Clozapine Therapy for Long-Term Prophylaxis in Bipolar Patients; Prescription Rates and Efficacy

Bipolar Hastaların Uzun Vadeli Proflaksisinde Klozapin Tedavisi; Reçetelenme Oranları ve Etkinliği

Bipolar Uzun Vadeli Proflaksisinde Klozapin; Reçetelenme Oranları ve Etkinliği
Clozapine for Long-term Prophylaxis in Bipolars; Prescription Rates and Efficacy

Tonguç Demir Berkol[1], İlker Özyıldırım[2], Sibel Çakır[3], Olcay Yazıcı[3]
[1]Dışkapı Yıldırım Beyazıt Eğitim ve Araştırma Hastanesi, Ankara, [2]Ünye Devlet Hastanesi, Ordu,
[3]İstanbul Üniversitesi İstanbul Tıp Fakültesi Psikiyatri Birimi, İstanbul, Türkiye

Long-Term Prophylaxis with Clozapine in Patients with Bipolar Disorder; Case Study. XIV. World Congress of Psychiatry. Journal of Czech and Slovak Psyhiatry, Volume 104 (Suppl. 2) Page 1208. Prague, Czech Republic. (2008)

Özet

Amaç: Klozapin' in tedaviye dirençli bipolar hastalarda idame tedavisi açısından etkili olabileceği bildirilmektedir. Bu çalışmanın amacı; klozapin reçete oranını değerlendirmek, bipolar bozukluğu olan ve klozapin profilaksisi alan hastaların özellikleri ve klozapin profilaksisinin etkinliğini değerlendirmektir.Gereç ve Yöntem: DSM IV tanı kriterlerine göre bipolar bozukluk tip I tanısı alan ve en az 1 yıl boyunca klozapin idame tedavisi alan 280 hasta çalışmaya dâhil edilmiştir. Bu hastaların tıbbi kayıtları ve yaşam boyu duygudurum çizelgeleri geçmişe yönelik taranmıştır. Bulgular: 280 hastanın 12 tanesi (%4,8) profilaksi amaçlı ömürleri boyunca en az bir dönem klozapin kullanmıştı. Hastaların 7 tanesi sadece klozapin alırken, 5 hastada klozapin ve valproik asit kombinasyonu alıyordu. Bu 12 hastanın klozapin prolaksisi öncesinde en az iki farklı idame tedavisine direnci mevcuttu. Çalışmada klozapin proflaksisi alan hastaların tümünde pozitif sonuçlar gözlemlenmiştir. Tartışma: Bu bulgular klozapinin, bipolar bozukluğun dirençli hastaların tedavisi için etkili bir profilaktik seçenek olduğunu göstermektedir. Sonuç olarak ağır hastaların farklı dirençli proflaksi stratejilerinde klozapin kullanımının güvenli ve etkili olduğunu bulunmuştur. Çalışmamızın retrospektif yapısı bir sınırlama oluşturmaktadır, ancak bu konuda yapılan çalışmaların azlığı belirgindir, daha kapsamlı prospektif kontrollü çalışmalara hala ihtiyaç vardır.

Anahtar Kelimeler

Bipolar Bozukluk; Klozapin; Profilaksi

Abstract

Aim: It is reported that clozapine maintenance treatment could be effective in treatment-resistant bipolar patients. The aim of this study is to evaluate the prescription rates of clozapine, features of patients on clozapine prophylaxis and efficacy of clozapine prophylaxis in patients with bipolar disorder. Material and Method: 280 patients with DSM-IV diagnostic criteria for bipolar disorder, type I were included in the study. The patients' medical records and life-charts were reviewed retrospectively and patients who took clozapine for maintenance treatment for at least one year were identified. Results: Twelve of 280 patients (4.8 %) took clozapine for prophylaxis for at least one period during lifetime. Among them 7 patients have only received clozapine, while 5 patients have used combination of clozapine and valproic acid. All of these twelve patients had resistance to at least two different maintenance treatments before clozapine prophylaxis. However, positive results were observed in all of the patients with clozapine prophylaxis. Discussion: These findings suggest that clozapine is regarded as an effective prophylactic choice for treatment of resistant patients with bipolar disorder. Consequently, this study demonstrates effectiveness and safety of clozapine use even in severe patients refractory to various strategies of prophylaxis. Retrospective nature of our study constitutes a limitation. However, when considering limited number of studies on this subject, it may still have a significant contribution. But more comprehensive prospective controlled studies are still needed.

