Eur Arch Psychiatry Clin Neurosci (2005) 255 : 10–14 DOI 10.1007/s00406-004-0528-8

ORIGINAL PAPER

Bettina S. Fehr · M. Erkan Ozcan · Trisha Suppes

Low doses of clozapine may stabilize treatment-resistant bipolar patients

Received: 2 July 2003 / Accepted: 27 April 2004 / Published online: 12 November 2004

Abstract Open, uncontrolled studies suggest clozapine can have mood-stabilizing effects in treatment-resistant bipolar disorder. Unfortunately, the side effect profile limits clozapine's use at high doses. We report a series of nine bipolar I disorder patients who improved on relatively low doses of clozapine add-on therapy (250 mg or lower). Retrospectively abstracted clinical data identified nine patients with bipolar I disorder, as defined by DSM-IV criteria, treated with low-dose clozapine at inpatient and outpatient settings. Monthly symptom evaluations were collected prospectively using standard assessments. Symptoms of mania and mood lability improved in all patients. Three patients demonstrated striking mood stabilization and returned to previous levels of functioning; five patients evidenced moderate improvement in mood stabilization and functioning; and one patient showed a minimal response. Overall, clozapine did not have a significant antidepressant effect. The mean clozapine dose at the end of the study was 156.3 ± 77.6 mg/day, and duration of treatment was 12 months. Residual side effects were mild. The symptomatic improvement in these prospectively evaluated patients is consistent with our clinical impression in the majority of patients with bipolar disorder taking clozapine.

Key words clozapine · bipolar disorder · efficacy · side effects · treatment-resistant · combination treatment

B. S. Fehr, M.D.
VA Hospital
The University of Texas Southwestern Medical Center
Dallas, Texas, USA

M. E. Ozcan, M.D. · T. Suppes, M.D., Ph.D. (✉)
Bipolar Disorder Research Program
Department of Psychiatry
The University of Texas Southwestern Medical Center
5323 Harry Hines Blvd.
Dallas, TX 75390-9121, USA
Tel.: +1-214/648-6924
Fax: +1-214/648-6922
E-Mail: Trisha.Suppes@UTSouthwestern.edu

EAPCN 528

Introduction

Although conventional antipsychotics are effective as antimanic agents, their use in bipolar disorder is associated with a number of limitations, such as acute and long-term neurological side effects and insufficient antidepressant properties. Over the past decade, use of the atypical antipsychotic drugs has significantly changed the treatment of schizophrenia (Gaebel et al. 2003). One of these drugs, clozapine, is highly effective in treating different psychotic disorders in children and adults (Kowatch et al. 1995; Mc Elroy et al. 1991). These disorders include acute and chronic schizophrenia (Kane et al. 1988; Shopsin et al. 1979), organic psychoses and schizoaffective disorder (Naber et al. 1992). Atypical antipsychotics are now often used for the management of bipolar disorder in the United States (American Psychiatric Association 2002; Brown et al. 2001; Guille et al. 2000), and use is expanding in Europe, and Great Britain. Good results have been achieved with currently available atypical antipsychotics, including clozapine, in reducing symptoms of acute mania, especially when added to mood stabilizers (Weizman et al. 2001). In open, uncontrolled studies, clozapine has demonstrated mood-stabilizing effects in treatment-resistant bipolar disorder (Banov et al. 1994; Calabrese et al. 1996), including mixed episodes (Suppes et al. 1992), rapid cycling (Calabrese et al. 1991; Suppes et al. 1994), and bipolar disorder in children (Kowatch et al. 1995). Clozapine is recommended at 300–600 mg/day doses in schizophrenia, while it has been suggested that clozapine's average daily effective dose in psychotic mood disorders is 315 mg/day (Frye et al. 1998).

Clozapine use is accompanied by multiple side effects, most of which appear to be dose related (Baldessarini et al. 1991). Sialorrhea, weight gain, and sedation often limit compliance at higher doses. However, low doses of clozapine can be effective in certain groups, such as psychiatrically ill geriatric patients (Chengappa et al. 1995; Oberholzer et al. 1992) or those with mental

disorders related to Parkinson's disease (Rabey et al. 1995; Wolk et al. 1992). In addition, several reports have shown effectiveness in treatment resistant bipolar disorders, even at low doses (250 mg/day or lower) (Frye et al. 1998; Suppes et al. 1999), or as monotherapy (Calabrese et al. 1991, Suppes et al. 1992). Few published cases have addressed the use of clozapine at doses under or equal to 250 mg/day in bipolar disorder (Frankfurter 1993; Fuchs 1994; Privitera et al. 1993, Puri et al. 1995).

