Clozapine in Treatment-Resistant Patients With Schizophrenia, Schizoaffective Disorder, or Psychotic Bipolar Disorder: A Naturalistic 48-Month Follow-Up Study

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Background: The aim of this study was to evaluate the long-term efficacy and safety of clozapine in patients with treatment-resistant schizophrenia, schizoaffective disorder, or bipolar disorder with psychotic features.

Method: 101 patients with a DSM-III-R diagnosis of schizophrenia (N = 34); schizoaffective disorder, bipolar type (N = 30); or bipolar disorder with psychotic features (N = 37) were naturalistically treated with clozapine at flexible doses over a 48-month period. Data were collected from 1994 to 2000. The Brief Psychiatric Rating Scale (BPRS) and Clinical Global Impressions-Severity of Illness scale total predicted scores over time were estimated with random-effects regression models. Time to response to clozapine, defined as 50% reduction of BPRS score, was analyzed in the 3 diagnostic groups using the Kaplan-Meier method. Survival curves were compared using the log-rank test.

Results: The BPRS total predicted score halved its baseline value in 3 months for bipolar disorder patients, in 6 months for schizoaffective disorder patients, and in 24 months for schizophrenia patients. The proportion of subjects who satisfied the criterion for response to clozapine after 48 months of follow-up was significantly ($p < .01$) higher in the schizoaffective and bipolar disorder groups (90.0% and 83.8%, respectively) than in the schizophrenia group (64.7%). Baseline scores on the Global Assessment of Functioning (GAF) showed low levels of psychosocial and occupational functioning in all 3 groups. After 48 months of treatment, GAF scores showed a functional improvement in all 3 groups, with significantly ($p < .01$) greater improvement in the bipolar disorder group compared with the other groups.

Conclusion: The findings of this study confirm the efficacy and safety of clozapine for treatment-resistant patients with a diagnosis of schizophrenia, schizoaffective disorder, or bipolar disorder with psychotic features. Patients with schizoaffective disorder and those with bipolar disorder show greater clinical improvement than those with schizophrenia. Patients with bipolar disorder have the shortest time to response and the highest psychosocial and occupational functioning levels. Patients with schizoaffective disorder have the lowest treatment discontinuation rate.

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In the last decade, several studies extended the use of clozapine therapy from treatment-resistant schizophrenia[1,2] to schizoaffective disorder, severe mood disorders, borderline personality disorder, and substance abuse disorder.[3]

Patients with bipolar disorder and schizoaffective disorder[4] who were treated with clozapine monotherapy showed a drastic reduction of mood episodes and rehospitalization, and mood-stabilizing effects have been reported in patients with refractory mania.[5–11] Clinical studies on clozapine were mainly based on chart reviews and short-term evaluations.[7,12–18]

In a 12-month prospective follow-up study of clozapine in patients with schizophrenic spectrum disorders, a greater improvement was found in patients with bipolar features than in those without, suggesting that mood symptoms could be associated with a good response to clozapine.[19] McElroy et al.,[20] in a 26-month study based on review of patient records, found a greater response to clozapine in schizoaffective and psychotic bipolar disorder than in schizophrenia.

More recently, Suppes et al.[21] pointed out the antimanic and mood-stabilizing properties of clozapine therapy during a period of 12 months in 38 treatment-resistant patients with schizoaffective or bipolar disorder.

Our previous naturalistic open-label 24-month follow-up study[22] gave further evidence of the utility of clozapine in treatment-refractory patients with schizophrenia, schizoaffective disorder, or bipolar disorder with psychotic features.

The present naturalistic prospective 48-month follow-up study, an extension of the previous study, evaluated the long-term efficacy and safety of clozapine in 101 patients with treatment-resistant schizophrenia (N = 34), schizoaffective disorder (N = 30), or bipolar disorder with psychotic features (N = 37).

METHOD

Study Sample

A cohort of 101 patients was consecutively recruited for a clozapine treatment follow-up program at the day-hospital service and wards of the Department of Psychiatry, University of Pisa (Pisa, Italy). Data were collected from 1994 to 2000. All patients met DSM-III-R diagnostic criteria[23] for schizophrenia, bipolar disorder with psychotic features, or schizoaffective disorder, bipolar type, and gave their consent to participate in the study after procedures and possible side effects were explained to them. The study was approved by the Local Ethical Committee in accordance with the Declaration of Helsinki (1996) and with the Guidelines for Good Clinical Practice (1995).

The method of this naturalistic follow-up study has been described in detail elsewhere.[22] Diagnostic evaluations and psychopathologic assessments were performed by 2 resident psychiatrists (M.C.C., M.F.), who were skilled clinical researchers with at least 3 years of clinical experience in diagnostic evaluation and psychopathologic assessment of treatment-resistant psychotic patients, using the scales administered in the current study. The diagnosis was confirmed by a senior psychiatrist (A.C.). Patients were selected because of their resistance to classical antipsychotic drugs, and they had to be free from depot neuroleptics for a period of at least 8 weeks before entering the study.

