Low-Dose Clozapine in Acute and Continuation Treatment of Severe Borderline Personality Disorder

Francesco Benedetti, M.D., Laura Sforzini, M.D., Cristina Colombo, M.D., Cesare Maffei, M.D., and Enrico Smeraldi, M.D.

Background: Psychotic-like symptoms in patients affected by borderline personality disorder (BPD) are usually treated with low-dose neuroleptics, which show controversial acute effects and lead to a worsening of affective-related symptoms and to severe neurologic side effects after prolonged administration. Clozapine lacks the neurologic side effects of traditional neuroleptics and has been shown to successfully treat psychotic-like symptoms in BPD patients at medium dose. We performed an open-label trial of low-dose clozapine in severe BPD patients.

Method: Twelve BPD inpatients (DSM-IV criteria) with severe psychotic-like symptoms were studied. Exclusion criteria included comorbid Axis I and medical pathologies. All patients had followed a therapeutic program without improvement for at least 4 months before admission. The clozapine dose was titrated upward on an individual basis until the complete disappearance of psychotic-like symptoms was achieved. Clinician-rated scales were completed at the beginning of the study and after 4 and 16 weeks.

Results: All patients completed the 16-week study. Individual clozapine doses ranged from 25 to 100 mg/day. Psychotic-like symptoms decreased within the first 3 weeks of treatment, as confirmed by a statistically significant decrease in Brief Psychiatric Rating Scale scores. This amelioration was coupled with an overall improvement, including a reduction in impulsive behaviors and in affective-related symptoms (Hamilton Rating Scale for Depression) and an increase in global functioning (Global Assessment of Functioning).

Conclusion: Low-dose clozapine for acute and continuation treatment led to improvement in overall symptomatology in a small sample of severe BPD patients.

(J Clin Psychiatry 1998;59:103–107)

Received Nov. 14, 1996; accepted Aug. 20, 1997. From the Istituto Scientifico Ospedale San Raffaele, Department of Neuropsychiatric Sciences, University of Milan, School of Medicine, Italy.

Preliminary data presented at the Second European Congress on Personality Disorders, June 26–29, 1996, Milan, Italy.

Reprint requests to: Francesco Benedetti, M.D., Istituto Scientifico Ospedale San Raffaele, Department of Neuropsychiatric Sciences, Via Prinetti 29, 20127 Milano, Italy.

The purpose of the present open study was to investigate the effects of low-dose clozapine in the treatment of patients affected by severe borderline personality disorder (BPD). Severe BPD patients[1,2] show a marked impairment in interpersonal and social functioning and make an extensive use, though often with little lasting benefit, of health and social services. Despite the preeminent role of psychotherapy in the long-term treatment of these patients, many of them can be managed only with the use of psychotropic medication,[3,4] and, even in outpatient settings, the majority of BPD patients had prior exposure to psychotropic drugs.[5,6]

Nevertheless, no clear-cut guidelines for pharmacotherapy in BPD patients, in the absence of Axis I diagnoses, can be drawn from the literature.[7,8] BPD patients present several possible symptomatologic areas as targets for pharmacotherapy,[9–11] basically impulsivity, affective-related symptoms, and psychotic-like symptoms. The definition of the therapeutic target for drug therapy is based on the clinical evaluation of the relative relevance, in each patient, of these different symptomatologic clusters. While promising results have been reported in the pharmacologic treatment of impulsivity and affective-related symptoms using serotonin selective reuptake inhibitors and mood stabilizers,[8,10,12–15] the drug management of psychotic-like symptoms in BPD patients is still highly controversial.