Keywords

Bipolar Disorder; Clozapine; Prophlaxis

DOI: 10.4328/JCAM.2373 Received: 27.02.2014 Accepted: 26.03.2014 Printed: 01.11.2015 J Clin Anal Med 2015;6(6): 772-775
Corresponding Author: Tonguç Demir Berkol, Dodurga Mahallesi, Özdebirlik Sitesi, Ada:103 16/A, 06810, Türkkonut, Çayyolu, Yenimahalle, Ankara, Türkiye.
T.: +90 3125962000 F.: +90 3123186690 E-Mail: tberkol@gmail.com

Introduction

Studies evaluating prophylactic treatments in bipolar patients have shown that recurrences and chronic signs are common in these cases [1]. Despite various options with accepted effectiveness, resistant patients with inadequate response to long-term prophylactic treatment are common. For instance 30-40% of the patients are reported to be non-responsive to lithium, which is still gold standard in prophylactic treatment of bipolar disorder (BD) [2, 3].

Studies demonstrating effectiveness of clozapine, an antipsychotic drug, especially in resistant bipolar patients for prophylaxis were reported [4, 5, 6, 7, 8, 9, 10, 11]. However, they are limited to open-labeled studies with small sample sizes or case reports [12, 13]. In a review study, success of maintenance strategies comprising clozapine was reported in almost 70% of the patients [12]. In the only randomized controlled study assessed treatment resistant patients diagnosed with schizoaffective disorder and bipolar disorder in the one year fallow up period it was reported that in the end of a one-year follow up period. 13 patients whose treatment included clozapine in addition to their routine treatment had more positive results than those patients whose treatment did not include clozapine [11]. Retrospective evaluation of 17 bipolar patients receiving mood stabilizer and clozapine combination in a study conducted in Turkey revealed that all patients benefited from this approach [14]

In this study we aimed to assess the prescription rates of clozapine, features of patients on clozapine prophylaxis (CP) and efficacy of CP.

Material and Method

Study sample and psychiatric diagnosis

This study was conducted in Istanbul University, Istanbul Faculty of Medicine, Department of Psychiatry. The life charts of 280 patients with BD type I, who have been followed up in Istanbul Faculty of Medicine, Psychiatry Department, Mood Disorders Unit were evaluated retrospectively. The diagnoses of patients were evaluated by at least two experienced physicians according to Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) [15]. The psychiatric history, treatments and treatment responses are collected from patients, family members with detailed interviews and collateral hospital records. The patients are followed with mood charts and all clinical changes are recorded in every visit so all clinical data is updated regularly to create an optimum life chart. All participants gave a written informed consent and the Local Ethics Committee approval was obtained for the study.

Inclusion criteria and comparison groups

a) The patients older than 18 who met DSM-IV criteria for BD type-I were included in the study.

b) The patients who had at least one year CP were assigned for the determination of clozapine frequency (clozapine group).

c) The clinical features of patients who had CP were collected and compared with the features of patients who had no CP (non-clozapine group).

Maintenance treatment response

The efficacy of CP was determined with 'mirror design' method [16]. Zero point was indicated to be the time when maintenance treatment has started and maintenance treatment period was compared with the same duration of drug-free period prior to zero point. In order to determine response forms of patients with multiple drugs maintenance treatment period, their maintenance treatment periods were compared with the same duration of drug-free period prior to treatment.

Clinical evaluations of patients were transferred to a mood chart. Another follow-up scale is not used in this process.

According to their response features;

a) The treatment responder patients were described as those who never had any recurrence (good response) or those who had a recurrence during maintenance treatment period with a decrease in severity, period and frequency (moderate response) compared to the same period prior to maintenance treatment.

b) The treatment non-responder patients were described as those who had a recurrence during maintenance treatment period similar or even worse in severity, period and frequency in regard to the same period prior to maintenance treatment (poor response). Minimum duration for the maintenance treatment was 1 year. However, shorter durations were included if a clear conclusion can be made according to the mirror design when treatment changed earlier because of recurrences.

Side effects

Side effects were collected by a special section that belongs to side effects and adverse events in mood charts and reports of physicians in every visit retrospectively.

Statistical analysis

Statistical analyses were conducted by Statistical Package for Social Sciences (SPSS)-Version 11. Fisher exact test, independent sample t-test and Chi square were used for statistical analyses. Point for statistical significance was $p< 0.05$ and confidence interval was assumed to be 95%.

Results

Frequency of prophylactic treatment prescription that includes Clozapine Twelve of 280 patients (4.8 %) took clozapine for prophylaxis for at least one period during lifetime. Among them 7 patients have only received clozapine, while 5 patients have used combination of clozapine and valproic acid (VA).

Sociodemographic and clinical variables

Mean age of clozapine treated patients was 46 (28-65) with seven females and five males. Severe and manic episodes were predominant in eleven patients (%91.7). All patients have been hospitalized at least once. Psychotic signs have been observed during at least one episode in all of them and 9 patients have experienced psychotic signs during more than half of the episodes (Table 1).