Recently, Suppes et al. (1999) reported that clozapine add-on therapy was associated with a significant clinical improvement in their sample of treatment-resistant bipolar I, or schizoaffective, bipolar type, patients. In that study, bipolar patients, and particularly non-psychotic bipolar patients, appeared to stabilize on lower doses of clozapine. They found that the mean peak daily dose of clozapine was significantly lower in the patients with bipolar I disorder (234 mg/day) in comparison to those with schizoaffective disorder, bipolar type (623 mg/day).

Currently, there is no clear understanding whether clozapine doses effective for bipolar I disorder with or without psychotic features are similar to doses used in patients with schizophrenia. Also, the use of clozapine for non-psychotic bipolar patients is relatively unstudied. The present study therefore describes a group of patients with treatment resistant bipolar I disorder treated with low doses of clozapine (250 mg or lower).

Methods

The participants in this study were nine patients with bipolar I disorder selected from a larger group of 38 patients with bipolar I or schizoaffective disorder, bipolar type, originally described by Suppes et al. (1999). All nine were enrolled in a one-year trial of clozapine treatment at doses of 250 mg or lower. Inclusion criteria were: diagnosis of bipolar I disorder by investigator team consensus and a Structured Clinical Interview (Spitzer et al. 1992) according to DSM-IV criteria; occurrence of a mood episode within the preceding twelve months; age between 18–65 years with onset of illness before age 40; ongoing symptoms of illness; and a documented history of treatment resistance or medication intolerance. The patients were seen either at an inpatient unit of a general hospital or at a local community health clinic. They were severely ill and high users of services, both of inpatient and outpatient facilities. Treatment resistance was defined as persistent symptoms despite adequate and simultaneous treatment with two mood stabilizers (lithium plus valproate or carbamazepine) at standard therapeutic levels. If the patients exhibited psychotic symptoms, documented failure of treatment with a typical antipsychotic together with mood stabilizers was required. Inability to meet these criteria due to intolerance of medications was also sufficient to classify patients as treatment-resistant. Patients who were pregnant, breast-feeding, or not using contraception, patients with unstable general medical conditions, and patients with current active alcohol or substance abuse were excluded.

Of the nine patients described in this study, the average duration of illness was 21 years, ranging from 9 years (case 1) to 31 years (case 8), and most patients had been hospitalized within the previous two years. Prior to clozapine treatment, these patients had remained unstable, despite multiple mood stabilizers and antipsychotics (where indicated) or electro-convulsive treatment (ECT). Ages ranged from 29 (case 1) to 51 (case 8), with onset of illness ranging from age 10 (case 4) to age 20 (cases 1.7, and 8). At baseline, patients were administered the 18-item Brief Psychiatric Rating Scale (BPRS; minimum score was 18) (Overall et al. 1962), the Bech-Rafaelsen Mania Scale ((BRMS) (Bech et al. 1979), and the 24-item Hamilton Rating Scale for Depression ($HRSD_{24}$) (Hamilton 1960). The rating scale battery was administered monthly for a total of one year from study enrollment (every two weeks during the first three months).

Demographic data for the nine patients treated with low-dose clozapine (250 mg or less) are summarized in Table 1.

The mean clozapine dose at 12 months was 156.3 ± 77.6 mg/day, range 50 (case 4) to 250 mg/day (cases 5, and 6). All patients were diagnosed as bipolar 1 disorder by DSM-IV criteria. Seven had histories of psychosis during manic or depressive episodes, and cases 1, 4, and 9 were rapid cyclers. Cases 1 and 7 were on ECT maintenance treatment prior to the clozapine initiation, and case 3 had ECT treatments in the past. Case 9 had a second Axis I diagnosis of obsessive-compulsive disorder and trichotillomania. Three patients had history of substance abuse (in remission for several months prior to entering the study). None of the patients were able to work due to the severity of their illness prior to entering the study.

