The Effects of Long-Term Clozapine Add-On Therapy on the Rehospitalization Rate and the Mood Polarity Patterns in Bipolar Disorders

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Objective: We investigated the effect long-term clozapine add-on therapy has on rehospitalization rate and mood polarity patterns in patients with bipolar disorders.

Method: Clinical data from medical records of 51 patients with bipolar disorder (DSM-IV) treated with clozapine add-on for more than 6 months at the Refractory Bipolar Disorders Clinic of Seoul National University Hospital were retrospectively analyzed. Patients had been registered from 1995 to 2004. Rehospitalization rates were compared before and after clozapine add-on. The clinical polarity of episodes resulting in hospitalizations was also compared. Twenty-seven bipolar patients treated with clozapine add-on for more than 3 years were further analyzed for long-term stability.

Results: The number of hospital days per year was reduced in 90.2% of patients after clozapine add-on. Total number and duration of hospitalizations per year decreased, and the effect size of clozapine add-on was substantially large (Wilcoxon $z = -5.48$, $p < .01$ for number of hospitalizations/year; Wilcoxon $z = -5.32$, $p < .01$ for hospital days/year; $r = -0.54$ and -0.53, respectively). Significant reductions were found in the number and duration of hospitalizations associated with manic, depressive, and hypomanic episodes. Number and duration of hospitalizations associated with mixed episodes did not show significant changes. The long-term efficacy of clozapine add-on was supported by continuous reduction in hospital days per year in the 27 selected patients.

Conclusion: Long-term clozapine add-on therapy was effective in reducing the number and duration of rehospitalizations of bipolar patients resistant to conventional treatment. A significant reduction was found in rehospitalizations associated with manic, depressive, and hypomanic episodes, whereas mixed episode–associated rehospitalizations did not show significant changes.

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Composed of unpredictably recurring episodes, mood disorders are chronic disorders that tend to cause cognitive dysfunctions and social incompetence as severe as schizophrenia.[1,2] Among them, bipolar disorder has been reported to cause significantly more rehospitalizations than nonpsychotic or psychotic depressions in a long-term prospective follow-up study.[3] The recurrent episodes of bipolar disorder and consequent rehospitalizations can negatively impact the overall functioning and treatment compliance of bipolar patients,[4] hence the practical goals of maintenance therapy in bipolar patients presumably are both preventing recurrent episodes and reducing the length of hospital days.

Rehospitalization rate and long-term course of bipolar disorder can be significantly improved by extending the remission period at an early phase of pharmacotherapy.[3,5] However, conventional lithium treatment is not effective in 30% to 50% of patients with classic mania and 60% to 70% of patients with mixed mania,[6–8] and it may even worsen depressive episodes during long-term maintenance therapy.[9] Mood-stabilizing anticonvulsants also

show limitations in treating some populations of bipolar patients due to their side effects and lack of efficacy.[10] Recent studies showed that about half of the patients with manic episodes who were undergoing conventional treatment were suffering from repeated hospitalizations and social maladjustment.[11] In this context, Sachs[12] suggested working criteria for treatment resistance in mania, bipolar depression, and mood cycling based on the history of remission and diminished cycling resulting from adequate therapeutic trials using antidepressants, mood stabilizers, and antipsychotics.

In Korea, atypical antipsychotics are generally used in preference to typical antipsychotics for treating psychotic features of bipolar disorder to avoid extrapyramidal side effects.[13] There is no private health insurance system in Korea, and the National Health Insurance Corporation does not have a mandate on the limitation of duration of psychiatric hospitalizations. Therefore, Korean psychiatrists may seem to be more permissive to hospitalization-based treatment than U.S. psychiatrists. However, the results of the field trials of the Korean Medication Algorithm Project for Bipolar Disorder[13,14] based on the Expert Consensus Guideline Series Medication Treatment for Bipolar Disorder 2000[15] demonstrated that the characteristics of clinical practices for bipolar disorder in Korea, including indications of administration, diagnostic approaches, and strategies of pharmacotherapy, do not significantly deviate from those recommended by the American Psychiatric Association.