Other maintenance treatments before clozapine prophylaxis

Nine patients received lithium, eight patients VA and two patients received antipsychotic (AP) monotherapy as prophylaxis prior to CP. Moreover, seven patients have used lithium and VA, four patients have used lithium and AP, one patient VA and

Table 1. Comparison of groups with and without clozapine maintenance treatment in terms of sociodemographic and clinical characteristics

	Clozapine Group n=12 (%)	Non Clozapine Group n=268 (%)	p
Gender (female)	7 (58.3)	174 (64.6)	NS
Mean episode severity (severe)	11 (91.7)	156 (58.2)	0.031[a]
Psychotic features	12 (100)	202 (75.4)	NS[b]
Suicide attempt	2 (16.7)	44 (16.4)	NS
	(S.D.)	(S.D.)	
Age	46.0 (12.4)	41.8 (12.8)	NS
Age of onset	23.3 (6.0)	24.4 (8.9)	NS
Total number of episodes	17.6 (12.8)	10.0 (8.7)	NS[c]
Total number of manic episodes	11.6 (8.9)	4.7 (4.1)	0.022[a]
Total number of hypomanic episodes	1.5 (2.8)	2.1 (3.8)	NS
Total number of mix episodes	0.5 (1.1)	0.5 (1.4)	NS
Total number of depressive episodes	3.9 (5.3)	2.6 (4.2)	NS
Cycling interval (month)	11.8 (6.2)	13.1 (8.4)	NS
Total number of hospitilization	4.0 (3.1)	2.5 (2.2)	0.033[a]
Age of clozapine prophylaxis onset	41.5	-	-
Clozapine prophylaxis (month)	41.0	-	-
Average dose of clozapine (mg)	256	-	-

NS: not significant, [a]p<0.05, [b]p=0.075, [c]p=0.0

AP (other than clozapine) and three patients have received VA and AP combination treatment. Rationale for initiating clozapine was; inadequate response to prophylactic treatment in 11 patients, and inadequate response and treatment necessity for tardive dyskinesia (TD) in one patient. One patient has received five, two patients have received four, three patients have received three and the remaining six patients have used two different prophylactic treatments before CP.

Responsiveness to maintenance with Clozapine

All clozapine group patients have responded to clozapine comprising prophylaxis strategies. When considered in detail, no recurrence (good response) was observed in six of seven patients who have used clozapine monotherapy and in one of five patients receiving VA and clozapine (totally good response in 7 of 12 patients). In other five trials of CP, frequency and severity were significantly decreased compared to drug-free period despite recurrences (moderate response). Manic episodes occurred once in five patients who experienced recurrence. Depressive recurrence was also occurred in two of these patients during clozapine treatment. When depressive episodes were separately evaluated according mirror image, it was found that all patients except one were benefited from clopazine treatment.

Average clozapine doses, duration of maintenance that includes clozapine and side effects

Mean clozapine dosage was 256 mg/day (min.75 - max.600 mg/day) and mean duration of use was 41.0 months (min.12 - max.96 months). No serious side effect, such as TD, agranulocytosis and seizures, was observed. Patients with pre-treatment TD were benefited from clozapine treatment.

Discussion

12 of 280 BD-I patients have used a prophylactic treatment of clozapine for at least one year. Good results have been achieved in all patients and this is consistent with previous studies reporting high rates of positive results [7, 9, 11]. In spite of these positive results, clozapine is prescribed only if other maintenance strategies fail because of its some serious side effects such as agranulocytosis. Therefore, starting age of clozapine maintenance treatment is relatively old. Negative responsiveness of patients to various strategies before CP indicates the necessity of considering clozapine more frequently especially in refractory cases.

When clozapine users were compared with other patients, it was seen that episodes were more severe, and total number of previous manic episodes and hospitalizations were higher. Although it did not reach significant level, they displayed higher levels of psychotic signs (p=0.075) and experienced more episodes (p=0.067). These findings indicate that those clozapine treatments are used in more severe BD cases and explain why they are refractory to first line prophylactic strategies (such as lithium and valproate).

Bipolar patients are considered to be susceptible to the side effect of TD occurring with typical antipsychotic drug use [17]. No patients experienced TD during clozapine treatment in our study; conversely a patient with TD was benefited from clozapine treatment. This activity supports various reports suggesting potential effectiveness of clozapine in TD treatment [18, 19]

Retrospective nature of our study constitutes a limitation. However, when considering limited number of studies on this subject, it may still have a significant contribution. In a review of studies evaluating clozapine prophylaxis, mean duration of clozapine use was found to be 18.2 months [12]. Mean duration of 41.0 months achieved in our study is a substantially long period of time when compared to other studies and offers an opportunity to evaluate effectiveness of clozapine in longer prophylaxis treatments and is an advantage of our study.