Psychotic-like symptoms in BPD patients include cognitive and perceptual distortions, such as referential thinking, paranoid ideation, illusions, and dissociation, which are usually transient but worsen in close relationship with psychosocial stresses, thus leading to a marked impairment in global functioning.[16–20] Psychotic-like symptoms have been reported to be ameliorated by the administration of neuroleptic drugs,[21–23] but a recent double-blind placebo-controlled study has questioned the efficacy of traditional neuroleptics in this symptomatologic domain.[24] Moreover, the persistent and recurrent nature of symptoms in BPD often leads to prolonged pharmacologic treatments. The long-lasting administration of traditional neuroleptics to BPD patients can result in a worsening of affective-related symptoms and in an induction of neurologic side effects.[25,26]

Clozapine is an atypical antipsychotic drug that has proven efficacy in the treatment of schizophrenia and lacks the neurologic side effects induced by traditional neuroleptics.[27,28]

In recent years, promising results have been reported after the administration of medium-dose clozapine to BPD patients with severe self-destructive behaviors (single case treated with 300 mg/day)[29] or with treatment-resistant psychotic symptoms (due to comorbid Axis I psychotic disorder not otherwise specified; mean dose = 253.3 mg/day).[30] Given this preliminary evidence, we undertook an open-label trial with clozapine administered at the lowest effective dose to severe BPD patients with psychotic-like features.

METHOD

Subjects

Twelve inpatients who met DSM-IV[31] criteria for BPD on the Structured Clinical Interview for the Diagnosis of Axis II Disorders (SCID-II)[32] were studied (10 women, 2 men; mean ± SD age = 29.8 ± 5.5 years). Axis II codiagnoses included schizotypal (N = 2), antisocial (N = 1), and narcissistic (N = 1) personality disorders.

Hospitalization occurred because of severe psychotic-like symptoms with behavioral abnormalities, which were clinically selected as the main symptomatologic area. Psychotic-like symptoms included paranoid and referential thinking (both present in all patients), transient (in lifetime history) and stress-related. Five of 12 patients reported visual and auditory illusions, and 5 of 12 hypnagogic phenomena. Two patients showed odd beliefs, magical thinking, and eccentric behavioral abnormalities, meeting criteria for schizotypal personality disorder. Patients were included if these symptoms never reached a clear-cut delusional or hallucinatory quality.

Previous psychiatric history of the patients showed repeated hospitalization periods (mean ± SD hospitalization during the previous 12 months = 86.4 ± 85.1 days), repeated unsuccessful drug treatments, and a marked functional impairment (all patients stopped working or studying at least 6 months before). Previous pharmacologic treatments (identified from clinical charts and interviews with psychiatrists previously in charge of the patients) included neuroleptics (9/12 patients), serotonin selective reuptake inhibitors (11/12), mood stabilizers (7/12), and benzodiazepines (10/12).

Exclusion criteria included current major depression, current or past psychotic disorder including bipolar disorder, and major medical or neurologic disorders.[15] All patients were required to have followed a therapeutic program (including both psychotherapeutic and psychopharmacologic treatments) for a minimum of 4 months before the current hospitalization and to be free of any psychotropic drug for at least 2 weeks prior to the beginning of the study.

All subjects gave their informed consent to participate in the study after the procedures of the study and the possible side effects of the treatment were fully explained.

Treatment

Patients were treated for 16 weeks with open-label clozapine given orally every day at 10 p.m. Medication was started at 12.5 mg/day and then individually increased, as tolerated, during the hospitalization period, the duration of which was determined by clinical need. The upward titration of dose was stopped when psychotic-like symptoms completely disappeared. No concurrent psychotropic medication was administered.

Since clozapine is known to induce severe hematologic side effects such as granulocytopenia and agranulocytosis in about 0.8% of treated patients, total white blood cells (WBC) and absolute neutrophil count were monitored weekly.[33,34]

After discharge, patients began a follow-up program that included weekly psychotherapeutic sessions and monitoring of side effects.

