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MAINTENANCE TREATMENT TRENDS, THERAPEUTIC OUTCOMES AND THEIR ASSOCIATION WITH CLINICAL FEATURES IN REMITTED BIPOLAR DISORDER

İYİLEŞME DÖNEMİNDEKİ BİPOLAR BOZUKLUKTA SÜRDÜRÜM TEDAVİSİ TRENDLERİ, SAĞALTIM SONUÇLARI VE KLİNİK ÖZELLİKLER İLE İLİŞKİSİ

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Abstract

The evidence base data regarding long-term treatment of bipolar disorder (BD) is less than satisfactory. With the first-line rank of lithium and valproate; antipsychotics (AP) and anticonvulsants (AC) considered options for prolonged treatment in remitted bipolar patients. Literature demonstrates various treatment options in remitted patients with different clinical features. The aim of this study to present and assess clinical outcomes of maintenance treatment for BD with various clinical features. In total 186 bipolar patients in remission were enrolled in this study. All the patients were evaluated with SCID-I (Structured Clinical Interview for DSM-IV) ; and lifelong psychiatric comorbidities were determined. Sociodemographical and clinical features, and lifelong pharmacological treatment of the patients were assessed. Semi-structured interview schedules were filled. 71% lithium, 44% AC, 18% AP monotherapies and 23% lithium-AC, 15% lithium-AP, 25% AC-AP combination therapies were used as maintenance treatment. 61% and 62% of the patients were responders of lithium and AC monotherapies respectively. AC and AP combination had the highest response level. The predictors on the probability of treatment response for lithium were being married, non-psychotic, to show seasonal pattern and less severe episodes. Anticonvulsants were effective in males, divorces, suicide attempters, and the patients with predominance of mixed features in periods. Obsessive-compulsive disorder was the most common comorbid diagnosis in study group. Lithium monotherapy was tended to use in prevention, however treatment combinations which contain APs might be effective alternative to monotherapy. Individualized medication ought to be administered for each patient, with the consideration of clinical features and tolerability.

Keywords: antipsychotics; bipolar disorder; maintenance; remission

Özet

İki uçlu bozuklukta uzun dönem tedavisine ilişkin kanıtlar yeterince tatmin edici değildir. İyilik döneminde başta lityum ve valproat olmak üzere, antipsikotik ve antikonvülzan ajanlar sürdürüm tedavisi seçeneklerindendir. Bu tedavilerle olumlu sonuçlar literatürde gösterilse de, farklı klinik özellikler gösteren hastaların farklı ajanlara yanıtlarına dair çalışmalar yetersizdir. Bu çalışmada, söz konusu ajanların duygudurum ataklarından koruyuculuğunu belirlemek ve daha uygun ilaç seçimi sağlamak için; ilaçların kullanım sıklıklarının, elde edilen yanıt düzeylerinin ve bunların klinik özellikler ile ilişkisinin araştırılması amaçlanmıştır. Haseki Eğitim ve Araştırma Hastanesi Psikiyatri Polikliniği'nde izlenmekte olan yüz seksen altı bipolar bozukluk tanılı hasta çalışmaya alınmıştır. Hastaların tümüne SCID-I (Structured Clinical Interview for DSM-IV); uygulanmış; İki uçlu bozukluğa eşlik eden ek psikiyatrik tanılar saptanmıştır. Her iki hasta grubunun sosyodemografik ve klinik özelliklerini ve yaşam boyu farmakolojik tedavilerini değerlendiren yarı yapılandırılmış görüşme çizelgesi doldurulmuştur. Bu çizelgeler klinik görüşme ile yeniden değerlendirilmiş ve gözden geçirilmiştir. Hastaların sürdürüm tedavisinde %71 lityum, %44 antikonvülzan, %18 antipsikotik monoterapileri ve %23 lityum-antikonvülzan, %15 lityum-antipsikotik, %25 antikonvülzan-antipsikotik kombine tedavilerinin hastalığın herhangi bir döneminde kullanıldığı belirlenmiştir. Lityum monoterapisi alan hastaların %61'inin, antikonvülzan monoterapisi alan hastaların %62'sinin tedaviye yanıt verdiği saptanmıştır. Antikonvülzan-antipsikotik kombine sürdürüm tedavisi alan hastalarda daha yüksek yanıt oranı bulunmuştur. Evli olmak, psikotik belirtilerin yokluğu, mevsimsellik ve atakların hafif seyretmesi lityum tedavisine yanıtın öngörücüleri olarak saptanmıştır. cevap vermiştir. Erkek, boşanmış, intihar girişimi olan ve duygudurum ataklarında karma

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özelliğin baskınlığı antikonvulzan ilaçlara iyi yanıtın belirleyicileri olarak saptanmıştır. İki uçlu bozukluğa eşlik eden en sık ek psikiyatrik bozukluk obsesif-kompulsif bozukluk olarak saptanmıştır. İki uçlu bozuklukta nüksetme riskini en aza indirmek için etkin ve uygun sürdürüm tedavisinin belirlenmesi esastır. Lityum monoterapisi, sürdürümde en sık tercih edilen seçenek olsa da, antipsikotiklerin yer aldığı kombine tedavilerin etkin alternatifler olabileceği görülmektedir. Klinik özelliklerin ve tolerabilitenin göz önünde bulundurularak kişiselleştirilmiş tedavi seçeneklerinin planlanması önem arz etmektedir.