Subjects enrolled were defined as "treatment-resistant" if they had persistent psychotic symptoms despite adequate treatment with 3 different classes of antipsychotics at doses equivalent to 300–600 mg/day of chlorpromazine for at least 12 weeks.

Clozapine was titrated by starting with a dose of 25 mg/day and increasing the dose to a maximum of 600 mg/day. During the 48-month follow-up period, clozapine doses were adjusted on the basis of clinical response to a lower but effective dose.

Combination of clozapine (25–600 mg/day) with selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), sodium valproate, lithium, and/or typical neuroleptics was permitted. Types, number, and dosages of adjunctive agents were registered at 3 and 48 months. The rating scale scores were not considered for changing medications.

Assessment

Severity of psychopathology was assessed at baseline and after 1, 3, 6, 12, 18, 24, 36, and 48 months using the 18-item Brief Psychiatric Rating Scale (BPRS),[24] scored on a 0-to-6 scale. The Clinical Global Impressions-Severity of Illness scale (CGI-S)[25] was also administered at baseline and after 12, 24, 36, and 48 months.

Psychosocial and occupational functioning were measured using the Global Assessment of Functioning (GAF),[26] which contains questions referring to the patient's status over the past year. The GAF was administered at clozapine therapy first intake and after 48 months of treatment.

The outcome measure of clinical response was defined a priori as a reduction of at least 50% in BPRS total score in 1 evaluation with respect to baseline. The outcome measure of psychosocial and occupational functioning was defined a priori as a GAF score of at least 51, corresponding to "moderate symptoms or moderate difficulties in social, occupational, or school functioning."[23(p20)] The following sociodemographic and clinical data were also collected at baseline: age, gender, marital status, employment, education, duration of illness, age at onset, aggressive behavior, and suicide attempt or ideation.

Statistical Analysis

Patients' characteristics were compared among diagnostic groups using contingency tables for categorical variables (exact p values) and Kruskal-Wallis nonparametric tests for continuous variables. Since continuous variables showed highly skewed distributions, nonparametric tests were preferred. Differences in GAF score between baseline and after 48 months were assessed using the Wilcoxon signed rank test. BPRS and CGI total predicted scores over time were estimated with random-effects regression models to account for potential correlation within patients' repeated observations.[27] The missing-value generating process was assumed to be "at random."[28] Timepoint and diagnosis were introduced as independent covariates by means of indicator variables. Confidence intervals were computed and Wald tests were performed for all estimated coefficients of the regression models. p Values less than .05 were considered significant unless otherwise specified. Interaction terms were kept in the models only when significant. Other covariates were also considered, namely, suicidal ideation, aggressiveness, age at first episode, and sex. These appeared to be neither confounders nor effect modifiers and were kept out of the models. Time to 50% reduction in BPRS total score was compared among the 3 groups of patients with different diagnosis using Kaplan-Meier survival curves and Mantel-Cox log-rank tests (based on chi-square asymptotic approximation). Statistical analysis was performed using commercially available statistical software (Stata Corporation, College Station, Tex.).

RESULTS

Of 101 patients enrolled in this study, 34 fulfilled DSM-III-R criteria for schizophrenia; 30, for schizo-

Table 1. Sociodemographic and Clinical Characteristics at Baseline of 101 Psychotic Patients Treated With Clozapine Over a 48-Month Follow-Up

Characteristic	Schizophrenia (N = 34)	Schizoaffective Disorder, Bipolar Type (N = 30)	Bipolar Disorder With Psychotic Features (N = 37)
Age, mean ± SD, y	33.3 ± 11.7	32.0 ± 7.4	37.2 ± 14.0
Males, N (%)	22 (64.7)	23 (76.7)	25 (67.6)
Married, N (%)[a]	2 (5.9)	7 (23.3)	14 (37.8)
Unemployed, N (%)	22 (64.7)	16 (53.3)	18 (48.6)
Education (at least 8 y), N (%)	29 (85.3)	28 (93.3)	35 (94.6)
Duration of illness, mean ± SD, y	13.7 ± 11.0	13.5 ± 6.5	13.0 ± 8.0
Age at onset, mean ± SD, y	19.6 ± 5.3	18.5 ± 3.0	24.2 ± 11.0
Aggressive behavior, N (%)	27 (79.4)	21 (70.0)	21 (56.8)
Suicide attempt or ideation, N (%)	10 (29.4)	10 (33.3)	9 (24.3)
CGI-S baseline score, mean ± SD[b]	5.8 ± 0.7	5.5 ± 0.8	5.2 ± 0.8
GAF baseline score, mean ± SD[c]	29.8 ± 7.1	32.0 ± 8.7	34.2 ± 6.6
BPRS baseline score, mean ± SD	51.4 ± 14.1	50.4 ± 13.3	46.4 ± 13.6
BPRS factor score, mean ± SD			
Anxiety-depression	10.1 ± 5.76	12.3 ± 5.6	10.9 ± 4.4
Anergia[b]	11.4 ± 3.6	9.6 ± 2.9	7.6 ± 3.9
Thought disorder[c]	12.9 ± 3.8	11.6 ± 4.0	9.9 ± 5.8
Activity	8.1 ± 4.4	8.7 ± 3.9	9.0 ± 2.6
Hostility-suspiciousness	8.8 ± 4.6	8.3 ± 3.5	9.0 ± 4.6