Clozapine, an atypical antipsychotic that has been widely used for chronic schizophrenia,[16,17] is regarded as a very effective agent for schizophrenic patients showing treatment resistance, suicidality, or intolerable extrapyramidal symptoms developed with the use of other antipsychotics.[18–20] Numerous studies whose results show actual benefits of clozapine in treating affective disorders not responding to conventional treatment[21–23] support the possible efficacy of clozapine in treating clinically difficult cases such as lithium-resistant rapid-cycling episodes or dysphoric mania.[24–26] In fact, along with other atypical antipsychotics, clozapine is now considered as one of the effective treatment alternatives for bipolar patients resistant to lithium or anticonvulsant treatment.[27]

Even though clozapine has been proven to be effective in managing treatment-resistant patients as well as patients with acute mania[28–30] and extending the remission period,[24,31,32] it may induce agranulocytosis or lower seizure threshold. These serious or potentially life-threatening side effects limit clozapine use in bipolar patients to extremely severe cases and result in relatively scarce clinical data on long-term maintenance clozapine add-on treatment compared to other atypical antipsychotics such as olanzapine or risperidone. Nonetheless, as clozapine has established a firm place in the therapeutic algorithm of schizophrenia due to outstanding efficacy in treatment-resistant cases, more aggressive use of clozapine, with hematologic monitoring and cautious titration, may be favored by clinicians for a broader range of refractory bipolar patients.

Since it is essential in the treatment of bipolar disorders to extend the remission period and community stay as much as possible,[33] the aim of this study is to assess the long-term stability of clozapine treatment in bipolar disorders by analyzing changes in rehospitalization pattern before and after clozapine add-on and to evaluate the differential effects of clozapine on the clinical polarity of episodes.

METHOD

Subjects

All study subjects were recruited from the Refractory Bipolar Disorders Clinic of Seoul National University Hospital (Seoul, Republic of Korea). Records of all patients registered from 1995 to 2004 were screened for inclusion, while patients with any history of organic brain disease, substance abuse (including alcohol abuse), neurologic diseases, or traumatic head injury were excluded. Three psychiatrists conducted a retrospective chart review for screened subjects and identified all patients who had received clozapine treatment with a clinical diagnosis of bipolar I or II disorder according to DSM-IV criteria. Patients who received additional treatment with mood stabilizers, antipsychotics, or antidepressants to control mood symptoms after introduction of clozapine add-on were excluded. A total of 67 patients were selected for the study after this review process. From these 67 patients, 4 patients were deemed ineligible for this study because the duration of clozapine treatment at the time of chart review was less than 6 months, and 5 were excluded due to the use of sertraline (25–100 mg/day) to manage obsessive-compulsive symptoms that developed after clozapine add-on. Another 4 patients who dropped out before 6 months due to intolerable side effects (excessive sedation for 2 patients, hypersalivation for 1 patient, and disabling dizziness for 1 patient) were also excluded. In addition, 3 patients with a history of antidepressant use at the onset of first manic episode were also excluded by team discussion. Therefore, this post hoc analysis was based on a total of 51 bipolar patients treated with clozapine add-on for more than 6 months.

After receiving a full explanation of the aim of this study, 51 subjects provided written informed consent for the use of their medical records. Patients were assured that there would be no impact on treatment decisions or plans regardless of whether they agreed to participate in the study or not. After the introduction of clozapine add-on, no changes were observed in the use of mood

stabilizers except intermittent dose titration according to medical conditions and blood levels of agents. The details of the study design were scrutinized and approved by the Seoul National University Institutional Review Board. All patients had a history of treatment with 2 or more different classes of antipsychotics for add-on therapy before taking clozapine, as well as at least 2 of the 3 major mood-stabilizing agents (lithium, valproate, and carbamazepine). Twenty-seven bipolar patients treated with clozapine for more than 3 years were selected from the 51 study subjects to extract additional data for the assessment of long-term efficacy of clozapine add-on therapy.

