

Clozapine for Treatment-Refractory Schizophrenia, Schizoaffective Disorder, and Psychotic Bipolar Disorder: A 24-Month Naturalistic Study

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Background: The aim of this study was to evaluate the 24-month response to clozapine in patients with schizophrenia, schizoaffective disorder, or psychotic bipolar disorder.

Method: Ninety-one psychotic patients with a principal DSM-III-R diagnosis of schizophrenia (N = 31), schizoaffective disorder (N = 26), or bipolar disorder with psychotic features (N = 34) were treated naturalistically with clozapine at flexible dosages over a 24-month period. Improvement was assessed by the 18-item Brief Psychiatric Rating Scale and the Clinical Global Impressions-Severity of Illness scale.

Results: All patients showed significant improvement 24 months from intake ($p < .001$). Such an improvement was significantly greater among patients with schizoaffective disorder or bipolar disorder than in patients with schizophrenia ($p < .05$). The presence of suicidal ideation at intake predicted greater improvement at endpoint.

Conclusion: Clozapine appears to be effective and relatively well tolerated in acute and long-term treatment of patients with psychotic bipolar disorder or schizoaffective disorder who have not responded to conventional pharmacotherapies.

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The use of atypical antipsychotics recently expanded to several psychiatric conditions other than schizophrenia, including severe mood disorders, schizoaffective disorder, borderline personality disorder, and substance abuse disorder.¹ In particular, there is increasing interest in evaluating clozapine in acute and long-term treatment of patients with refractory schizoaffective disorder and psychotic bipolar disorder.²

Clozapine efficacy in schizoaffective disorder was reported by several authors; however, most of these studies were based on chart reviews or assessed short-term outcome.³⁻⁶ In a small sample of 17 patients with bipolar or schizoaffective disorder, Zarate et al.⁷ found that clozapine monotherapy was effective in preventing rehospitalization or major affective episodes over a 16-month period in 64% of patients.

In a previous 12-month study on the efficacy of clozapine in patients with schizophrenia spectrum disorders, Cassano et al.⁸ found that patients with bipolar features had a greater improvement than those without, suggesting that the presence of an affective component was a predictor of good response.

In 1977, Muller and Heipertz,⁹ and more recently, other authors,^{4,10-15} confirmed the efficacy of clozapine in patients with acute mania refractory to mood-stabilizing treatments. Few studies are available on the long-term efficacy of clozapine. A sustained improvement has been reported in 41 severely ill bipolar patients with and without psychotic features naturalistically treated with clozapine over a period of 12 months.¹⁶ McElroy et al.,¹² investigating the effectiveness of clozapine in patients with bipolar disorder with psychotic features, schizoaffective disorder, or schizophrenia, found in the first 2 groups a significantly higher response rate than in the schizophrenia group. Although the mean duration of treatment was 26 months, this study was based on a review of patients' records, and response was determined by interview with the primary treating clinician.

The aim of the present naturalistic prospective study was to evaluate the efficacy of clozapine over a 2-year period in patients with schizophrenia, schizoaffective disorder, or psychotic bipolar disorder.

METHOD

Study Sample

Our naturalistic follow-up study comprised a cohort of 91 patients who were consecutively referred to our clozapine follow-up program from the day-hospital service and

wards of the Department of Psychiatry at the University of Pisa (Pisa, Italy) because of resistance to treatment with standard antipsychotic drugs. All patients met a diagnosis of schizophrenia, schizoaffective disorder, or bipolar disorder with psychotic features according to DSM-III-R criteria.¹⁷ Diagnostic and psychopathologic evaluations 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 psychotic disorders and with substantial familiarity with DSM-III-R criteria. Interrater reliability for the Brief Psychiatric Rating Scale (BPRS) and the Clinical Global Impressions scale (CGI) was not measured in this study because the 2 raters had previous experiences with the use of these instruments, showing a satisfactory interrater reliability. The diagnosis was definitively confirmed by 2 senior psychiatrists (A.C., L.D.). Each patient enrolled provided written informed consent.