Outcome Measures

The choice of outcome measures raised a number of methodological issues. To our knowledge, no available rating scale is specifically structured to assess changes in symptomatologic intensity of BPD patients, and traditional rating scales are ill-suited to assess changes in the polymorphous and fluctuating symptomatology of BPD. Self-ratings were avoided, both because of the great variability in BPD symptomatologic intensity over brief periods, and because of the difficulty that severe BPD patients have in labeling internal states.[10,35]

The psychiatric status of the subjects was rated by a research psychiatrist at the beginning of the treatment and after 4 and 16 weeks. The Brief Psychiatric Rating Scale (BPRS)[36] was completed. Following previous studies,[10,15] the physician's ratings of change in mood, anxiety, anger, impulsivity, rejection sensitivity, and overall pathology were obtained using 7-point scales similar to the Clinical Global Impressions scale, but with choices labeled "much less," "less," "somewhat less," "same," "somewhat more," "more," and "much more." Although the Hamilton Rating Scale for Depression (HAM-D)[37] has been shown to be of little utility in characterizing the quality of depression in BPD patients,[38] mood was rated on the HAM-D because a significant worsening of HAM-D scores has been reported in BPD patients after prolonged administration of traditional neuroleptics.[26]

Global functioning was assessed at the beginning (ratings of current state and last 6-month period) and at the end of the treatment using the DSM-IV Global Assessment of Functioning (GAF) scale.[31] Number of days of hospitalization during the 4 months before treatment and the 4 months after discharge from the ward were re-

Table 1. Changes in Rating Scale Scores for 12 Borderline Personality Disorder Patients Treated With Clozapine*

	4 Months Before Treatment		Admission		After 1 Month Clozapine Treatment		After 4 Months Clozapine Treatment	
Rating Scale	Mean	SD	Mean	SD	Mean	SD	Mean	SD
BPRS			49.83	6.83	26.75	4.07	24.00	3.57
BPRS psychotic cluster			14.83	5.39	7.50	1.38	6.50	1.31
CGI-mood					2.92	1.08	2.67	0.98
CGI-anxiety					1.83	0.58	1.58	0.67
CGI-anger					1.83	0.72	1.33	0.49
CGI-impulsivity					1.83	0.72	1.33	0.49
CGI-rejection sensitivity					3.08	0.79	2.75	0.87
CGI-overall pathology					2.42	0.51	1.92	0.67
HAM-D			18.58	7.73	8.08	3.70	6.33	3.60
GAF	36.89	13.39	26.67	10.17			58.83	10.98
Days of hospitalization	33.33	40.56			0	0	0.25	0.87
Suicidal attempts	2.17	0.17					1.64	0.39
Physical fights	5.16	6.70					0.67	1.50

*Abbreviations: BPRS = Brief Psychiatric Rating Scale; CGI = modified version of Clinical Global Impressions scale; GAF = DSM-IV Global Assessment of Functioning; HAM-D = Hamilton Rating Scale for Depression.

corded, together with number of severe suicide attempts (i.e., requiring emergency room treatment) and number of physical fights.

Statistics

Values were compared using Student's paired two-tailed t test.

RESULTS

Clozapine dose ranged from 25 to 100 mg/day (mean ± SD = 43.8 ± 18.8 mg/day). Mean ± SD length of the hospitalization after the beginning of the treatment was 20.3 ± 7.2 days.

Changes in outcome measures are summarized in Table 1. Clozapine treatment was followed by a decrease in psychotic-like symptoms within the first 2 weeks. After 1 month, BPRS scores showed a statistically significant mean decrease to 54% of baseline levels ($t = 10.18$, $df = 11$, $p < .001$), with 4 of 12 subjects showing an improvement greater than 50%, and 8 of 12 greater than 25%. Considering the five BPRS items related to psychotic-like symptoms (items 4, 8, 11, 12, 15), 6 of 12 patients showed a 50% reduction after 1 month, and 8 of 12 after 4 months.

The rapid change in this symptomatologic area was part of a broad amelioration in the overall course of pathology that included a substantial improvement in both impulsivity and affective instability, as rated on CGI scores. The number of both suicide attempts and physical fights was significantly reduced (respectively, $t = 4.69$, $df = 11$, $p < .001$; $t = 2.57$, $df = 11$, $p = .026$).