[a]p value < .01 by exact test.
[b]p value < .01 by Kruskal-Wallis.
[c]p value < .05 by Kruskal-Wallis.
Abbreviations: BPRS = Brief Psychiatric Rating Scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, GAF = Global Assessment of Functioning.

affective disorder, bipolar type; and 37, for bipolar disorder with psychotic features.

Age, gender, education, rate of unemployment, age at onset, and duration of illness did not significantly differ among the 3 groups; married subjects were significantly less represented among patients with schizophrenia than among patients with bipolar disorder (Table 1).

Patients presented with severe symptomatology and high impairment in social functioning, as shown by baseline BPRS and GAF scores (Table 1). The 3 diagnostic groups did not significantly differ in baseline psychopathology as assessed by BPRS total score. The scores for the anxiety-depression, activity, and hostility-suspiciousness BPRS factors[24] did not differ among the 3 diagnostic groups. The anergia and thought disorder factor scores were significantly lower in patients with bipolar disorder than in those with schizophrenia (Table 1).

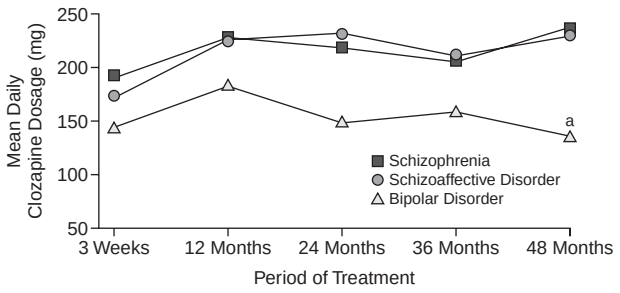
Baseline GAF scores were significantly higher in patients with bipolar disorder than in patients with schizophrenia (Table 1). Baseline CGI-S scores were significantly higher in patients with schizophrenia than in those with bipolar disorder (Table 1). Aggressive behavior and suicidal ideation did not significantly differ among the 3 groups (Table 1).

Fifty-four patients (53.5% of the sample; 58.8% of those with schizophrenia, 36.7% of those with schizoaffective disorder, and 62.2% of those with bipolar disorder) discontinued clozapine treatment during the 48-month follow-up period: 18 (17.8%) discontinued clozapine during the first 12 months of treatment; 17 (16.8%), between 12 and 18 months; 3 (3.0%), between 18 and 24 months; 6 (5.9%), between 24 and 36 months; and 10 (9.9%), between 36 and 48 months. Reasons for discontinuation were (1) inadequate response to treatment (worsening of symptomatology, relapse [defined as hospitalization for psychopathology], or rehospitalization) in 15 subjects (14.9%), (2) noncompliance in 17 subjects (16.8%), (3) side effects (sedation, sleep cycle inversion, weight gain, leukopenia) in 5 subjects (5.0%), and (4) other reasons in 17 subjects (16.8%): inability to regularly reach our center due to distance (N = 13), pregnancy (N = 2), or spontaneous treatment interruption due to improvement (N = 2). Inadequate response to clozapine was experienced by 7 patients (20.6%) with schizophrenia, 2 patients (6.7%) with schizoaffective disorder, and 6 patients (16.2%) with bipolar disorder. Subjects who discontinued clozapine therapy did not significantly differ from those who completed in gender, marital status, severity of illness as assessed by BPRS and CGI-S scores, suicidal ideation, or aggressive behaviors.

Response to Treatment

The mean daily dose of clozapine did not differ within each of the 3 diagnostic groups over the 48-month period. Mean daily clozapine doses after 3 weeks, 12 months, 24 months, and 36 months were as follows: 190 mg, 227 mg, 218 mg, and 206 mg in patients with schizophrenia; 172 mg, 223 mg, 231 mg, and 211 mg in patients with schizoaffective disorder; and 144 mg, 184 mg, 149 mg, and 160 mg in patients with bipolar disorder. After 48 months, the mean daily doses of clozapine were significantly lower in patients with bipolar disorder (137 mg) than in patients with schizoaffective disorder (228 mg) or schizophrenia (236 mg) as shown in Figure 1.

