenia.

In a recently completed open-label trial evaluating the safety and tolerability of quetiapine, 728 subjects with schizophrenia and other psychotic disorders were randomly assigned in a 3:1 ratio to quetiapine (553 subjects) or risperidone (175 subjects).[17] Quetiapine-treated subjects had significantly lower occurrence of substantial EPS than risperidone-treated subjects throughout the trial. The quetiapine group had significantly ($p = .03$) greater improvement on Hamilton Rating Scale for Depression (HAM-D) scores than the risperidone group.[17]

Given the above preliminary data and encouraging results with other atypical antipsychotic agents, we hypothesized that patients with psychotic mood disorders (bipolar disorder and major depression with psychotic features) would respond better to quetiapine than patients

without these features. To test this hypothesis, we surveyed a consecutive series of patients receiving quetiapine at McLean Hospital (Belmont, Mass.), a private, nonprofit psychiatric hospital.

METHOD

In a retrospective chart review, we identified all patients consecutively admitted to McLean Hospital over 9 months between October 1997 and June 1998. Patients included in this study were men and women aged 18 years and older who were newly treated with quetiapine and who had received a discharge diagnosis of bipolar disorder (manic, mixed, or depressive type), major depression with psychotic features, schizophrenia, schizoaffective disorder (bipolar or depressive type), delusional disorder, or psychosis not otherwise specified (NOS) according to DSM-IV criteria.[18] We have previously shown high rates of agreement (93%) between the discharge diagnosis assigned by the treating clinician and that assigned by the "best-estimate procedure."[4] Using similar methodology, we randomly selected 20 charts from this study population. We photocopied these charts, and the patients' names and any mention of their medical chart diagnosis were concealed. A "best-estimate" diagnosis was obtained for these patients by 2 senior clinicians blind to the treating clinician's diagnosis. There was agreement in all but one diagnosis (95% agreement). We used the same methods for this report as those used to examine the clinical predictors of acute response with olanzapine in psychotic mood disorders.[12]

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

Response to quetiapine was assessed according to a 4-point scale used in another study.[12] 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* are defined as patients displaying a moderate-to-marked response (score = 2–3) to treatment and *nonresponders* are defined as patients displaying no-to-minimal response (score = 0–1) to treatment. Response by diagnostic group was calculated by comparing one diagnosis with all other diagnostic categories combined.

For bivariate statistical analyses, categorical variables were compared using the chi-square test or the 2-tailed Fisher exact test when expected cell sizes were less than 5. Continuous variables were compared using the Wilcoxon rank-sum test or unpaired t test as appropriate. For multivariate analyses, stepwise forward selection logistic regression was used.

RESULTS

From October 1997 to June 1998, there were 2856 admissions, of which 145 consecutive patients (5%) were newly treated with quetiapine. Fifty-one of those patients (35%) experienced at least one side effect; however, no patient discontinued quetiapine because of intolerable side effects, and all are included in the analysis. These adverse events in order of prevalence were sedation (15%), dizziness (6%), hypotension (4%), dyspepsia (4%), headache (3%), tremor (1%), and akathisia (< 1%). Twenty patients (14%) discontinued quetiapine because of lack of response. Thus, 145 patients were included for analysis. This group consisted of 37 patients (26%) with bipolar disorder with psychotic features (19 manic, 13 mixed, and 5 depressed type), 37 (26%) with major depression with psychotic features, 31 (21%) with schizoaffective disorder (22 bipolar, 9 depressive type), 19 (13%) with schizophrenia, 19 (13%) with psychosis NOS, and 2 (1%) with delusional disorder. The proportion of patients newly treated with quetiapine to admitted patients during the 9-month period within each diagnostic group was as follows: 4% (37/954) with bipolar disorder with psychotic features (5% [19/412] manic, 4% [13/302] mixed, 2% [5/240] depressed type), 6% (37/644) with major depression with psychotic features, 4% (31/738) with schizoaffective disorder (7% [21/305] bipolar and 2% [9/433] depressive type), 6% (19/301) with schizophrenia, 10% (19/188) with psychosis NOS, and 7% (2/31) with delusional disorder, for a total of 5% (145/2856).

Twenty-nine of the patients (20%) received quetiapine alone, while the remaining 116 (80%) received other psychoactive drugs, including typical antipsychotics, risperidone, olanzapine, clozapine, antidepressants, lithium, valproate, carbamazepine, gabapentin, and lamotrigine, in addition to quetiapine.