Results

Clinical response was measured with standard psychiatric symptom scales and clinical assessment. None of the patients were actively psychotic at baseline or during the study. BPRS, $HRSD_{24}$ and BRMS scales are presented on Table 2.

Three patients (cases 2, 5, and 9) demonstrated marked clinical response and achieved stabilization of their illness complete enough to resume normal levels of psychosocial function over several months of clozapine treatment (i. e., resuming stable employment and stabilization of relationships). In addition to mood stabilization, case 9 experienced remission of obsessive compulsive symptoms and trichotillomania at 100 mg of clozapine.

Four patients (cases 1, 3, 6, 7 and 8) showed significant improvement, but symptoms still interfered with

Table 1 Demographics of the sample

	N	Average	SD
Age (years)	9	37.2	6.9
Female	7		
Male	2		
Duration of illness before clozapine (years)	9	21.0	6.4
# of hospitalizations before clozapine	9	5.6	5.2
# of hospitalizations after clozapine[a]	9	0.1	0.3
# of medications before clozapine[b]	9	2.6	2.0
# of medications after clozapine[c]	8	3.1	1.2
Clozapine dose at 12 months (mg/day)	8	156.3	77.6
History of psychosis	7		
History of rapid cycling	3		

Medication After Clozapine number of medications after one year of treatment with add-on clozapine; *SD* standard deviation

[a] Case 8 hospitalized once while on clozapine due to delirium as a result of probable overdosing

[b] Case 1 was on ECT maintenance and on one medication (thioridazine 200 mg/day), after clozapine on 100 mg clozapine monotherapy; and Case 7 was only on ECT maintenance

[c] One of medications was clozapine; case 8 excluded; none receiving ECT

Table 2 Clinical response of the sample

	BPRS			$HRSD_{24}$			BRMS		
Case	Before	6 Months	12 Months	Before	6 Months	12 Months	Before	6 Months	12 Months
1	45	27	32	14	9	8	10	3	1
2	35	22	25	14	8	13	3	2	1
3	37	38	20*	11	25	11*	0	3	1*
4	41	20	19**	22	10	4**	9	1	6**
5	35	23	20	15	8	7	6	1	1
6	26	18	39	9	1	29	13	0	2
7	47	42	43	31	33	18	6	1	5
8	47	23	NA	19	7	NA	4	3	NA
9	27	23	22	11	11	9	3	2	1
Mean	37.78	26.22	27.50	16.22	12.44	12.38	6.00	1.78	2.25
SD	7.93	8.24	9.37	6.87	10.00	7.93	4.06	1.09	2.05

BPRS Brief Psychiatric Rating Scale; *$HRSD_{24}$* 24-item Hamilton Rating Scale for Depression; *BRMS* Beck-Rafaelsen Mania Scale
* measured at 8 months, after which patient dropped out due to noncompliance
** measured at 10 months, after which patient dropped out due to side effects and noncompliance

functioning (e. g., maintaining a stable job situation and stability of relationships). In all of these cases, manic symptoms remitted or significantly diminished. Prior to starting clozapine, case 1 was treated with ECT maintenance and thioridazine. On clozapine, mood swings stabilized and ECT was discontinued. Her mood remained stable at 200 mg of clozapine monotherapy, and residual depressive symptoms did not require additional medication. Case 7 responded only to ECT maintenance prior to entering the study. Although he experienced residual depressive symptoms on clozapine 100 mg/day, fluoxetine 80 mg/day, and imipramine 150 mg/day, he did not manifest manic symptoms and did not continue ECT maintenance. Case 3 dropped out of the study after eight months due to noncompliance with medication. Case 6 historically had a manic episode every summer before initiation of clozapine. On clozapine he developed a major depressive episode in the summer instead of a manic episode. His high BPRS score was due to depressive symptoms. Oversedation prohibited further increases of clozapine. Despite antimanic efficacy and clinical improvement, he chose to discontinue the drug after one year. When he discontinued, he was on clozapine 250 mg/day, lithium 1800 mg/day, fluoxetine 20 mg/day, and diazepam 10–30 mg/as needed.