Figure 1. Mean Daily Clozapine Dose for Patients With Schizophrenia (N = 34), Schizoaffective Disorder (N = 30), or Bipolar Disorder With Psychotic Features (N = 37)



[a]p < .05 by Kruskal-Wallis test.

During the 48-month follow-up period, adjunctive agents were added to clozapine for patients from each diagnostic category. In the schizophrenia group, patients were administered typical neuroleptics (47.1%; 16/34), anticonvulsants (17.6%; 6/34), antidepressants (47.1%; 16/34), and benzodiazepines (8.8%; 3/34). In the schizoaffective disorder group, patients were administered typical neuroleptics (43.3%; 13/30), lithium (6.7%; 2/30), anticonvulsants (13.3%; 4/30), antidepressants (60.0%; 18/30), and benzodiazepines (23.3%; 7/30). In the bipolar disorder group, patients were administered typical neuroleptics (37.8%; 14/37), lithium (27.0%; 10/37), anticonvulsants (35.1%; 13/37), antidepressants (37.8%; 14/37), and benzodiazepines (8.1%; 3/37).

Overall, mean baseline BPRS total score did not significantly differ between those treated with clozapine monotherapy (18/101; 17.8%) and those treated with a combination of clozapine and typical neuroleptics (43/101; 42.6%).

When changes in the dosages and/or number of adjunctive agents (converted to standardized equivalent doses of chlorpromazine, sodium valproate, fluvoxamine, and imipramine) over the whole period of follow-up were evaluated, only the patients who completed the study (N = 47) were considered (Table 2). No data on benzodiazepine doses were reported, as these medications were occasionally administered at variable doses, only to control acute anxiety symptomatology.

Between the third and 48th months of follow-up, in all 3 diagnostic groups, a clinically relevant reduction was observed in the number of patients treated with a combination of clozapine and a typical neuroleptic (from 12 patients at the third month to 6 patients at the 48th month among those with schizophrenia, from 14 to 9 patients in those with schizoaffective disorder, and from 6 to 3 patients in those with bipolar disorder with psychotic features), and a clinically relevant decrease was observed in the highest equivalent doses of chlorpromazine administered (from 300 mg/day to 53 mg/day). Discontinuation of sodium valproate was observed more often in patients with schizophrenia and schizoaffective disorder (from 7 to 1 patients and from 15 to 2 patients, respectively) than in bipolar patients (from 10 to 8 patients). The highest equivalent doses of sodium valproate administered to patients in all diagnostic groups decreased over the follow-up period from 1200 to 400 mg/day.

No patient with schizophrenia received lithium therapy. The number of patients with schizoaffective disorder and bipolar disorder with psychotic features receiving lithium therapy dropped from 3 to 1 and from 6 to 4, respectively.

The number of patients with schizophrenia or schizoaffective disorder receiving SSRI therapy increased from 2 to 5 and from 5 to 11, respectively, while in patients with bipolar disorder with psychotic features, the number rose from 6 to 7. A similar trend was observed for tricyclic antidepressants in patients with schizophrenia (from 2 to 5 patients) and those with schizoaffective disorder (from 1 to 6 patients).

In all diagnostic groups, the equivalent doses of fluvoxamine or imipramine generally did not change over the period of observation. The only exception was the group of patients with schizoaffective disorder treated with SSRIs who were taking higher maximum doses at both 6 and 48 months (300 and 243 mg/day, respectively) with respect to the other 2 groups of diagnosis (107 and 150 mg/day, respectively, in patients with schizophrenia; and 120 and 160 mg/day, respectively, in patients with bipolar disorder with psychotic features) (Table 2).

The percentage of patients on clozapine monotherapy increased among patients with schizophrenia, while it did not change among patients with schizoaffective disorder or bipolar disorder with psychotic features. With the exception of schizophrenic patients, the percentage of patients treated with only 1 adjunctive agent increased. A decrease in the percentage of patients treated with 3 or more adjunctive agents was observed in schizoaffective and bipolar patients (Table 2).

BPRS total score at baseline and after 1, 3, 6, 12, 18, 24, 36, and 48 months and CGI-S score at baseline and after 12, 24, 36, and 48 months were evaluated in the overall sample (N = 101) using random-effects regression models (Figure 2). Each of the 3 diagnostic groups showed a progressive and significant reduction of predicted BPRS total scores during the period of follow-up (Table 3).

