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The Role of Clozapine as a Mood Regulator in the Treatment of Rapid Cycling Bipolar Affective Disorder

Oğuzhan KILINÇEL[1], Şenay KILINÇEL[2], Cem GÜNDÜZ[3], Şengül CANGÜR[4], Cengiz AKKAYA[5]

SUMMARY

Objective: In this study, we aimed to investigate the effect of the clozapine on the course of the rapid cycling Bipolar Affective Disorder.

Method: The study group was formed with the patients aged between 18 and 65 years of age, who met the criteria for the diagnosis of Bipolar Affective Disorder according to the Diagnostic and Statistical Manual of Mental Disorders 4th Edition, with rapid cycling characteristics. Variables like the number of mania and depressive episodes, the days spent in mania and in depression and the number of hospitalization and attempted suicide, in the year before starting clozapine were determined and compared with the annual data after starting the clozapine.

Results: Eleven female and two male patients who met the inclusion criteria were included in this study. The group`s average daily use of clozapine was 180 mg (25-600 mg). There was a statistically significant difference in the number of days spent in the depression, the days spent in the mania, the number of depressive episodes and manic episodes, the number of hospitalizations and the suicide attempts after the clozapine use.

Conclusion: In this study, it was determined that clozapine was effective as a mood stabilizer in Bipolar Affective Disorder treatment. The results show that clozapine reduces the episode frequency and the duration in rapid cycling Bipolar Affective Disorder which does not respond to all conventional treatments, including lithium, valproic acid, carbamazepine and antipsychotic drugs.

Keywords: Rapid cycling bipolar, clozapine, mood regulator

INTRODUCTION

Bipolar affective disorder (BAD) is a disease characterized by episodic attacks, high remission rate, and frequent hospitalizations, that can disrupt quality of life, and social and career functioning due to its chronic progress (Akkaya et al. 2007). Rapid cycling of episodes in the course of BAD is an indicator of poor prognosis (Carvhalho and Mcintyre 2015) and, hence, of poor response to treatment (Bauer 2008). In addition, increased incidences of suicidal attempts and substance use disorder have been observed in rapid cycling BAD (Carvalho and Mcintrye 2015, Garno 2005). Some studies consider rapid cycling in BAD as the subtype with a much severer course rather than as an indicator of poor prognosis (Yıldız 2001). This patient group comprises 15-20% of BAD patients (Calabrase et al. 1991) and It was reported that 77% of all BAD cases with a bad course of disease were of the rapid cycling type (Akdeniz 1997).

The term “rapid cycling” was first used to describe the disease with four or more attacks in one year (Dunner and Fieve 1974). However, the rapidity in the cycling of the episodes is not a constant feature of BAD and risk factors such as

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[1]M.D., Sakarya Yenikent State Hospital, Department of Psychiatry, Sakarya, [2]M.D., Specialist, Sakarya University Education and Research Hospital, Department of Child and Adolescent Psychiatry, Sakarya, [3]M.D., Gemlik State Hospital, Department of Psychiatry, Bursa, [4]Assoc. Prof., Düzce University Faculty of Medicine, Department of Biostatistics and Medical Informatics, Düzce, [5]Prof., Uludağ University Faculty of Medicine, Department of Psychiatry, Bursa, Turkey.

e-mail: *okilincel@gmail.com*

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the female gender, temperament, thyroid function disorder, and treatment with antidepressants may take effect on the response to treatment at any time in the course of the disease (Kesebir et al. 2005, Bauer et al. 2008). The original criterion of four episodes per annum for identification of rapid cycling has been widely accepted (Bauer et al. 1994) as there have not been any convincing data to propose another cut off limit (Kupka et al. 2005); and this criterion has been included as a course modifier of Bipolar I and Bipolar II in the DSM-IV (American Psychiatric Association 1994).

Clozapine is the first antipsychotic drug used with effectiveness in the long term treatment of rapid cycling BAD (Calabrase et al. 2001), probably by reducing the frequency and severity of the episodes (Calabrase 1991). However, the few reports available on the subject have not satisfactorily accounted for the disease since difficulties are faced in treating the patients who do not respond well to mood stabilizers (Post et al. 1990) and often multiple drugs have to be used with high doses (Calabrase et al. 1996, 2001). Therefore, it has been aimed in this study to investigate the effectiveness of clozapine on the course of rapid cycling BAD.