After seven months, case 8 accidentally overdosed on multiple medications and had to be hospitalized with delirium, at which time clozapine was stopped. One patient (case 4) partially responded to treatment with clozapine at a very low dose, 50 mg/day. However she could not tolerate medication increase due to oversedation, weight gain, and sialorrhea. After 10 months, she was removed from the study due to relapse of comorbid polysubstance abuse.

Discussion

Nine patients with bipolar I disorder treated with relatively low doses of clozapine (250 mg or lower) were selected from a larger group of bipolar and schizoaffective (bipolar type) patients included in a study of clozapine add-on therapy versus treatment as usual (Suppes et al. 1999). In all of these nine severely ill patients, mood lability improved or disappeared altogether, although most patients experienced residual depressive symptoms (which required additional treatment). Manic symptoms disappeared in all except one (case 6 continued to experience some hypomanic symptoms). Residual side effects of clozapine were mild, primarily limited to weight gain, mild sedation, and/or sialorrhea.

Three patients (cases 2,5, and 9) showed marked response on clinical rating scales to the addition of clozapine to their current medication regimen, with stabilization of mood cycling and normalization of psychosocial functioning. According to clinical observations, all three patients experienced improvement in relationships and capacity to enjoy life, and were reintegrated into stable and satisfactory work situations.

Prior to the initiation of clozapine, two patients (cases 1 and 7) had experienced illness that was resistant to all medications and that could only be controlled with repeated ECT. One of these two patients, case 1, was a woman with severe rapid cycling bipolar illness who remained stable on low-dose clozapine monotherapy and required no additional medications or ECT. Both ECT and clozapine have broad effects on the brain, influencing multiple systems of neurotransmission, and both are reserved for bipolar illness otherwise treatment resistant to traditional pharmacotherapy (Frankenburg 1993).

Contrary to preliminary findings in other studies (Banov et al. 1994) in the present group of patients we did not find an antidepressant effect of clozapine. The early clinical experience of clozapine as a potential mood stabilizer suggests greater antimanic than antidepressant properties (Frye et al. 1998; Zarate et al. 1995). More significant antidepressant effects have been noted with other atypical antipsychotics (Shelton et al. 2001).

Because of the recurring nature of bipolar illness

(0.40 episodes per year reported in the study by Angst et al. 2003), it is possible that the mood stabilization of these nine patients resulted from spontaneous disease remission. It is also possible that their improvement occurred as the result of frequent office visits *per se* (and not as the result of clozapine add-on therapy). However, these issues were addressed in the original larger study by Suppes et al. (1999), which included a control group of patients with treatment as usual (no clozapine). These randomized control patients were of matched severity and symptomatology as the experimental subjects, with roughly the same number of clinical visits. Thus, while spontaneous remission or conventional therapy factors cannot be entirely ruled out as potential confounds, we believe these explanations are unlikely.

Often clozapine is not initiated due to concerns about tolerability at the doses used with patients with schizophrenia. While other reports have noted the effectiveness of clozapine to treat patients with bipolar disorder (Frye et al. 1993; Zarate et al. 1995), none have focused on the potential for patients with bipolar disorder to respond at significantly lower doses than recommended for treatment of schizophrenia. The present report, focusing on the response of nine patients who received clozapine as part of a randomized add-on study (Suppes et al. 1999), highlights the potential for response at relatively low doses.

Reports have suggested that obsessive-compulsive symptoms can occasionally be worsened or induced by clozapine (Baker et al. 1992; Patel et al. 1992, 1993; Suppes et al. 1996). Case 9 describes a woman with obsessive-compulsive disorder poorly controlled until starting clozapine. Not only did mood swings improve upon addition of clozapine to her current medication regimen, but also checking and ritualistic behaviors and trichotillomania. Residual compulsive symptoms disappeared completely after the addition of sertraline. This patient was treated with much lower doses of clozapine (100 mg/day) than patients in previous reports (Baker et al. 1992; Patel et al. 1992, 1993), suggesting worsening of obsessive-compulsive symptoms could be a dose-dependent phenomenon.