Data Collection

Clinical data were collected from psychiatric records to investigate demographic characteristics, overall history of pharmacotherapy, clinical polarity of episodes resulting in hospitalizations, and the total number and duration of hospitalizations before and after clozapine add-on for each patient. The clinical polarity of each episode associated with hospitalization was reviewed and confirmed by research psychiatrists according to DSM-IV criteria. *Hospital days per year* was also calculated to quantify and compare the differences in the length of remission and community stay brought about by clozapine add-on. All clinical data collected from the period of post–clozapine add-on were compared to the data from the pre-clozapine period of the same length.

Statistical Analyses

To test whether the distribution of data could be considered normal, the Kolmogorov-Smirnov test was used. Since the result of the test was highly significant for the numeric items of collected data, it was preferable to use assumption-free nonparametric tests rather than parametric statistics. Because there were 2 different conditions (before and after clozapine add-on) and the same subjects were used in both conditions, comparisons of the numeric items between groups were performed by Wilcoxon signed-rank test. Correlation between the mean dosage of clozapine and hospital days per year after clozapine add-on was tested by bivariate Kendall's τ_b under the hypothesis of a negative relationship between these 2 variables. Finally, Friedman's analysis of variance (ANOVA) and follow-up Wilcoxon tests with Bonferroni correction were performed to test the statistical differences in hospital days per year between 3 conditions (before clozapine treatment, during 2-year clozapine treatment, and after 2 years or more of clozapine treatment) in 27 patients treated with clozapine for more than 3 years. Except for correlations, all tests were 2-tailed and set at a significance level of .05 unless otherwise specified. All statistical procedures were carried out using SPSS 12.0 for Windows (SPSS Inc., Chicago, Ill.).

Table 1. Demographic and Clinical Characteristics of Total Bipolar Patients Treated With Clozapine Add-On and a Subgroup of Bipolar Patients Treated With Clozapine Add-On for More Than 3 Years

Characteristic	All Patients (N = 51)	Treated for More Than 3 Years (N = 27)
Age, y		
Mean ± SD	30.8 ± 7.1	30.3 ± 8.3
Range	18–58	21–58
Gender, N (%)		
Male	23 (45.1)	16 (59.3)
Female	28 (54.9)	11 (40.7)
Education, mean ± SD, y	12.8 ± 2.1	12.7 ± 2.1
Age at onset, mean ± SD, y	22.9 ± 5.8	20.1 ± 5.0
Diagnosis, N (%)		
Bipolar I	46 (90.2)	26 (96.3)
Bipolar II	5 (9.8)	1 (3.7)
Duration of clozapine add-on, mean ± SD, d	1166.0 ± 537.2	1591.5 ± 322.3
Clozapine dosage, mean ± SD, mg/d	201.6 ± 75.9	208.6 ± 78.3

RESULTS

Among the 51 subjects recruited in this study, 23 were male (45.1%) and 28 were female (54.9%), with an age range of 18 to 58 years (mean ± SD = 30.8 ± 7.1 years). The mean ± SD length of education was 12.8 ± 2.1 years, and the mean age at onset was 22.9 ± 5.8 years. Mean duration of clozapine add-on was 1166 days (3.19 years), and the mean ± SD daily dose of clozapine was 201.6 ± 75.9 mg/day (Table 1). The 201.6-mg/day mean dose of clozapine in this study is relatively lower than the 315-mg/day dose reported in a review of clozapine treatment in bipolar patients[34] and the 600-mg/day dose reported in patients with treatment-resistant schizophrenia.[35] All 51 subjects were taking 1 or 2 of 3 major mood stabilizers (lithium, carbamazepine, and valproate). No significant differences in demographic variables except gender ratio were noted between 24 subjects with less than 3 years of clozapine add-on and 27 subjects with more than 3 years of clozapine add-on.