Subjects were defined as treatment resistant if they presented with persistent psychotic symptoms despite separate trials with 3 different classes of antipsychotics at doses equivalent to 300 to 600 mg/day of chlorpromazine for at least 12 weeks. Enrolled subjects did not take depot neuroleptics for at least 8 weeks before starting clozapine treatment. In general, clozapine was started gradually, beginning with 25 mg/day, and the dose was increased as tolerated to a maximum of 600 mg/day. During the follow-up period, the dose of clozapine was adjusted on the basis of clinical response to a lower but effective dose.

Assessment of Psychopathology

Patients were referred to our clozapine follow-up program within 2 weeks of the initiation of clozapine because a substantial number of patients were in need of an immediate control of psychotic symptomatology. The baseline evaluations, therefore, were made during the 2 weeks between the initiation of clozapine and inclusion in this study.

Severity of psychopathology was assessed at baseline and at 1, 6, 12, and 24 months by the 42-item BPRS-Expanded Version (BPRS-E)¹⁸ on a 0–6 scoring scale. Patients were also administered the CGI-Severity of Illness scale (CGI-S)¹⁹ at baseline and at 12- and 24-month follow-up.

The presence of concomitant panic-agoraphobic symptoms, obsessive-compulsive symptoms, and social phobia, as well as aggressive behavior and suicidal ideation, was assessed at baseline by the interviewer on the basis of clinical judgment.

Reduction of total score on the 18-item BPRS (disembedded from the BPRS-E to facilitate more direct comparisons with previous studies) and CGI-S score was used to evaluate the clinical response to clozapine. In both Kaplan-Meier and last-observation-carried-forward (LOCF) analyses, improvement was defined as a reduction of at least 50% in BPRS total score maintained for 2 adjacent evaluations. Clozapine side effects, clozapine dose, and concomitant treatments were registered.

Follow-up assessments were performed by the same raters who performed baseline evaluations.

Patients were given clozapine, 25 to 600 mg/day, either alone or in combination with other drugs if necessary for the relief of symptoms of psychosis, depression, or anxiety. These other drugs included selective serotonin reuptake inhibitors, tricyclic antidepressants, anticonvulsants, lithium, and/or traditional neuroleptics.

Statistical Analyses

Categorical variables were compared using chi-square tests. The 2-tailed Fisher exact test was adopted for all pairwise comparisons within the groups. Analysis of variance (ANOVA) was used to compare continuous variables between the 3 groups. Differences in BPRS and CGI-S scores between groups were assessed using Mann-Whitney and Kruskal-Wallis nonparametric tests. Kaplan-Meier survival analysis was used to assess the 1-year and 2-year response to clozapine. In addition, the LOCF analysis was carried out. The last observed value is used to fill in missing values at a later point in the study. This method applies only to data for which multiple observations have been made on the variable in question. In both analyses, differences in the survival curves between groups were assessed using the log-rank test. Statistical analyses were performed using the SPSS Statistical Package, Version 7.5 (SPSS, Inc., Chicago, Ill.).

RESULTS

Of the 91 patients included in this study, 31 fulfilled DSM-III-R criteria for schizophrenia, 26 for schizoaffective disorder, and 34 for bipolar disorder with psychotic features. As shown in Table 1, mean age, gender distribution, education level, rate of unemployment, and duration of illness did not differ among the 3 groups. Married subjects were significantly less represented in the schizophrenia group than in the bipolar disorder group ($\chi^2 = 7.892$, $df = 2$, $p < .02$).

Clinical Characteristics at Baseline

Patients enrolled had severe symptomatology and substantial impairment in social functioning. In addition, all patients were refractory to standard pharmacologic treatment including typical antipsychotics, lithium, antidepressants, carbamazepine, valproate, and combinations of these agents.

The 3 diagnostic groups did not differ significantly on baseline level of psychopathology (T0) as assessed by BPRS total score, although they differed on CGI-S score, which was significantly higher among schizophrenia than among bipolar disorder patients ($z = -3.36$, $df = 2$, $p < .001$; see Table 1).