In summary, these results support that clozapine, even at relatively low doses: 1) may have powerful mood stabilizing effects in treatment-resistant patients with bipolar disorder; 2) was effective at low doses in some patients responding to ECT treatment only; 3) was effective primarily on the symptoms of mood lability and mania; and 4) patients remained stable for a significant period of time. Further study is required to understand and identify which subgroups among patients with severe bipolar illness may respond to clozapine at lower doses. Controlled trials are needed to delineate this atypical antipsychotic and other atypical agents' range of effectiveness.

Acknowledgements This research was supported in part by Mental Health Connections, a partnership between Dallas County Mental Health Mental Retardation and the Department of Psychiatry of the University of Texas Southwestern Medical Center (TS); a Young Investigator Award from the National Alliance for Research on Schizophrenia and Depression (TS); the Forest E. Lattner Foundation (TS), the Stanley Medical Research Institute (TS, MEO); NIMH grant MH-53799 (TS); and Novartis Pharmaceuticals (for medication).

References

1. American Psychiatric Association (2002) Practice guideline for the treatment of patients with bipolar disorder (Revision). Am J Psychiatry 159(suppl 4):1–50
2. Angst J, Gamma A, Sellaro R, Lavori PW, Zhang H (2003) Recurrence of bipolar disorders and major depression. A lifelong perspective. Eur Arch Psychiatry Clin Neurosci 253:236–240
3. Baker RW, Chengappa KNR, Baird JW (1992) Emergence of obsessive-compulsive symptoms during treatment with clozapine. J Clin Psychiatry 53:439–442
4. Banov MD, Zarate CA Jr, Tohen M, Scialabba D, Wines JD Jr, Kolbrener M, Kim JW, Cole JO (1994) Clozapine therapy in refractory affective disorders: polarity predicts response in long-term follow-up. J Clin Psychiatry 55:295–300
5. Bech P, Bolwig TG, Kramp T, Rafaelsen OJ (1979) The Bech-Rafaelsen Mania Scale and the Hamilton Depression Scale: Evaluation of homogeneity and inter-observer reliability. Acta Psychiatr Scand 59:420
6. Brown ES, Thomas NR, Carmody T, Mahadi S, Nejtek VA (2001) Atypical antipsychotics in bipolar and schizoaffective disorders. Pharmacopsychiatry 34:80–81
7. Calabrese JR, Kimmel SE, Woyshville MJ, Rapport DJ, Faust CJ, Thompson PA, Meltzer HY (1996) Clozapine for treatment-refractory mania. Am J Psychiatry 153:759–764
8. Calabrese JR, Meltzer HY, Markowitz PJ (1991) Clozapine prophylaxis in rapid cycling bipolar disorder. J Clin Psychopharmacol 11:396–397
9. Chengappa KN, Baker RW, Kreinbrook SB, Adair D (1995) Clozapine use in female geriatric patients with psychoses. J Geriatr Psychiatr Neurol 8:12–15
10. Frankenburg F (1993) Clozapine and bipolar disorder. J Clin Psychopharmacol 13:289–290
11. Frye MA, Ketter TA, Altshuler LL, Denicoff K, Dunn RT, Kimbrell TA, Cora-Locatelli G, Post RM (1998) Clozapine in bipolar disorder: treatment implications for other atypical antipsychotics. J Affect Disord 48:91–104
12. Fuchs DC (1994) Clozapine treatment of bipolar disorder in a young adolescent. J Am Acad Child Adolesc Psychiatry 33: 1299–1302
13. Gaebel W, Riesbeck M, Janssen B, Schneider F, Held T, Macklenburg H, Sass H (2003) Atypical and typical neuroleptics in acute schizophrenia and related delusional disorders. Drug choice, switching and outcome under naturalistic treatment conditions. Eur. Arch Psychiatry Clin Neurosci 253:175–184
14. Guille C, Sachs GS, Ghaemi SN (2000) A naturalistic comparison of clozapine, risperidone, and olanzapine in the treatment of bipolar disorder. J Clin Psychiatry 61:638–642
15. Hamilton M (1960) Rating scale for depression. J Neurol Neurosurg Psychiatry 23:56
16. Kane J, Honigfeld G, Singer J, Meltzer HY (1988) Clozapine for the treatment-resistant schizophrenic. A double-blinded comparison with chlorpromazine. Arch Gen Psychiatry 45:789–796
17. Kowatch RA, Suppes T, Gilfillan SK, Fuentes RM (1995) Clozapine treatment of children and adolescents with bipolar disorder and schizophrenia. A clinical case series. J Child Adolesc Psychopharmacol 5:241–253
18. McElroy SL, Dessain EC, Pope HG, Cole JO, Keck PE Jr, Frankenberg FR, Aizley HG, O'Brien S (1991) Clozapine in the treatment of psychotic mood disorders, schizoaffective disorder, and schizophrenia. J Clin Psychiatry 52:411–414
19. Naber D, Holzbach R, Perro C, Hippius H (1992) Clinical management of clozapine patients in relation to efficacy and side effects. Br J Psychiatry 160(suppl 17):54–59