Changes in Hospitalization Pattern of Bipolar Patients

The number and total length of hospitalizations, as well as the number of hospital days per year, were carefully calculated for the comparison between before and after the clozapine add-on period for all 51 subjects. Forty-six (90.2%) of the 51 subjects showed fewer hospital days per year after clozapine add-on than before clozapine add-on. The comparisons of numeric data before and after clozapine add-on are presented in Table 2 with Wilcoxon test statistics. The number of hospitalizations per year and hospital days per year after clozapine add-on were significantly less than before clozapine add-on (Wilcoxon $z = -5.48$, $p < .01$ for number of hospitalizations/year; Wilcoxon $z = -5.32$, $p < .01$ for hospital days/year), and

Table 2. Analysis of Hospitalization Pattern and Clinical Polarity of Episodes Resulting in Hospitalizations of 51 Bipolar Patients Treated With Clozapine

Variable	Before Clozapine Add-On, Mean ± SD	After Clozapine Add-On, Mean ± SD	t[a]	p
No. of hospitalizations/y	0.95 ± 0.95	0.23 ± 0.33	19.00	< .01
Hospital days/y	31.60 ± 33.63	6.02 ± 10.05	96.00	< .01
No. of episodes resulting in hospitalizations/y				
Manic episodes	0.46 ± 0.48	0.12 ± 0.30	18.00	< .01
Hypomanic episodes	0.11 ± 0.34	0.02 ± 0.09	1.00	.028
Mixed episodes	0.10 ± 0.24	0.05 ± 0.16	8.00	.161
Depressive episodes	0.30 ± 0.62	0.05 ± 0.13	9.00	< .01
No. of hospital days due to each type of episode/y				
Manic episodes	15.50 ± 18.86	3.68 ± 9.75	75.00	< .01
Hypomanic episodes	2.48 ± 9.78	0.35 ± 1.52	1.00	.046
Mixed episodes	3.96 ± 11.88	1.00 ± 3.55	11.00	.093
Depressive episodes	8.84 ± 19.79	0.99 ± 3.45	5.00	< .01

[a]Wilcoxon signed-rank test statistic (sum of positive ranks).

the estimated effect size indicated that the effect of clozapine on these 2 variables was substantively large according to the widely accepted criteria of the effect sizes (r = –0.54 and r = –0.53, respectively). The finding of more than 3 weeks of reduction in the mean number of yearly hospital days was expected in bipolar patients treated with clozapine add-on for at least 6 months (Figure 1A). In terms of dose-response relationship, Kendall's τ_b value did not support any relationship between the daily dose of clozapine and the hospital days per year ($\tau_b = 0.137$, p = .103).

Changes in Clinical Polarity of Episodes Resulting in Hospitalization

Wilcoxon signed-rank tests were also carried out to test the differences between 2 conditions (before and after clozapine add-on) with regard to hospitalizations caused by each type of episode per year (Table 2). Compared with before clozapine add-on, a significant reduction was observed in the number of manic and depressive episodes resulting in hospitalizations after clozapine add-on, and the effect size of clozapine for this variable was substantially large for manic episodes and moderate for depressive episodes (Wilcoxon z = –4.69 for manic episodes, –3.70 for depressive episodes; p < .01 for both; r = –0.46 for manic episodes, –0.34 for depressive episodes). There was also a statistically significant decrease in the number of hypomanic episodes resulting in hospitalization (Wilcoxon z = –2.20, p = .028), but the total number of hypomania-associated hospitalizations observed in 51 subjects was too small, whereby the effect of clozapine on this variable was not substantial (r = –0.20). The number of hospitalizations associated with mixed episodes did not significantly differ between both conditions (Wilcoxon z = –1.40, p = .161).

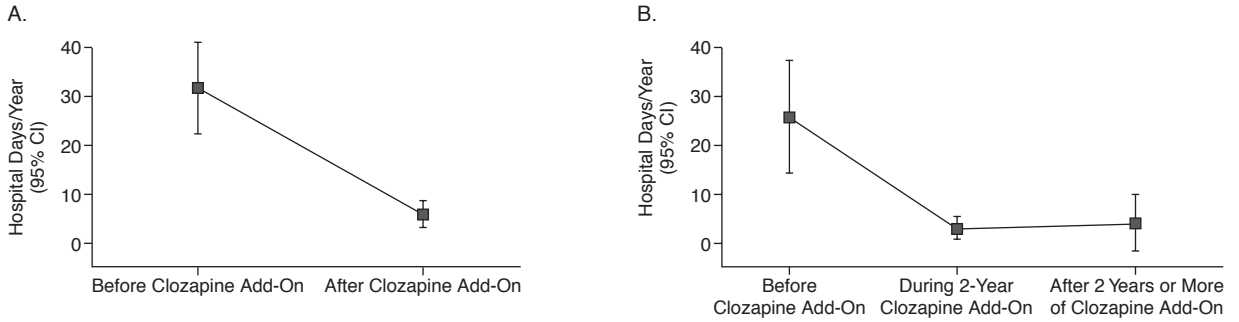
Hospital days due to each type of episode per year were also compared between the 2 conditions (Table 2). There were significant reductions in hospital days per year due to manic and depressive episodes (Wilcoxon z = –4.29 for manic episodes and –4.05 for depressive episodes; p < .01 for both), and the effects of clozapine add-on were considered accountable for a substantial proportion of these reductions in both manic episodes and depressive episodes (r = –0.42 for manic episodes and –0.40 for depressive episodes). Hospital days per year associated with hypomanic episodes significantly decreased (Wilcoxon z = –1.99; p = .046), but the effect of clozapine add-on was not substantial (r = –0.20). There was no significant difference in mixed episode–associated hospital days per year between the 2 conditions (Wilcoxon z = –1.68, p = .093).