The predicted BPRS total scores showed that clozapine induced a significant improvement over time. Although their values at baseline were similar, patients with bipolar disorder showed significantly ($p < .05$) more rapid improvement than patients in the other 2 groups during the first 3 months of treatment, while patients with schizoaffective disorder showed significantly ($p < .05$) more rapid improvement than patients with schizophrenia

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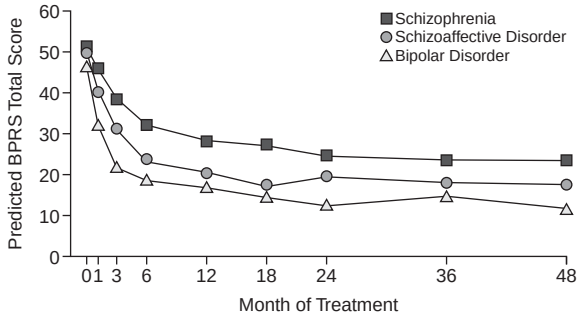
Table 2. Number, Classes, and Range of Standardized Equivalent Doses of Drugs Added to Clozapine Therapy for Each Diagnostic Group at 3 and 48 Months

	Schizophrenia (N = 14)		Schizoaffective Disorder, Bipolar Type (N = 19)		Bipolar Disorder With Psychotic Features (N = 14)	
Treatment	3 Months	48 Months	3 Months	48 Months	3 Months	48 Months
Clozapine monotherapy, N (%)	2 (14.3)	5 (35.7)	2 (10.5)	2 (10.5)	1 (7.1)	1 (7.1)
Clozapine and 1 other drug, N (%)	2 (14.3)	2 (14.3)	4 (21.1)	7 (36.9)	4 (28.6)	6 (42.8)
Clozapine and 2 other drugs, N (%)	7 (50.0)	4 (28.6)	6 (31.6)	8 (42.1)	3 (21.4)	4 (28.6)
Clozapine and 3 or more other drugs, N (%)	2 (14.3)	2 (14.3)	7 (36.9)	2 (10.5)	6 (42.8)	3 (21.4)
Typical neuroleptics						
N (%)	12 (85.7)	6 (42.9)	14 (73.7)	9 (47.4)	6 (42.9)	3 (21.4)
Chlorpromazine equivalents, mg/day	50–300	25–50	32–300	25–53	27–300	8–50
Anticonvulsants						
N (%)	7 (50.0)	1 (7.1)	15 (78.9)	2 (10.5)	10 (71.4)	8 (57.1)
Sodium valproate equivalents, mg/day	400–1200	100–300	600–1200	300–400	400–1200	100–400
Lithium						
N (%)	0 (0.0)	0 (0.0)	3 (15.8)	1 (5.3)	6 (42.9)	4 (28.6)
Dose, mg/day			450–900	450	600–900	600–900
SSRIs						
N (%)	2 (14.3)	5 (35.7)	5 (26.3)	11 (57.9)	6 (42.9)	7 (50.0)
Fluvoxamine equivalents, mg/day	50–107	89–150	48–300	115–243	55–120	100–160
Tricyclics						
N (%)	2 (14.3)	5 (35.7)	1 (5.3)	6 (31.6)	1 (7.1)	1 (7.1)
Imipramine equivalents, mg/day	7.5–75	7.5–75	75	10–75	30	18

Abbreviation: SSRI = selective serotonin reuptake inhibitor.

Figure 2. BPRS Scores Predicted by Random-Effects Regression Models for Patients With Schizophrenia (N = 34), Schizoaffective Disorder (N = 30), or Bipolar Disorder With Psychotic Features (N = 37)[a]



[a]Differences of trend over time among the 3 groups were significant ($p < .05$).
Abbreviation: BPRS = Brief Psychiatric Rating Scale.

during the first 6 months of treatment. Observed and predicted BPRS values are listed in Table 3.

The CGI-S predicted scores showed a progressive and significant reduction in each of the 3 groups (Figure 3). Patients with schizophrenia reported significantly higher values than those with schizoaffective disorder, who showed significantly higher values than bipolar patients. Observed and predicted values of CGI-S are listed in Table 3.

The analyses of the 5 BPRS factor scores showed a progressive and significant reduction in the 3 diagnostic groups (Table 3). The factors thought disorder (including the items conceptual disorganization, grandiosity, hallucinatory behavior, and unusual thought) and anergia (including the items emotional withdrawal, motor retardation, blunted affect, and disorientation) showed a more rapid and clinically relevant decrease in patients with bipolar and schizoaffective disorder than in patients with schizophrenia, especially during the first 6 months of treatment (Table 3). After 48 months of treatment, the scores of the 2 factors mentioned above were significantly ($p < .05$) lower in patients with bipolar disorder and schizoaffective disorder than in patients with schizophrenia (Table 3).

Kaplan-Meier survival curves showed that more than 50% of patients with bipolar and schizoaffective disorder responded before the third and sixth months of treatment, respectively, while more than 50% of patients with schizophrenia did not respond until the 24th month (Figure 4). More than 75% of patients with bipolar and schizoaffective disorder responded by the 12th and 18th months of treatment, respectively, while patients with schizophrenia never reached this percentage. By the 48th month, 83.8% of patients with bipolar disorder, 90.0% of patients with schizoaffective disorder, and 64.7% of patients with schizophrenia had responded.