Overall, frequencies of panic-agoraphobic, obsessive-compulsive, and social phobic symptoms during the last 6

Table 1. Sociodemographic and Clinical Characteristics of 91 Psychotic Patients Treated With Clozapine for 24 Months^a

Characteristic	Schizophrenia (N = 31)	Schizoaffective Disorder (N = 26)	Psychotic Bipolar Disorder (N = 34)
Age, mean $\pm$ SD, y	33.4 $\pm$ 12.2	32.2 $\pm$ 7.6	36.5 $\pm$ 14.1
Men	20 (64.5)	19 (73.1)	24 (70.6)
Married ^b	2 (6.5)	6 (23.1)	12 (35.3)
Unemployed	22 (71.0)	13 (50.0)	18 (52.9)
Medium education level (8 y)	20 (64.5)	16 (61.5)	23 (67.6)
Duration of illness, mean $\pm$ SD, y	13.6 $\pm$ 11.5	13.7 $\pm$ 6.6	12.7 $\pm$ 8.2
Panic-agoraphobic symptoms	11 (35.5)	14 (53.8)	11 (32.4)
Obsessive-compulsive symptoms	19 (61.3)	22 (84.6)	20 (58.8)
Social phobic symptoms	15 (48.4)	13 (50.0)	6 (17.6)
Aggressive behavior ^c	26 (83.9)	18 (69.2)	18 (52.9)
Suicide attempt or ideation	10 (32.3)	8 (30.8)	8 (23.5)
Dose of clozapine at endpoint, mean $\pm$ SD, mg/d	236 $\pm$ 144	237 $\pm$ 140	160 $\pm$ 128
BPRS baseline score, mean $\pm$ SD	50.6 $\pm$ 14.4	49.3 $\pm$ 13.5	46.9 $\pm$ 14.7
CGI-S baseline score, ^d mean $\pm$ SD	5.77 $\pm$ 0.76	5.46 $\pm$ 0.86	5.09 $\pm$ 0.75

^aValues shown as N (%) unless specified otherwise. Abbreviations: BPRS = Brief Psychiatric Rating Scale, CGI-S = Clinical Global Impressions-Severity of Illness scale.

^b $\chi^2 = 7.892$, $df = 2$, $p < .02$ for schizophrenia vs. bipolar disorder patients.

^c $\chi^2 = 7.165$, $df = 2$, $p < .03$ for schizophrenia vs. schizoaffective disorder and psychotic bipolar disorder patients.

^d $z = -3.36$, $df = 2$, $p < .001$ for schizophrenia vs. bipolar disorder patients.

months were 39.6% (36/91), 67.0% (61/91), and 37.4% (34/91), respectively, with no significant differences among the 3 diagnostic groups. Aggressive behavior at intake was significantly more frequent in schizophrenia (26/31; 83.9%) than in schizoaffective disorder (18/26; 69.2%) or bipolar disorder patients (18/34; 52.9%) ($\chi^2 = 7.165$, $df = 2$, $p < .03$). The presence of reported suicidal ideation did not differ significantly in the 3 diagnostic groups (see Table 1).

Thirty-eight (41.8%) of the subjects (13 with schizophrenia, 5 with schizoaffective disorder, and 20 with bipolar disorder; $\chi^2 = 9.497$, $df = 2$, $p < .01$) withdrew from treatment during the 2-year follow-up period. Reasons for dropout were inadequate response to treatment in 15 subjects (16.5%), no compliance to clozapine in 12 subjects (13.2%), side effects (sedation, sleep cycle inversion, weight gain, leukopenia) in 5 subjects (5.5%), and other reasons (2, pregnancy; 4, inability to regularly reach our center due to distance) in 6 subjects (6.6%). Specifically, inadequate response to clozapine was noted by 9 bipolar disorder patients (26.5%), 5 schizophrenia patients (16.1%), and 1 schizoaffective disorder patient (3.8%) ($\chi^2 = 10.228$, $df = 4$, $p < .05$). Subjects who dropped out of the study did not differ from the counterparts regarding gender, marital status, severity of illness as assessed by

BPRS and CGI-S scores, or rates of anxiety symptomatology, suicidal ideation, and aggressive behaviors.