The proportion of patients responding to quetiapine with a moderate-to-marked response according to various demographic and clinical characteristics are presented in Table 1. Results of bivariate analyses are also included in Table 1. These results indicate that very few of the demographic or clinical characteristics distinguished responders from nonresponders. Patients with a diagnosis of bipolar disorder (manic, mixed, or depressed) and schizoaffective disorder, bipolar type displayed higher response

Table 1. Demographic and Treatment Characteristics of 104 Patients Responsive to Quetiapine[a]

Variable	Condition	Moderate-to-Marked Response N	Moderate-to-Marked Response %[b]	Odds Ratio	95% CI for Odds Ratio
Dichotomous measures					
Gender	Male	40	76	1.35	0.63 to 2.90
	Female	64	70		
Race	White	96	72	1.30	0.37 to 4.57
	Other	8	67		
Marital status	Married	13	81	1.81	0.49 to 6.72
	Not married	91	71		
Diagnosis					
Schizophrenia	Yes	14	74	1.12	0.36 to 3.34
	No	90	71		
Schizoaffective, bipolar	Yes	19	86	2.83*	0.79 to 10.15
	No	85	69		
Schizoaffective, depressed	Yes	4	44	0.29*	0.07 to 1.13
	No	100	74		
Schizoaffective, all	Yes	23	74	1.17	0.48 to 2.88
	No	81	71		
Bipolar, manic	Yes	16	84	2.30	0.63 to 8.37
	No	88	70		
Bipolar, mixed	Yes	10	77	1.35	0.35 to 5.17
	No	94	71		
Bipolar, depressed	Yes	4	80	1.60	0.17 to 14.76
	No	100	71		
Bipolar, all	Yes	30	81	1.97	0.79 to 4.93
	No	74	69		
Major depression, psychotic	Yes	21	57	0.40**	0.18 to 0.87
	No	83	77		
Psychosis, NOS	Yes	14	74	1.12	0.38 to 3.34
	No	90	71		
Nonresponsive to standard antipsychotics	Yes	57	71	0.74	0.27 to 2.09
	No	47	72		
Severe EPS from standard antipsychotics	Yes	39	76	1.01	0.41 to 2.45
	No	65	69		
Nonresponsive to risperidone	Yes	33	75	…	…
	No	71	70		
Intolerance to risperidone	Yes	8	89	0.92	0.35 to 2.41
	No	96	71		
Nonresponsive to clozapine	Yes	14	78	…	…
	No	90	71		
Intolerance to clozapine	Yes	6	100	…	…
	No	98	71		
Nonresponsive to olanzapine	Yes	23	79	0.43	0.09 to 2.08
	No	81	70		
Intolerance to olanzapine	Yes	26	79	0.40	0.13 to 1.28
	No	78	70		

	No-to-Minimal Response Mean ± SD	Moderate-to-Marked Response Mean ± SD	Mean Difference	t[c]	p[c] Value
Nondichotomous measures					
Age, y	39.2 ± 15	39.3 ± 16	0.1	0.04	NS
Length of stay, d	35.6 ± 51	27.6 ± 21	–8.0	–1.4	NS
Duration of illness, y	15.8 ± 12	11.3 ± 11	–4.5	–2.20	.03
Number of hospitalizations	7.3 ± 6	7.7 ± 7	0.4	0.35	NS
Quetiapine dose, mg/d	188.4 ± 148	245.0 ± 180	–64.6	–1.79	NS
Length of stay prior to quetiapine, d	4.5 ± 8.41	2.7 ± 4	1.7	1.64	NS
Duration of quetiapine trial, d	18.0 ± 22	20.0 ± 16	–1.9	–0.60	NS
Quetiapine response[d]	0.85 ± 0.4	2.4 ± 0.5	…	–17.99	< .001

[a]Abbreviations: … = statistical tests not applicable, CI = confidence interval, EPS = extrapyramidal side effects, NOS = not otherwise specified, NS = not significant.
[b]Percentages are calculated on the total N in each category.
[c]Based on log-linear analysis of variance, except for the categorical variable quetiapine response, for which the Wilcoxon rank-sum test was used.
[d]Response: 0 = no response, 1 = minimal improvement, 2 = moderate improvement, 3 = marked improvement.
*p < .15.
**p < .05.

rates (> 74%) compared with patients with schizophrenia. However, this finding did not achieve statistical significance. A diagnosis of major depression with psychotic features was associated with less chance of responding ($\chi^2 = 5.49$, df = 1, p = .02; odds ratio [OR] = 0.40, 95% confidence interval [CI] = 0.18 to 0.87). Longer duration of illness also was associated with less chance of responding (t = –2.20, df = 143, p = .03).

Of the 145 patients treated with quetiapine, 37% had previously discontinued risperidone, 43% had discontinued olanzapine, and 17% had previously discontinued clozapine because of either nonresponse or intolerance (see Table 1). A history of either intolerance or failure to respond to risperidone, olanzapine, or clozapine failed to predict response or lack of response to quetiapine; still, 76% (110/145) of these patients subsequently responded to quetiapine (see Table 1).

Patients with schizoaffective disorder and psychotic mood disorders were more likely to receive concomitant thymoleptics than those with schizophrenia (90/105 [86%] vs. 10/19 [53%]; $\chi^2 = 11.28$, df = 1, p = .0008). However, responders in these former groups were not more likely than nonresponders to receive thymoleptics. Patients with schizoaffective, major depression, or bipolar disorder who responded to treatment were not more likely to receive a thymoleptic than those who did not respond.