METHOD

The study was approved by the Ethics Committee of Uludağ University Faculty of Medicine. The experimental group was formed after retrospective screening all BAD patients followed up between 2007 and 2017 at the Mood Disorder Clinic of Uludağ University Faculty of Medicine, Department of Mental Health and Diseases. During this time period, out of the 1000 BAD patients followed up, 30 patients with ages in the 18-65 year range had been prescribed clozapine. After the initial assessment with the Structured Clinical Interview for the DSM-IV Axis I Disorders (SCID-I), 13 of these 30 patients had data showing that they met the diagnostic criteria for rapid cycling BAD, with a history of 4 or more attack episodes in a year and by not responding to treatment in two consecutive bouts of trial despite adequacy of dose and duration. Also, as with all the other patients being followed up at the Mood Disorder Clinic, they were tested psychometrically and considered to be in depressive episode with a score of ≥16 on the Hamilton Depression Rating Scale (HAM-D), or in manic attack episode with a score of ≥7 on the Young Mania Rating Scale (YMRS). All 13 patients were started on clozapine after hospitalization. All known risk factors had been assessed and the patients were followed for 1 year after the start of the clozapine therapy. The numbers and durations of the manic and depressive attacks, and the numbers of hospitalizations and suicidal attempts one year before and after the start of clozapine therapy were compared.

Statistical analyses were performed on SPSS 22 program. All descriptive factors such as the mean, standard deviation, median, interquartile range, minimum, maximum and percentile, were calculated. Normality of quantitative variables was assessed with the Shapiro Wilk test. Wilcoxon signed-rank test was used for comparing clinical data before and after initiating clozapine treatment. Binomial and Chi-square tests were used in the comparison of ratios. A value of $p<0.05$ was considered to represent statistical significance.

RESULTS

A total of 11 female and 2 male patients who met the inclusion criteria were included in the study. The sociodemographic and clinical characteristics of the patients are presented in detail in Table 1. Sociodemographic variables, excluding gender, were found to be homogenous among the patients ($p>0.05$ for each variable, Table 1).

Table 1. Sociodemographic Characteristics.

		n	%	p
Sex	Female	11	84.6	0.022
	Male	2	15.4	
Educational Status	Elementary	1	7.7	0.116
	Middle school	1	7.7	
	High school	5	38.5	
	University	6	46.2	
Marital status	Single	6	46.2	0.695
	Married	4	30.8	
	Divorced	3	23.1	
Career	Housewife	4	30.8	0.506
	Government official	4	30.8	
	Worker	2	15.4	
	Retired	1	7.7	
	Unemployed	1	7.7	
	Student	1	7.7	
Lives with	Family	8	61.5	0.581
	Spouse and/or children	5	38.5	

The mean clozapine dose given to the group was 180 mg/day (range: 25-600 mg/day). After using clozapine, statistically significant changes were observed in the number of days with depression, days with mania, depressive episodes, manic episodes, hospitalizations, and suicide attempts (Table 2).

All patients were using dual mood stabilizers before starting clozapine therapy. Two patients continued to use dual mood stabilizers and nine patients continued treatment with a single mood stabilizer after starting clozapine treatment, while two patients only used clozapine.

Table 2. Comparison of Before and After Use of Clozapine

	Mean	Std. Deviation	Median	Interquartile Range	Minimum	Maximum	p
Clozapine dose	180.77	163.03	100.00	162.50	25	600	
Number of manic episodes							<0.001
Before clozapine	10.69	4.66	11.00	6.00	3	21	
After clozapine	0.23	0.44	0.00	0.50	0	1	
Number of depressive episodes							<0.001
Before clozapine	5.15	3.26	4.00	5.50	2	11	
After clozapine	0.31	0.63	0.00	0.50	0	2	
Number of hospitalizations							<0.001
Before clozapine	5.62	3.71	5.00	5.50	1	14	
After clozapine	0.38	0.87	0.00	0.50	0	3	
Number of suicide attempts							<0.001
Before clozapine	2.00	3.08	1.00	2.50	0	11	
After clozapine	0.00	0.00	0.00	0.00	0	0	
Number of days with mania							<0.001
Before clozapine	34.38	13.36	35.00	22.00	14	60	
After clozapine	2.31	4.39	0.00	5.00	0	10	
Number of days with depression							<0.001
Before clozapine	16.46	13.24	14.00	20.50	0	45	
After clozapine	3.08	9.69	0.00	0.00	0	35	