Among the subsample of subjects who completed the 48 months of follow-up (N = 47), the clinical outcome was met by 92.9% of patients with bipolar disorder, 89.5% of patients with schizoaffective disorder, and 78.6% of patients with schizophrenia. GAF scores at 48 months were significantly higher than baseline values in all 3 groups (schizophrenia, $p < .001$; schizoaffective disorder, $p < .001$; bipolar disorder, $p < .001$). At the end of treatment, mean GAF scores were significantly lower in patients with schizophrenia and in patients with schizo-

Table 3. Predicted (and observed) Values of BPRS Factors, BPRS Total Scores, and CGI-S Total Scores by Random-Effects Regression Models of 101 Psychotic Patients Treated With Clozapine

		Month of Treatment							
Scale	Baseline	1	3	6	12	18	24	36	48
CGI-S total score[a]									
Schizophrenia	5.8 (5.9)				4.2 (4.1)		3.7 (3.6)	3.6 (3.5)	3.4 (3.3)
Schizoaffective disorder	5.5 (5.5)				3.6 (3.6)		3.1 (3.2)	3.1 (3.1)	3.0 (2.8)
Bipolar disorder	5.2 (5.0)				3.1 (3.2)		2.8 (2.8)	2.7 (2.6)	2.2 (2.4)
BPRS total score[a,b]									
Schizophrenia	51.4 (51.4)	45.5 (45.5)	38.2 (38.2)	32.3 (32.1)	27.6 (28.3)	26.8 (27.3)	24.4 (24.9)	23.6 (23.5)	26.4 (23.5)
Schizoaffective disorder	50.4 (50.4)	40.3 (40.3)	30.6 (30.6)	23.5 (23.5)	20.1 (20.2)	16.4 (17.1)	18.7 (19.4)	17.0 (17.5)	17.6 (17.4)
Bipolar disorder	46.4 (46.4)	32.2 (32.2)	22.2 (22.2)	19.6 (18.7)	17.4 (17.1)	15.7 (14.5)	13.6 (12.4)	16.9 (15.2)	9.8 (11.4)
BPRS factor									
Anxiety-depression[a]									
Schizophrenia	10.1 (11.2)	9.0 (9.2)	7.5 (7.3)	6.3 (5.6)	5.7 (5.3)	5.0 (4.6)	4.3 (4.5)	3.8 (4.6)	5.5 (4.7)
Schizoaffective disorder	12.3 (11.9)	10.4 (10.0)	8.2 (8.0)	6.5 (6.7)	6.1 (6.1)	5.5 (5.4)	6.0 (5.2)	5.7 (5.4)	6.5 (5.4)
Bipolar disorder	10.9 (10.3)	8.2 (8.4)	6.0 (6.4)	5.2 (5.1)	5.0 (4.5)	3.9 (3.8)	3.3 (3.6)	4.4 (3.8)	2.9 (3.8)
Anergia[a,b]									
Schizophrenia	11.4 (11.4)	11.0 (11.0)	9.7 (9.7)	8.6 (8.4)	7.1 (7.0)	6.8 (6.4)	6.4 (5.8)	6.4 (5.5)	7.0 (5.8)
Schizoaffective disorder	9.6 (9.6)	7.9 (7.9)	6.7 (6.7)	5.3 (5.3)	4.5 (4.5)	3.8 (3.7)	4.5 (4.4)	4.1 (3.9)	4.1 (3.6)
Bipolar disorder	7.6 (7.6)	5.8 (5.8)	4.2 (4.2)	4.0 (3.7)	3.5 (3.4)	3.1 (3.1)	2.4 (2.4)	2.9 (2.9)	1.5 (2.3)
Thought disorder[a,b]									
Schizophrenia	12.9 (12.9)	11.6 (11.6)	10.3 (10.3)	9.3 (9.0)	8.0 (8.0)	7.7 (7.6)	7.2 (7.0)	6.9 (6.6)	6.7 (6.0)
Schizoaffective disorder	11.6 (11.6)	9.4 (9.4)	6.7 (6.7)	5.0 (5.0)	3.7 (4.0)	2.9 (3.3)	3.2 (3.7)	3.1 (3.5)	2.9 (3.0)
Bipolar disorder	9.9 (9.9)	6.8 (6.8)	4.7 (4.7)	4.3 (4.0)	3.8 (3.8)	3.8 (3.1)	3.6 (3.1)	4.2 (3.5)	2.3 (2.7)
Activity[a]									
Schizophrenia	8.1 (9.0)	6.6 (6.6)	5.0 (4.8)	3.9 (3.7)	3.1 (3.4)	3.4 (3.2)	3.1 (3.1)	3.1 (3.1)	3.4 (2.9)
Schizoaffective disorder	8.7 (8.7)	6.7 (6.3)	4.8 (4.5)	3.4 (3.5)	2.8 (3.2)	2.0 (2.9)	2.5 (2.9)	2.1 (2.9)	2.5 (2.7)
Bipolar disorder	9.0 (8.2)	5.5 (5.8)	3.6 (4.0)	3.0 (2.9)	2.6 (2.6)	2.5 (2.4)	2.1 (2.3)	2.8 (2.3)	1.9 (2.1)
Hostility-suspiciousness[a]									
Schizophrenia	8.8 (9.5)	7.2 (7.2)	5.7 (5.3)	4.3 (4.4)	3.7 (4.1)	3.9 (3.8)	3.3 (3.7)	3.1 (3.5)	3.8 (3.3)
Schizoaffective disorder	8.3 (8.4)	5.9 (6.0)	4.2 (4.2)	3.2 (3.4)	2.8 (2.9)	2.2 (2.7)	2.5 (2.6)	1.9 (2.4)	1.6 (2.2)
Bipolar disorder	9.0 (8.2)	5.9 (5.8)	3.6 (4.0)	3.1 (3.0)	2.5 (2.7)	2.3 (2.4)	2.1 (2.3)	2.4 (2.1)	1.2 (1.9)