Maintenance of Long-Term Efficacy of Clozapine Add-On

To explore the possibility of differential benefits of clozapine add-on between short-term stabilization and long-term maintenance, patients with more than 3 years of clozapine treatment (N = 27) were selected from the original 51 patients. Among the other 24 patients not included in this further analysis, 23 patients were continuously receiving clozapine add-on, but the total duration of clozapine add-on lay between 6 months and 3 years. One patient with a total history of over 3 years of clozapine add-on was excluded during the voluntary discontinuation period (about 6 months) without any identifiable cause (e.g., intolerable side effects or lack of efficacy) after 2 years of clozapine add-on.

Twenty-seven patients were analyzed for differences between 3 conditions (before clozapine add-on, during 2-year clozapine add-on, and after 2 years or more of clozapine add-on) in terms of hospital days per year (Figure 1B). Mean duration of clozapine add-on was 1592 days (4.36 years), and the mean ± SD daily dose of clozapine was 208.6 ± 78.3 mg/day in this group. Friedman's ANOVA showed that the number of hospital days per year was affected by clozapine add-on ($\chi^2 = 32.46$, df = 2,

Figure 1. Changes in Hospital Days per Year [a] in (A) the Total Sample of Bipolar Patients Treated With Clozapine Add-On (N = 51) and (B) the Subgroup of Bipolar Patients Treated With Clozapine Add-On for More Than 3 Years (N = 27)



[a]The error bar depicts the substantial decrease in hospital days per year of all subjects treated with clozapine (A) and also shows the maintenance of decreased hospital days per year after 2 years or more of clozapine add-on therapy in 27 patients treated with clozapine for more than 3 years (B).

$p < .01$). Follow-up Wilcoxon tests were used for pairwise comparisons and revealed that hospital days per year significantly decreased during 2 years (Wilcoxon $z = –4.04$, $p < .01$) and after 2 years or more of clozapine add-on (Wilcoxon $z = –3.51$, $p < .01$) compared to before clozapine add-on. The effect size of clozapine on the changes in this variable was large ($r = –0.55$ and $–0.48$, respectively). However, hospital days per year did not significantly differ after 2 years or more of clozapine add-on compared to during 2-year clozapine add-on (Wilcoxon $z = –0.77$, $p = .44$).

DISCUSSION

This retrospective chart review study examined the long-term efficacy of clozapine add-on in treatment-resistant bipolar patients in terms of repeated hospitalizations and diminished community stay. Records of 51 bipolar patients treated with clozapine add-on for more than 6 months were used for the analyses of this study. The results of the analyses showed that clozapine add-on treatment of treatment-resistant bipolar disorder can be substantially effective in reducing hospital days and extending community stay. The additional analyses of 27 bipolar patients with more than 3 years of clozapine add-on revealed that the efficacy of clozapine add-on can be maintained for a protracted period without significant change.