Consequently, this study suggests effectiveness and safety of clozapine use even in severe patient's refractory to various strategies of prophylaxis. But more comprehensive prospective controlled studies are still needed.

Competing interests

The authors declare that they have no competing interests.

References

1. Judd JL, Akiskal HS, Schettler PJ, Endicott J, Maser J, Solomon DA et al. The long-term natural history of the weekly symptomatic status of bipolar I disorder. Arch Gen Psychiatry 2002;59:530-7.
2. Goldberg JF, Harrow M, Leon AC. Lithium treatment of bipolar affective disorders under naturalistic followup conditions. Psychopharmacol Bull 1996;32:47-54.
3. Hartong EG, Moleman P, Hoogduin CA, Broekman TG, Nolen WA. Prophylactic efficacy of lithium versus carbamazepine in treatment-naive bipolar patients. J Clin Psychiatry 2003;64(2):144-51.
4. Hummel B, Dittmann S, Forsthoff A, Matzner N, Amann B, Grunze H. Clozapine as Add-On Medication in the Maintenance Treatment of Bipolar and Schizoaffective Disorders. Neuropsychobiology 2002;45(1):37–42.
5. Vacheron-Trystram MN, Braitman A, Cheref S, Auffray L. Antipsychotics in bipolar disorders. Encephale 2004;30(5):417-24.
6. Kusumakar V. Antidepressants and antipsychotics in the long-term treatment of bipolar disorder. The Journal of Clinical Psychiatry 2002;63(10):23-8.
7. Ciapparelli A, Dell'Osso L, Pini S, Chiavacci MC, Fenzi M, Cassano GB. Clozapine for treatment-refractory schizophrenia, schizoaffective disorder, and psychotic bipolar disorder: a 24-month naturalistic study. J Clin Psychiatry 2000;61:329-34.
8. Chen, Chin-Kang; Shiah, I-Shin; Yeh, Chin-Bin; Mao, Wei-Chung; Chang, Chuan. Combination Treatment of Clozapine and Topiramate in Resistant Rapid-Cycling Bipolar Disorder. Case Report, Clinical Neuropharmacology 2005;28:136–8.
9. Ciapparelli A, Dell'Osso L, Bandettini di Poggio A, Carmassi C, Cecconi D, Fenzi

M et al. Clozapine in treatment-resistant patients with schizophrenia, schizoaffective disorder, or psychotic bipolar disorder: a naturalistic 48-month follow-up study. The Journal of Clinical Psychiatry 2003; 64(4):451-8.
10. Poon SH, Sim K, Sum MY, Kuswanto CN, Baldessarini RJ. Evidence-based options for treatment-resistant adult bipolar disorder patients. Bipolar Disord 2012;14(6):573-84.
11. Suppes T, Webb A, Paul B, Carmody T, Kraemer H, Rush AJ. 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 1999;156:1164-9.
12. Brambilla P, Barale F, Soares JC. Atypical antipsychotics and mood stabilization in bipolar disorder. Psychopharmacology 2003;166(4):315-32.
13. Gitlin M. Treatment-resistant bipolar disorder. Molecular Psychiatry 2006;11: 227-40.
14. Sertöz Ö, Akdeniz F, Vahip S. Clozapine treatment in bipolar and schizoaffective disorders: A retrospective study. Klinik Psikofarmakoloji Bülteni 2002;12(3):142-7.
15. American Psychiatric Association. DSM-IV - Diagnostic and Statistical Manual of Mental Disorders, 4th ed. Washington DC: American Psychiatric Association; 1994.
16. Vieta E, Nieto E, Autet A, Rosa AR, Goikolea JM, Cruz N et al. A long-term prospective study on the outcome of bipolar patients treated with long-acting injectable risperidone. World J Biol Psychiatry 2008;9(3):219-24.
17. Gao K, Kemp D.E, Ganocy S.J, Gajwani P, Xia G, Calabrese R.J. Antipsychotic Inculded Extrapyramidal Side Effects in Bipolar Disorder and Schizophrenia. J Clin Psychopharmacol 2008;28(2):203–9.
18. Li CR, Chung YC, Park TW, Yang JC, Kim KW, Lee KH et al. Clozapine-induced tardive dyskinesia in schizophrenic patients taking clozapine as a first-line antipsychotic drug. World J Biol Psychiatry 2009; 10(4 Pt 3): 919-24.
19. Van Harten PN, Tenback DE. Tardive dyskinesia: clinical presentation and treatment. Int Rev Neurobiol 2011;98:187-210.

How to cite this article:
Berkol TD, Özyıldırım İ, Çakır S, Yazıcı O. Clozapine Therapy for Long-Term Prophylaxis in Bipolar Patients; Prescription Rates and Efficacy. J Clin Anal Med 2015;6(6): 712-5.