A multivariate analysis assessed the simultaneous impact of several potential predictors of response while controlling for age, gender, and whether or not patients were taking other atypical antipsychotics. A logistic regression with dichotomous response status as the dependent measure was conducted. Age, gender, and an indicator of whether or not a patient was taking other atypical antipsychotics were first forced into the equation. Then, the predictor variables of interest were submitted to a forward stepwise procedure. Four predictor variables were included in the analysis. These included the 2

Table 2. Results of Forward Stepwise Logistic Regression of Select Variables Predicting Response

Variable	β Coefficient	S.E.	p Value	Odds Ratio	95% CI for Odds Ratio
Male	–0.02	0.43	NS	0.98	0.42 to 2.29
Age, y	0.02	0.02	NS	1.02	0.98 to 1.05
Other antipsychotic	0.57	0.55	NS	1.77	0.60 to 5.21
Duration of illness, y	–0.04	0.02	.04	0.96	0.92 to 1.00
Major depression, psychotic features	–1.09	0.44	.01	0.34	0.14 to 0.80
Schizoaffective, depressed	–1.50	0.73	.04	0.22	0.05 to 0.94
Constant	1.17	0.66	.08		

variables that bivariate analysis indicated were significantly associated with response status: diagnosis of major depression and duration of illness. Because multivariate analysis can reveal unsuspected associations among variables, 2 other clinical indicators whose significance levels were lower than .15 were included in the analysis: a diagnosis of schizoaffective disorder bipolar type and a diagnosis of schizoaffective disorder depressive type ($\chi^2 = 3.52$, df = 1, p = .06; OR = 0.288, 95% CI = 0.73 to 1.13).

The results of the logistic regression analysis are presented in Table 2. The statistics for the model ($\chi^2 = 16.23$, df = 6, p = .01) indicated that the model performed significantly better than one with only the constant in it. Unfortunately, the model is still not a very good fit to the data. This is demonstrated by the fact that although the model predicts good response with 90% (94 of 104) accuracy, it is able to predict poor response with only 27% accuracy (11 of 41). However, the model does suggest that after taking gender, age, and whether or not a patient is taking other atypical antipsychotics into account, response is reduced with duration of illness (OR per year = 0.96, 95% CI = 0.92 to 1.00) and with a diagnosis of either major depression with psychotic features (OR = 0.34, 95% CI = 0.14 to 0.80) or schizoaffective disorder depressive type (OR = 0.22, 95% CI = 0.05 to 0.94). Diagnosis of schizoaffective disorder bipolar type did not enter into the final equation.

DISCUSSION

In this retrospective study, quetiapine was more likely to exert substantial therapeutic effects in patients with affective psychoses and in patients who were less chronically ill. The response rate in our patients with schizophrenia was 74%, higher than the 51% rate reported by Arvanitis and colleagues.[14] More importantly, the response rate to quetiapine for the majority of psychiatric diagnoses studied (such as bipolar disorder and schizoaffective disorder, bipolar type) was equal or superior to that of schizophrenia. Given the severity, chronicity, and treatment-refractory nature of some of these diagnoses (many patients were either intolerant or refractory to neuroleptics [90%], olanzapine [43%], risperidone [37%], or clozapine [17%]), these response rates are quite high.

Our initial hypothesis that patients with a diagnosis of affective psychoses would have a good response to quetiapine was confirmed only for bipolar disorder. All bipolar patients but 7 responded to quetiapine; however, this response rate did not reach statistical significance. Second, we speculated that patients with a diagnosis of major depression with psychotic features would be associated with a high rate of response. We did not find this to be the case. Patients with this diagnosis compared with other diagnoses were less likely to respond to quetiapine. The other factor predictive of poor response to quetiapine was chronicity of illness: the longer the psychiatric illness, the less chance of response to quetiapine.

Another finding in this study was the high response rate seen in patients with schizophrenia. As stated above, we found that 74% of patients with a diagnosis of schizophrenia had a favorable response to quetiapine. This rate of response is much higher than the 51% response rate reported previously by Arvanitis and colleagues,[14] but similar to that reported with olanzapine (76%) in another study.[12] Differences in the response rate may be in the methodology used; in the Arvanitis et al.[14] study, patients were studied in controlled conditions, whereas in the study of Zarate et al.[12] and the present study, response was assigned retrospectively by chart review.

The results of this survey are naturalistic and are affected by several important methodological limitations. Most importantly, patients received quetiapine under nonblind, uncontrolled conditions. Response was not rated blind 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. However, we found high agreement between the discharge diagnosis made by the treating clinicians and the diagnosis assigned (blind to the treating clinician's diagnosis) by a "best-estimate" procedure. 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 quetiapine may be a useful alternative or adjunctive treatment for patients with affective psychosis when used in conjunction with mood stabilizers. Controlled studies of quetiapine in patients with bipolar disorders (manic, mixed, or depressed phase of their illness) and major depression with psychotic features are needed to determine the exact nature and extent of this agent as an antimanic, antidepressant, and mood-stabilizing agent.

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

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