Response to Treatment

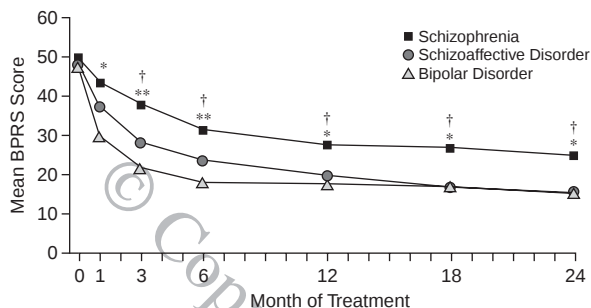
The mean daily dose of clozapine did not differ significantly in the 3 groups over the 24-month period. After 3 weeks from intake, daily doses were 197 mg for schizophrenia, 189 mg for schizoaffective disorder, and 140 mg for psychotic bipolar disorder patients ($F = 2.39$, $df = 2$, $p < .098$). After 12 months, the mean daily dose of clozapine was 242 mg for schizophrenia, 240 mg for schizoaffective disorder, and 189 mg for bipolar disorder patients ($F = 1.09$, $df = 2$, $p < .341$). At the 24-month assessment, the mean daily dose of clozapine was 236 mg for schizophrenia, 237 mg for schizoaffective disorder, and 160 mg for bipolar disorder patients ($F = 1.50$, $df = 2$, $p < .232$).

In the group of schizophrenia patients, 45.2% (14/31) of the subjects were also administered typical neuroleptics; 16.1% (5/31), anticonvulsants; 35.5% (11/31), antidepressants; and 6.5% (2/31), benzodiazepines. Among schizoaffective disorder patients, 26.9% (7/26) were also given neuroleptics; 11.5% (3/26), lithium; 19.2% (5/26), anticonvulsants; 57.7% (15/26), antidepressants; and 11.5% (3/26), benzodiazepines. Among bipolar disorder patients, 35.3% (12/34) were also given neuroleptics; 23.5% (8/34), lithium; 26.5% (9/34), anticonvulsants; 35.3% (12/34), antidepressants; and 2.9% (1/34) benzodiazepines. Patients received doses of concomitant neuroleptic therapy no greater than the equivalent of 150 mg/day of chlorpromazine.

Overall, mean baseline BPRS score did not differ significantly between patients in clozapine monotherapy (19/91; 19.8%) compared with those treated with a combination of typical neuroleptics (33/91; 36.3%) (47.6 ± 12.0 vs. 50.3 ± 16.8 , $t = -0.581$, $df = 49$, $p = .56$). The mean change in BPRS total score at 1 month (T1), 3 months (T3), 6 months (T6), 12 months (T12), 18 months (T18), and 24 months (T24) and of CGI-S scores at 12 and 24 months from baseline was evaluated in the overall sample of 53 patients (18 schizophrenia, 21 schizoaffective disorder, and 14 bipolar disorder patients) who completed the 24-month follow-up. Each of the 3 diagnostic groups showed a progressive and significant reduction in BPRS total score during the period of follow-up (schizophrenia: $T0 = 49.7$, $T1 = 43.5$, $T3 = 37.9$, $T6 = 31.5$, $T12 = 27.6$, $T18 = 26.7$, $T24 = 24.7$; $\chi^2 = 55.7$, $df = 6$, $p < .001$; schizoaffective disorder: $T0 = 47.8$, $T1 = 37.4$, $T3 = 28.3$, $T6 = 23.6$, $T12 = 19.6$, $T18 = 16.4$, $T24 = 15.1$; $\chi^2 = 86.7$, $df = 6$, $p < .001$; bipolar disorder: $T0 = 47.5$, $T1 = 29.8$, $T3 = 21.7$, $T6 = 18.1$, $T12 = 17.4$, $T18 = 16.7$, $T24 = 15.1$; $\chi^2 = 56.3$, $df = 6$, $p < .001$).

As shown in Figure 1, the mean BPRS total scores did not differ significantly between the schizoaffective disorder and bipolar disorder groups at any of the follow-up evaluations; however, compared with the schizophrenia

Figure 1. Mean BPRS Scores for Patients With Schizophrenia (N = 31), Schizoaffective Disorder (N = 26), Psychotic Bipolar Disorder (N = 34)^a



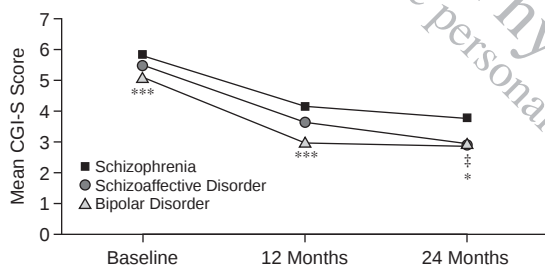
^aMann-Whitney test used for all comparisons.