Depressive symptomatology followed the general trend toward amelioration, and no worsening was observed with the prolonged administration of clozapine. HAM-D scores showed a significant and sustained decrease over time, with a mean decrease to 43% of baseline levels after 1 month ($t = 5.21$, $df = 11$, $p = .0003$), and to 34% after 4 months; 8 of 12 patients showed a 50% improvement after 1 month, and 10 of 12 after 4 months.

The broad symptomatologic amelioration included substantial changes in global functioning, as rated on the GAF scale ($t = 6.42$, $df = 11$, $p < .001$) and confirmed by the almost complete absence of further hospitalization.

Side effects included sedation (10 of 12 patients), which disappeared during the first month of treatment; hypersialorrhea (9 of 12); and decrease in WBC count (6 of 12), which never reached values outside a clinical range of safety.

DISCUSSION

Under our experimental conditions, clozapine administration to a small sample of BPD patients was followed by a rapid decrease in psychotic-like symptoms and by a broad amelioration in all symptomatologic areas.

These changes were observed with low drug doses, which lack antipsychotic properties in schizophrenia.[39,40] A positive effect of clozapine 75 to 550 mg/day in the treatment of 15 BPD patients with Axis I DSM-III-R psychotic disorder not otherwise specified has been reported after an average treatment of 4 months.[29] A comparison of our results with those of Frankenburg and Zanarini[30] shows that our patients had lower baseline BPRS scores (Student's two-sided $t = 2.06$, $df = 25$, $p = .050$) but similar baseline GAF scores ($t = 1.40$, $p = .17$), and that our patients had better final scores (on both BPRS and GAF; respectively, $t = 5.72$, $p < .0001$ and $t = 4.18$, $p = .0003$) with lower clozapine doses ($t = 4.39$, $p = .0002$). These differences are likely to be due to the exclusion of patients

with Axis I psychotic disorders from our study; the similarity in the broad symptomatologic improvement observed in the two studies suggests that the usefulness of clozapine in the treatment of BPD patients is not limited to the management of clear-cut psychotic symptomatology.

Despite the prolonged administration of clozapine, depressive symptomatology followed the general trend toward improvement. Traditional neuroleptic treatment has been reported to acutely ameliorate[4,41] and chronically worsen[26] depression that occurs with personality disorders. Clozapine has been reported to have both antimanic,[42,43] mood stabilizing,[44] and possibly antidepressant properties.[45] Although affective symptomatology in BPD patients seems to be both phenomenologically and biologically distinct from that in mood disorders,[46–49] it is arguable that the possible mood-stabilizing properties of clozapine could have both prevented the development of depressive symptomatology and contributed to the favorable outcome.

We are aware of the methodological issues raised by our study. First, the evaluation of the efficacy of a pharmacologic treatment requires double-blind placebo-controlled studies; such studies are needed to confirm our results. Second, under our experimental conditions, specific drug effects can hardly be distinguished from the effects of the psychotherapeutic program, which was concomitant with drug administration, or from possible erratic improvement.[50] Third, despite the long duration of our study, no indication regarding the long-term therapy of BPD patients (i.e., whether and when to stop the pharmacologic treatment) can be drawn from these data.

Some clinically relevant comments are nevertheless possible based on the further follow-up of the patients of our sample. One patient self-suspended clozapine because of perceived well-being at Week 33, and one patient had to stop clozapine treatment at Week 24 because of severe granulocytopenia (which spontaneously resolved in 2 weeks after withdrawal): both of these patients showed an abrupt reappearance of the same symptomatology that had led to the previous hospitalization; in the first case, the rapid reintroduction of clozapine resulted in a return to well-being.

Further research is needed to clarify these points. In this respect, our results are similar to those preliminary observations by Soloff et al.[22,23] after acute administration of traditional neuroleptics, which the same authors failed to replicate in a further study.[24] Interest in the effect of clozapine for the pharmacologic treatment of severe personality disorders is however warranted.

Drug name: clozapine (Clozaril).