[a]Significant reduction of predicted values over time ($p < .05$).
[b]Significant differences of time trend of predicted values among the 3 groups ($p < .05$).
Abbreviations: BPRS = Brief Psychiatric Rating Scale, CGI-S = Clinical Global Impressions-Severity of Illness scale.

affective disorder than in patients with bipolar disorder (schizophrenia, 53.6 ± 15.2; schizoaffective disorder, 52.4 ± 12.1; bipolar disorder, 71.4 ± 16.6; $p < .005$). Among completers, the psychosocial and occupational functioning outcome measure (GAF score > 50) was satisfied by 92.9% of patients with bipolar disorder versus 68.4% of patients with schizoaffective disorder and 42.9% of patients with schizophrenia ($p < .05$). It is worth noting that all patients who achieved the psychosocial and occupational functioning outcome measure also achieved the clinical outcome measure.

Patients with bipolar disorder showed the most rapid improvement in BPRS score and achieved the highest percentages of improvement within 18 months. After 48 months of treatment, GAF scores showed a functional improvement in all 3 groups, significantly ($p < .01$) higher in those with bipolar disorder compared with the other groups. Patients with schizoaffective disorder showed a steady improvement that was more rapid than that of patients with schizophrenia. Patients with schizophrenia showed the slowest improvement as measured by total BPRS score throughout the 48 months, significantly ($p < .01$) less than that of the other 2 groups, and the lowest psychosocial and occupational functioning level at 48 months.

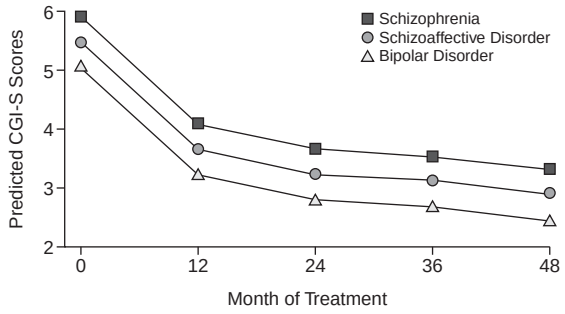
DISCUSSION

Long-term (48-month) clozapine treatment was investigated in this naturalistic prospective follow-up study of 101 treatment-resistant patients with a diagnosis of schizophrenia, bipolar disorder with psychotic features, or schizoaffective disorder, bipolar type.

About 46% of patients who continued the treatment over the 48-month follow-up had no relapses. The highest rate of treatment completion was found in the schizoaffective group (63.3%), and the lowest (37.8%) was found in the bipolar group. A long-term (4.3-year) prospective study by Gitling et al.[29] reported a rate of treatment compliance of 27%, although that study assessed patients with bipolar disorder who were not treatment-resistant to maintenance pharmacotherapy. Banov et al.[14] reported a rate of compliance after 18 months for bipolar patients (54.0%) that was lower than that observed in the present study at the same time of evaluation (66.8%).