* $p < .05$, schizophrenia vs. bipolar disorder.

** $p < .01$, schizophrenia vs. bipolar disorder.

† $p < .05$, schizophrenia vs. schizoaffective disorder.

Figure 2. Mean CGI-S Scores for Patients With Schizophrenia (N = 31), Schizoaffective Disorder (N = 26), and Psychotic Bipolar Disorder (N = 34)^a



^aMann-Whitney test used for all comparisons.

* $p < .05$, schizophrenia vs. bipolar disorder.

*** $p < .005$, schizophrenia vs. bipolar disorder.

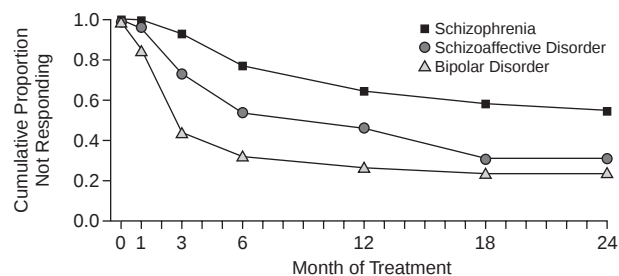
‡ $p < .01$, schizophrenia vs. schizoaffective disorder.

group, both the bipolar disorder and schizoaffective disorder groups showed a significantly greater reduction of total BPRS scores at each follow-up assessment, with the exception of T1 for the schizoaffective disorder group.

CGI-S scores showed a progressive and significant reduction in each of 3 diagnostic groups (schizophrenia: $T_0 = 5.8$, $T_{12} = 4.1$, $T_{24} = 3.8$; $\chi^2 = 23.13$, $df = 2$, $p < .001$; schizoaffective disorder: $T_0 = 5.5$, $T_{12} = 3.6$, $T_{24} = 3.0$; $\chi^2 = 31.55$, $df = 2$, $p < .001$; bipolar disorder: $T_0 = 5.1$, $T_{12} = 3.0$, $T_{24} = 2.9$; $\chi^2 = 27.4$, $df = 2$, $p < .001$). Such an improvement was significantly more pronounced in the bipolar group compared with the schizophrenia group at T_{12} and T_{24} and in the schizoaffective group versus the schizophrenia group at T_{24} (Figure 2).

A Kaplan-Meier survival analysis was used to assess 1-year and 2-year response to clozapine for each diagnostic group. The cumulative response rate to clozapine was significantly higher in bipolar disorder than in schizophrenia patients (log-rank test, $p < .005$) with a 60% cumulative response rate in the first 6 months, whereas 55% of

Figure 3. Last-Observation-Carried-Forward Analysis of 2-Year Response to Clozapine in Patients With Schizophrenia (N = 31), Schizoaffective Disorder (N = 26), and Psychotic Bipolar Disorder (N = 34)^a



^aSchizophrenia vs. bipolar disorder: $p < .005$, log-rank test.

Table 2. Effect of Baseline Level of Psychopathology, Diagnostic Status, Comorbidity, Aggressiveness, and Suicidality on 2-Year Outcome in Patients With Schizophrenia (N = 18), Schizoaffective Disorder (N = 21), and Psychotic Bipolar Disorder (N = 14) Completing 24-Month Follow-Up^a

Effect	F	p Value
BPRS score at baseline	6.47	.02
Diagnostic status	3.95	.03
Panic attacks	2.81	.10
Obsessive-compulsive symptoms	0.77	.38
Social phobia symptoms	0.53	.46
Aggressive behavior	1.40	.25
Suicidal ideation	4.73	.05

^aAnalysis of variance performed with 2-year BPRS score as the dependent variable and the effects listed above as independent variables. All effects were entered simultaneously.

schizoaffective disorder patients responded within 12 months and 56% of patients with schizophrenia responded within 18 months of treatment. The likelihood of remaining nonresponsive at 2 years was 44% for schizophrenia, 25% for schizoaffective disorder, and 17% for bipolar disorder patients. In addition, to evaluate whether the inclusion in the analyses of compliant subjects who dropped out could diminish the reported effect of clozapine, an LOCF analysis was performed (Figure 3). The cumulative response rate to clozapine after 2 years remained significantly higher in bipolar disorder patients than in schizophrenia patients (log-rank test, $p < .005$), as was similarly found using the Kaplan-Meier method. The probability of remaining nonresponsive was 55% in schizophrenia patients, 31% in schizoaffective disorder patients, and 24% in bipolar disorder patients.