DISCUSSION

This study found clozapine to be effective as a mood stabilizer in the treatment of BAD. The patients who were included in our study were found to have improved prognosis in the year after starting clozapine, compared to the previous year. This study demonstrates the effectiveness of clozapine in reducing the frequency and length of episodes in rapid-cycling BAD unresponsive to all conventional treatments including lithium, valproic acid, carbamazepine, and antipsychotic drugs. This result is consistent with the few number of studies in the literature on this subject (Calabrase et al. 1991, McElroy et al. 1991).

Advanced studies have found that clozapine's depression preventing properties are weaker than its mania preventing properties (Frye et al. 1998, Zarate et al. 1995). Within the 12 month study period, clozapine was found to reduce both the number of days with depression as well as the number of depressive episodes, demonstrating an ability to prevent depression. The only study consistent with the data we obtained was by Banov et al. (1993). The recommended clozapine dosage varies in the 300-600 mg/day range in the treatment of schizophrenia, with a preferred dose of 600mg/day for treatment of resistant schizophrenia (Frye et al. 1998). However, there is not a specified dosage of clozapine for the maintenance treatment of BAD while the mean management dose for psychotic mood disorder was determined as 315 mg/day (Frye et al. 1998). In mood disorder and schizoaffective disorder, the mean clozapine dose used was 341 mg/day (Banov et al. 1993). In our study, the mean effective clozapine dose was found to be 180 mg/day. The only other study determining a mean clozapine dosage of 235 mg/day for treatment of acute mania, and 156 mg/day for maintenance treatment of BAD was by Suppes et al. (1999). Other studies on clozapine use have included schizoaffective disorder patients and groups of patients with depression with psychotic features and the reported doses of clozapine are higher than ours.

Evaluation of the hospital records of 187 patients treated with clozapine for a period of 14.3 months, with 52 being diagnosed with BAD, 81 with schizoaffective disorder, 40 with schizophrenia, and 14 with psychotic major depression, showed that the BAD group of patients gave the best response to the treatment. Similarly to our study, it was also found that the number of hospitalizations significantly decreased after using clozapine.

Retrospectively evaluated treatment results on 85 patients with different psychiatric disorders switched to clozapine after intolerance of or inadequate response to antipsychotics, lithium, carbamazepine, and valproate, and also combinations of these, showed a better response by the 14 BAD patients than the schizophrenia patients in the group (McElroy 1991). Others have also shown treatment-resistant bipolar patients to have better response to clozapine compared to schizophrenia patients (Banov et al. 1993, McElroy et al. 1991) however; clozapine is less preferred in the treatment of bipolar disorders due to agranulocytosis risk and the necessity of weekly blood counts.

This study has a number of limitations. Investigation of a low number of patients is the most important limitation. Also, this study has all of the limitations of its retrospective nature. The open-label characteristic of the study is a factor that can increase researcher bias. However, given the limited number of studies on this subject, and the fact that this study investigated clozapine effects in the acute period and also being one of the few to investigate clozapine effect during the maintenance period set it apart from other studies. We believe it would be more appropriate to evaluate the results of this study as those of a preliminary study. We also believe that these results could be the initiator for the planning of a broad multicenter study.

This study has provided data indicating that use of clozapine could be an alternative treatment to be kept in mind for acute mania and maintenance in rapid-cycling BAD and thereby the treatment of resistant cases. Our study provides evidence that the effectiveness of clozapine is not only limited to resistant schizophrenia patients. In conclusion, although clozapine is difficult to tolerate with a wide range of side effects, it is an effective alternative in the maintenance treatment of rapid-cycling BAD patients.

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