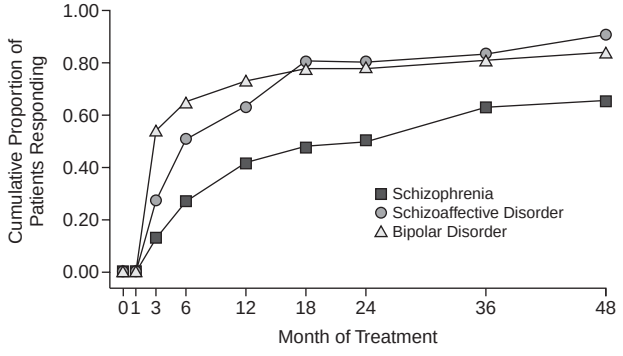
Data from the present study, analyzed by both BPRS total predicted scores and Kaplan-Meier survival curves, showed a significant improvement in the 3 diagnostic groups. BPRS total predicted scores halved their baseline values in 3 months for bipolar disorder, in 6 months for schizoaffective disorder, and in 24 months for schizo-

Figure 3. CGI-S Scores Predicted by Random-Effects Regression Models for Patients With Schizophrenia (N = 34), Schizoaffective Disorder (N = 30), or Bipolar Disorder With Psychotic Features (N = 37)[a]



[a]Differences of trend over time among the 3 groups were not significant, although the schizophrenia curve was significantly ($p < .05$) higher than the schizoaffective curve, which was significantly ($p < .05$) higher than the bipolar curve.
Abbreviation: CGI-S = Clinical Global Impressions-Severity of Illness scale.

Figure 4. Survival Analysis of 48-Month Response to Clozapine (defined as BPRS total score reduction of 50% with respect to baseline) in Patients With Schizophrenia (N = 34), Schizoaffective Disorder (N = 30), or Bipolar Disorder With Psychotic Features (N = 37)[a]



[a]Differences among the 3 curves were significant by log-rank test ($p < .01$).
Abbreviation: BPRS = Brief Psychiatric Rating Scale.

phrenia. These data are consistent with those of Suppes et al.,[21] who found that patients with bipolar and schizoaffective disorder who were followed up for 1 year improved significantly within 6 months of treatment.

At 24 months, the rate of improvement (expressed by BPRS total score reduction of 50% as clinical outcome measure) was significantly ($p < .01$) higher in patients with bipolar disorder (81.1%) and patients with schizoaffective disorder (80.0%) than in patients with schizophrenia (50.0%). Patients with schizophrenia and schizoaffective disorder continued to improve from the 24th through the 48th months of treatment.

In all 3 groups, patients who completed the 48 months of follow-up showed a significant improvement in psychosocial and occupational functioning, as assessed by the GAF. Good syndromal improvement and sufficient psychosocial and occupational adjustment were observed in 42.9% of patients with schizophrenia, 68.4% of patients with schizoaffective disorder, and 92.9% of patients with bipolar disorder. These data confirm previous findings that showed a greater efficacy of clozapine in patients with schizoaffective disorder than in patients with schizophrenia over long-term periods.[3,4,20]

The number of subjects receiving adjunctive treatment with a typical neuroleptic or valproate appeared to lower over time, and a decrease in the doses of adjunctive treatments was also detected. Such findings seem to support clozapine efficacy over a period of 48 months.

Mean daily doses of clozapine did not significantly differ within the 3 diagnostic groups until the 36th month of treatment. After 36 months, patients with bipolar disorder took lower doses of clozapine compared with the other 2 groups of patients, which suggests the efficacy of low doses of clozapine in maintenance therapy of bipolar patients.

The number of subjects receiving combined treatment with an SSRI or a TCA increased over the follow-up period. This treatment choice was mainly related to the presence of anxiety symptoms, particularly for obsessive symptomatology.[30–33] In bipolar patients, the prevalence of treatment with SSRIs or TCAs was low because of the risk of increasing manic symptoms or inducing rapid cycles. It is also important to note that, at the beginning of this follow-up, TCAs were preferred to SSRIs because they were provided free of charge by the Italian National Health System; SSRIs became free for patients only after 1999.

After 48 months of treatment, patients with schizoaffective disorder had the highest clinical improvement and the lowest treatment discontinuation rate. Patients with bipolar disorder had the shortest time to remission and the highest psychosocial and occupational functioning levels.

This study had some potential limitations: it lacked a parallel comparison group for treatment, data about concomitant medications were not completely available for dropout patients, interviewers were aware of psychiatric diagnosis, and psychosocial and functional levels were assessed using the GAF only at baseline and after 48 months of follow-up, hampering a survival analysis using functional outcome measures.

Despite these limitations, the findings of this study strongly support the efficacy of long-term clozapine therapy in treatment-resistant patients with schizophrenia, schizoaffective disorder, and bipolar disorder with psychotic features.

The patients with bipolar disorder also reached sufficient psychosocial and functional levels related to a

higher rate of retention than those described in other long-term studies of non–treatment-resistant subjects. Although our sample of patients with bipolar disorder with psychotic features presented with a high severity of illness, the percentage of patients who continued in the follow-up and showed good psychosocial and occupational functioning after 4 years of clozapine therapy was higher than that of other long-term studies with classical mood stabilizers.[4,29,34]

Drug names: chlorpromazine (Thorazine and others), clozapine (Clozaril and others), fluvoxamine (Luvox and others), imipramine (Tofranil and others).

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