REFERENCES

1. Kernberg OF. Severe Personality Disorders: Psychotherapeutic Strategies. London, England: Yale University Press; 1984
2. Norton K, Hinshelwood RD. Severe personality disorder: treatment issues and selection for in-patient psychotherapy. Br J Psychiatry 1996;168: 723–731
3. Gunderson JG. Pharmacotherapy for patients with borderline personality disorder. Arch Gen Psychiatry 1986;43:698–700
4. Stein G. Drug treatment of the personality disorders. Br J Psychiatry 1992; 161:167–184
5. Skodal A, Buckley P, Charles E. Is there a characteristic pattern to the treatment history of clinical outpatients with borderline personality? J Nerv Ment Dis 1983;171:405–410
6. Zanarini MC, Frankenburg FR, Gunderson JG. Pharmacotherapy of borderline outpatients. Compr Psychiatry 1988;29:372–378
7. Soloff PH. Is there any drug treatment of choice for the borderline patient? Acta Psychiatr Scand Suppl 1994;379:50–55
8. Coccaro EF, Siever LJ. The neuropsychopharmacology of personality disorders. In: Bloom FE, Kupfer DJ, eds. Psychopharmacology: The Fourth Generation of Progress. New York, NY: Raven Press; 1995:1567–1578
9. Sweeney DR. Treatment of outpatients with borderline personality disorder. J Clin Psychiatry 1987;48(8, suppl):32–35
10. Cowdry RW, Gardner DL. Pharmacotherapy of borderline personality disorder. Arch Gen Psychiatry 1988;45:111–119
11. Coccaro EF, Kavoussi RJ. Biological and pharmacological aspects of borderline personality disorder. Hosp Community Psychiatry 1991;42: 1029–1033
12. Gardner DL, Cowdry RW. Positive effects of carbamazepine on behavioral dyscontrol in borderline personality disorder. Am J Psychiatry 1986; 143:519–522
13. Cornelius JR, Soloff PH, Perel JM, et al. Fluoxetine trial in borderline personality disorder. Psychopharmacol Bull 1990;26:151–154
14. Markowitz PJ, Calabrese JR, Schulz SC, et al. Fluoxetine in the treatment of borderline and schizotypal personality disorders. Am J Psychiatry 1991; 148:1064–1067
15. Stein DJ, Simeon D, Frenkel M, et al. An open trial of valproate in borderline personality disorder. J Clin Psychiatry 1995;56:506–510
16. Lotterman AC. Prolonged psychotic states in borderline personality disorder. Psychiatr Q 1985;57:33–46
17. George A, Soloff PH. Schizotypal symptoms in patients with borderline personality disorder. Am J Psychiatry 1986;143:212–215
18. Chopra HD, Beatson JA. Psychotic symptoms in borderline personality disorder. Am J Psychiatry 1986;143:1605–1607
19. Shearer SL. Dissociative phenomena in women with borderline personality disorder. Am J Psychiatry 1994;151:1324–1328
20. Zlotnik C, Shea MT, Pearlstein T, et al. The relationship between dissociative symptoms, alexithymia, impulsivity, sexual abuse, and self-mutilation. Compr Psychiatry 1996;37:12–16
21. Goldberg SC, Schulz C, Schulz PM, et al. Borderline and schizotypal personality disorders treated with low-dose thiothixene vs placebo. Arch Gen Psychiatry 1986;43:680–686
22. Soloff PH, George A, Nathan RS, et al. Progress in pharmacotherapy of borderline disorders. Arch Gen Psychiatry 1986;43:691–697
23. Soloff PH, George A, Nathan S, et al. Amitriptyline versus haloperidol in borderlines: final outcomes and predictors of response. J Clin Psychopharmacol 1989;9:238–246
24. Soloff PH, Cornelius J, George A, et al. Efficacy of phenelzine and haloperidol in borderline personality disorder. Arch Gen Psychiatry 1993; 50:377–385
25. Soloff PH. Neuroleptic treatment in the borderline patient: advantages and techniques. J Clin Psychiatry 1987;48(8, suppl):26–30
26. Cornelius JR, Soloff PH, Perel JM, et al. Continuation pharmacotherapy of borderline personality disorder with haloperidol and phenelzine. Am J Psychiatry 1993;150:1843–1848
27. Kane J, Honigfeld G, Singer J, et al. Clozapine for the treatment-resistant schizophrenic. Arch Gen Psychiatry 1988;45:789–796
28. Tamminga CA, Thaker GK, Moran M, et al. Clozapine in tardive dyskinesia: observations from human and animal model studies. J Clin Psychiatry 1994;55(9, suppl B):102–106
29. Roy Chengappa KN, Baker RW, Sirri C. The successful use of clozapine in ameliorating severe self mutilation in a patient with borderline personality disorder. J Personal Disord 1995;9:76–82
30. Frankenburg FR, Zanarini MC. Clozapine treatment of borderline patients: a preliminary study. Compr Psychiatry 1993;34:402–405
31. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric

Association; 1994
32. Spitzer RL, Williams JBW, Gibbon M, et al. Structured Clinical Interview for DSM-III-R (SCID). New York, NY: Biometric Research, New York State Psychiatric Institute; 1989
33. Dev VJ, Rosenberg T, Krupp P. Agranulocytosis and clozapine. BMJ 1994;309:54
34. Dev VJ, Krupp P. Adverse event profile and safety of clozapine. Reviews in Contemporary Pharmacotherapy 1995;6:197–208
35. de Bonis M, De Boeck P, Lida-Pulik H, et al. Identity disturbances and self-other differentiation in schizophrenics, borderlines, and normal controls. Compr Psychiatry 1995;36:362–366
36. Overall JE, Gorham DR. The Brief Psychiatric Rating Scale. Psychol Rep 1962;10:799–812
37. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62
38. Southwick SM, Yehuda R, Giller EL. Psychological dimensions of depression in borderline personality disorder. Am J Psychiatry 1995;152: 789–791
39. Meltzer HY. Dimensions of outcome with clozapine. Br J Psychiatry 1992;160(suppl 17):46–53
40. Hasegawa M, Gutierrez-Esteinou R, Way L, et al. Relationship between clinical efficacy and clozapine plasma concentrations in schizophrenia: effects of smoking. J Clin Psychopharmacol 1993;13:383–390
41. Montgomery SA, Montgomery D. Pharmacological prevention of suicidal behavior. J Affect Disord 1982;4:291–298
42. Calabrese JR, Kimmel SE, Woyshville MJ, et al. Clozapine for treatment-refractory mania. Am J Psychiatry 1996;153:759–764
43. Barbini B, Scherillo P, Benedetti F, et al. Response to clozapine in acute mania is more rapid than that of chlorpromazine. Int Clin Psychopharmacol 1997;12:109–112
44. Calabrese JR, Meltzer HY, Markovitz PJ. Clozapine prophylaxis in rapid-cycling bipolar disorder. J Clin Psychopharmacol 1991;11:396–397
45. Parsa M, Ramirez LF, Loula EC, et al. Effect of clozapine on psychotic depression and parkinsonism. J Clin Psychopharmacol 1991;11:330–331
46. Lahmeyer HW, Reynolds CF III, Kupfer DJ, et al. Biologic markers in borderline personality disorder: a review. J Clin Psychiatry 1989;50:217–225
47. Gunderson JG, Phillips KA. A current view of the interface between borderline personality disorder and depression. Am J Psychiatry 1991;148: 967–975
48. Bellodi L, Battaglia M, Gasperini M, et al. The nature of depression in borderline depressed patients. Compr Psychiatry 1992;33:128–133
49. Rogers JH, Widiger TA, Krupp A. Aspects of depression associated with borderline personality disorder. Am J Psychiatry 1995;152:268–270
50. Najavits LM, Gunderson JG. Better than expected: improvements in borderline personality disorder in a 3-year prospective outcome study. Compr Psychiatry 1995;36:296–302