20. Oberholzer AF, Hendriksen C, Monsch AU, Heierli B, Stahelin HB (1992) Safety and effectiveness of low-dose clozapine in psychogeriatric patients: a preliminary study. Int Psychogeriatr 4: 187–195
21. Overall JE, Gorham DR (1962) The Brief Psychiatric Rating Scale (BPRS). Psycho Rep 1:799
22. Patel B, Tandon R (1993) Development of obsessive-compulsive symptoms during clozapine treatment. Am J Psychiatry 150:836
23. Patel VJ (1992) Development of transient obsessive-compulsive symptoms during treatment with clozapine. Am J Psychiatry 149:272
24. Privitera MR, Lamberti JS, Maharaj K (1993) Clozapine in a bipolar depressed patient. Am J Psychiatry 150:986
25. Puri BK, Taylor DG, Alcock ME (1995) Low-dose maintenance clozapine treatment in the prophylaxis of bipolar affective disorder. Br J Clin Pract 49:333–334
26. Rabey JM, Treves TA, Neufeld MY, Orlov E, Korczyn AD (1995) Low-dose clozapine in the treatment of levodopa-induced mental disturbances in Parkinson's disease. Neurology 45:432–434
27. Seeman P (1992) Dopamine receptor sequences: therapeutic levels of neuroleptics occupy D2 receptors, clozapine occupies D4. Neuropsychopharmacology 7:261–284
28. Shelton RC, Tollefson GD, Tohen M, Stahl S, Gannon KS, Jacobs TG, Buras WR, Bymaster FP, Zhang W, Spencer KA, Feldman PD, Meltzer HY (2001) A novel augmentation strategy for treating resistant major depression. Am J Psychiatry 158:131–134
29. Shopsin B, Klein H, Aaronson M, Collora M (1979) Clozapine, chlorpromazine, and placebo in newly hospitalized acutely schizophrenic patients. A controlled, double-blind comparison. Arch Gen Psychiatry 36:657–664
30. Spitzer RL, Williams JBW, Gibbon M, First MB (1992) The Structured Clinical Interview for DSM-III-R (SCID), I: history, rationale, and description. Arch Gen Psychiatry 49:624–629
31. Suppes T, Mc Elroy SL, Gilbert G, Dessain EC, Cole JO (1992) Clozapine in the treatment of dysphoric mania. Biol Psychiatry 32:270–280
32. Suppes T, Phillips K, Judd C (1994) Clozapine treatment of nonpsychotic rapid cycling bipolar disorder. A report of three cases. Biol Psychiatry 3:338–340
33. Suppes T, Rush JA (1996) Medication optimization during clozapine treatment. J Clin Psychiatry 57:307–308
34. Suppes T, Webb A, Paul B, Carmody T, Kraemer H, Rush AJ (1999) Clinical outcome in a randomized 1-year trial of clozapine versus treatment as usual for patients with treatment-resistant illness and a history of mania. Am J Psychiatry 156:1164–1169
35. Weizman R, Weizman A (2001) Use of atypical antipsychotics in mood disorders. Curr Opin Investig Drugs 2:940–945
36. Wolk SI, Douglas CJ (1992) Clozapine treatment of psychosis in Parkinson's disease: a report of five consecutive cases. J Clin Psychiatry 53:373–376
37. Zarate CA, Tohen M, Banov MD, Weiss MK, Cole JO (1995) Is clozapine a mood stabilizer? J Clin Psychiatry 56:108–112