The effect of several clinical variables on 2-year outcome is displayed in Table 2. The baseline BPRS total score was found to be the best predictor of response (i.e., the higher the baseline BPRS total score, the greater the change from baseline total score at endpoint), followed by the diagnosis. The presence of suicidal ideation at baseline correlated with a lower BPRS total score after 24

months. When the analyses were restricted to patients with suicidal ideation at baseline, a significant reduction in the BPRS-E suicide item score was found at 24 months (Wilcoxon mean rank = 3.50; $z = -2.214$, $p < .027$).

DISCUSSION

The results of this study suggest that patients with schizophrenia, schizoaffective disorder, and psychotic bipolar disorder showed a significant and persistent clinical improvement when treated naturalistically with clozapine over a 24-month period of time. Kaplan-Meier survival curves indicate that treatment response was significantly superior in bipolar disorder and schizoaffective disorder patients than in patients with schizophrenia, using the strict treatment-response criterion of a 50% reduction in BPRS total score. Eighty-three percent of patients with bipolar disorder were found to respond to clozapine after 24 months of treatment, compared with 75% of patients with schizoaffective disorder and 57% of patients with schizophrenia. These results are in agreement with the few available studies reporting a greater efficacy of clozapine in patients with psychotic bipolar disorder than in patients with schizophrenia over a long-term period.^{1,12,20}

With respect to the other 2 groups, bipolar disorder subjects showed the most rapid clinical improvement. These data are consistent with those of Suppes et al.,²¹ who found that 80% of subjects with bipolar disorder and schizoaffective disorder, followed for 1 year, improved significantly by 6 months of treatment.

The 3 groups of patients did not differ significantly on mean daily dosages of clozapine throughout the study. It is interesting that our patients received daily doses of clozapine that were lower than those that were usually reported in the literature. This reflects the strategy commonly adopted in our center for reaching a good compromise between efficacy and tolerability of clozapine, especially in bipolar disorder patients, who may have greater sensitivity to side effects.²¹ The rates of patients who dropped out before 24 months because of no response (16.5%), side effects (5.5%), or no compliance (13.2%) were considerably low. Nevertheless, the proportion of bipolar disorder subjects who dropped out outnumbered by about 2 times the rates of dropouts in the schizoaffective disorder and schizophrenia groups, indicating that severe bipolar disorder with psychotic features is a condition with high risk of dropout.

Clozapine was found to be effective in reducing suicidality after 24 months of treatment. Suicidal ideation at baseline was also found to be associated with a greater overall improvement of psychopathology after 24 months of treatment. Consistent with previous studies,²² these findings give further support to the use of clozapine for lowering suicide risk not only in patients with schizophrenia, but also in those with severe mood disorders.

Unlike previous investigators,^{23–26} we saw no evidence of an exacerbation of obsessive-compulsive symptoms induced by clozapine. We found that patients with pre-clozapine obsessive-compulsive symptoms had a worse response to clozapine, in terms of degree of overall improvement, during the first 12 months of treatment (data not presented here), but such a difference tended to disappear during the remaining year of treatment. Further systematic studies in larger cohorts of psychotic patients are needed to clarify the relationship between obsessiveness-compulsivity and clozapine and the extent to which this relationship may have an impact on the outcome of treating psychosis.

This study has several limitations. The lack of a pre-clozapine rating of psychopathology does not exclude the possibility that a worsening of symptomatology occurred within the 2 weeks that elapsed from the initiation of treatment with clozapine and the baseline assessment. Patients were treated naturalistically with different adjunctive drugs for which we did not collect data on dosages. Lastly, interviewers were not blinded to psychiatric diagnosis.

Despite these limitations, our findings support the efficacy of clozapine not only for patients with treatment-resistant schizophrenia,²⁷ but, even more, for many patients with schizoaffective disorder or severe bipolar disorder who are resistant to or intolerant of usual treatment options.

Drug names: carbamazepine (Tegretol and others), chlorpromazine (Thorazine and others), clozapine (Clozaril and others).

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