An enormous body of studies shows distinctive effects of atypical antipsychotics according to the clinical polarity of mood episodes[25,36–38] and shows that clozapine may have differential effects on the polarity or symptomatology of bipolar episodes.[26,39] This study also suggests that the rehospitalization-preventing effect of clozapine may be discriminative in nature according to clinical polarity of episodes. The analyses of clinical polarity indicated that clozapine may have greater effects on reducing or mitigating manic and depressive episodes than hypomanic or mixed episodes. While the result of this study appears to be inconsistent with previous studies,[25] only the episodes associated with hospitalizations were counted, and the number of hypomanic or mixed episodes was thereby too small compared to the number of manic or depressive episodes. The possibility exists that the effect of clozapine on these 2 types of episodes is underestimated. In addition, in light of studies suggesting distinct responses to pharmacotherapy[40,41] and diverse symptomatology[42–44] of hypomanic and mixed episodes, it may be necessary for researchers to identify and classify clinical characteristics of mixed or hypomanic episodes in terms of not only affective polarity but also other dimensions of psychopathology.[43]

Some authors have suggested that the mood-stabilizing effect of clozapine is bidirectional and effective in preventing both manic and depressive episodes in long-term maintenance[18,20] and have supported the view that clozapine monotherapy can reduce the risk of side effects in patients with refractory bipolar disorder.[22,24,25] The results of this study seem to lend support to the bidirectional efficacy of clozapine in bipolar patients. However, clozapine monotherapy itself should be approached with caution, since, when clinicians find practical benefits during clozapine add-on therapy, it is difficult to discriminate which drug component made the significant contribution toward overall outcome of bipolar patients[45] and rule out the possibility of therapeutic interplay between multiple agents. Therefore, a more discreet practice would be to use clozapine in combination with previously established mood stabilizers even though there may be dramatic changes in clinical status of bipolar patients after clozapine add-on.

Clozapine treatment is reported to be associated with reduced hostility[46,47] and reduced suicidality,[19,46,48] and one particular study even shows the superiority of clozapine in decreasing hostility over other antipsychotics regardless of antipsychotic effects.[49] Suppes et al.[50] also suggested that because clozapine improves functional outcome in

nonpsychotic bipolar patients, the decrease in hostility due to clozapine might be associated with its mood-stabilizing effects independent of its antipsychotic effects. Decreased hostile attitude and behaviors were observed in clozapine-treated patients diagnosed with a variety of psychiatric conditions such as mental retardation, autism, borderline personality, and schizophrenia.[51,52] Also, reduced suicidality in patients with schizophrenia or schizoaffective disorder by clozapine treatment was suggested by the results of a 2-year international multicenter study.[48] These maladaptive behavior–modifying effects of clozapine are expected to improve socio-occupational functioning and lengthen the duration of community stay when combined synergistically with bidirectional mood-stabilizing effect.

Many authors have insisted that frequent interviews and a psychoeducative approach can enhance not only drug adherence but also therapeutic outcome measured by the number of hospitalizations or frequency of relapses in bipolar patients.[53–55] Although the subjects in this study did not receive any kind of structured psychoeducative program, regular hematologic monitoring could make a substantial contribution toward early detection of relapse and decreased rehospitalization rate by providing clinicians with the chance to take more immediate actions against mood fluctuations of bipolar patients.

This study, however, has the following limitations: (1) even though it was a retrospective chart review, it might be possible that nonblind methods could have had some influence on the research processes; (2) the effects of mood stabilizers and other medications could not be evaluated as thoroughly as in the prospective studies; (3) the number of bipolar patients followed up for more than 3 years was relatively small; (4) there were no equivalent comparison groups treated with other antipsychotics or without antipsychotics; (5) psychosocial functioning and clinical outcome were evaluated only by changes in mood episodes associated with hospitalizations; and (6) increased tendency of a community-based approach could be accountable for some portion of the decreased number of hospital days shown in this study. Nonetheless, the findings in this study suggested that long-term clozapine add-on therapy can contribute substantially to significantly extending the community stay of bipolar patients and thus pave the way for regaining and maintaining an adequate level of psychosocial functioning.

Drug names: carbamazepine (Carbatrol, Equetro, and others), clozapine (Clozaril, FazaClo, and others), lithium (Lithobid, Eskalith, and others), olanzapine (Zyprexa), risperidone (Risperdal), sertraline (Zoloft).

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