Anahtar Sözcük: *antipsikotikler; iki uçlu bozukluk; iyileşme dönemi; sürdürüm*

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1. Introduction

Bipolar disorder is a complex chronic disorder associated with frequently repeated affective episodes. It is one of the first thirty diseases that cause most disability around the world (Murray & Lopez, 1997). Episodic and chronic nature of the disorder requires both acute and preventive approach. Acute treatment of bipolar episodes has been studied further to date, unlikely there is a paucity of research regarding prevention treatments and their clinical outcomes. Prevention treatment, as known as maintenance or long-term treatment, plays critical role in the management of bipolar disorder, due to its reducing effects not only in the risk of relapse, but also decreased requirement of acute intervention and hospitalization (Popovic, Reinares, Amann, Salamero, & Vieta, 2011). In terms of maintenance treatment in remitted bipolar patients, mood stabilizers like lithium and anticonvulsants (AC) are recognized as the headstones. Randomized controlled trials have demonstrated benefits of these agents in long-term management, however, their results were often criticised and disqualified. This condition was reasonably attributed to their study design, which often limited generalisation to routine clinical practice (Joas et al., 2017). Additionally, growing body of studies examining maintenance treatment agents, debilitated the wide belief on the high-efficacy of these conventional drugs. For instance, averagely 20-40% of patients were reported not to respond in a positive way to lithium protection accepted as the oldest mood stabilizer agent (Denicoff, Smith-Jackson, Disney, Ali, & Post, 1997; Muzina & Calabrese, 2005; O'Connell, Mayo, Flatow, Cuthbertson, & O'Brien, 1991). There is a similar limitedness for AC agents that be an alternative to lithium. Antipsychotic (AP) agents are considered as appropriate for short-term treatment particularly in mania episodes. Recent long-term placebo-controlled trials endeavor to demonstrate efficacy of APs in maintenance. A number of studies have concluded as reasonable to continue AP maintenance after ensuring remission following an acute episode and have associated better outcome to AP included combinations in prevention, however their role as long-term mood stabilizers remained uncertain (Geddes & Miklowitz, 2013). Additionally, to the best of our knowledge, the impact of clinical features such as illness course, comorbidity and sociodemographical variables on response rate was insufficiently studied in the regarding literature. At this point, it may be useful to determine how the response to different mood stabilizers changes with clinical features to investigate preventive efficiency of mood stabilizer drugs in bipolar patients and provide evidence for a better drug selection. Our objective with this study is to point out frequency of mood stabilizers' use regime, obtained response levels and its relation to clinical features.

2. Method

2.1. Clinical Evaluation

In total 186 bipolar patients in remission (175 bipolar I and 11 bipolar II patients) of whom informed consents were taken to enroll this study and were being followed in psychiatry outpatient clinic, Istanbul Haseki Training and Research Hospital between May – December 2016 were enrolled in this study. All the participants' ages were between 18-65 years. Structured clinical interview for DSM IV/clinical version (SCID-I/ CV) were applied to all participants (First, Spitzer, Gibbon, & Williams, 1997); and lifelong additional psychiatric diagnosis accompanying bipolar disorder were determined. All participants gave a written informed consent and the Local Ethics Committee approval was obtained for the study. The participants who did not complete full assessment process and give consent were excluded from the study.

A semi-structured interview schedule evaluating sociodemographic and clinical features, lifelong pharmacologic treatments of all patiens were filled by taking the patient's, its relatives and previous medical records into consideration, while admitting into mood disorders unit. These schedules were re-evaluated and reviewed with clinical interviews. The study was carried out retrospectively based on file scanning.

In this study, 'mirroring' method was used to evaluate response types to protective treatment of the cases (Vieta et al., 2008). Use of mirror-designated assesment was aimed to provide subjective but additional information about the state of remission besides rating scales scores. The point that protective treatment commenced was accepted as null point, and duration of preventive treatment was compared to itself and the run-in period before null point. While determining response type of patients of whose several preventive treatment periods were studied, prevention period of patients were compared to similar run-in period before treatment.

2.2. Study Groups

The patients were studied in two groups, categorized according to response specifications of the patients;

A. Treatment responder group: Consisted of patients who experienced no recurrence during prevention period or those experienced recurrences but the recurrence was less severe or frequent or transient frequent considering the same period before prevention.

B. Treatment non-responder group: Consisted of patients who experienced recurrence during prevention period and showed no progress for recurrence in terms of severity or frequency or duration frequent or deterioration against recurrences in the same period before prevention. The minimal time required for prevention treatment for responder groups was 1 year but treatment was shifted earlier due to recurrences, however, more short-term applications were also followed when a net proceeding is allowed according to mirroring.

2.3. Statistical Analysis

Descriptive measures of demographic and clinical features were computed as count and percent frequencies. The relations between groups and categorical features were evaluated by Pearson Chi-square test. Statistical significance level was accepted as <0.05. All statistical computations were performed by using PASW (ver. 18) package program.

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3. Results

124 (66.7%) and 62 (33.3%) of total 186 patients that enrolled in this study was respectively females and males. The average of age was 40. The most frequently used preventive treatments were lithium (70.4%) and AC (43.5%) monotherapies. The frequency of preventive treatments and obtained response ratio are given in Table 1. At any time of diseases of the patients 71% lithium, 44% AC, 18% AP monotherapies and 23% lithium and AC, 15% lithium and AP, 25% AC and AP (AC, AP), 4% lithium and AC and AP (Li, AC, AP) combined therapies were used as maintenance treatment.

Table 1: Frequency of preventive treatment use and rate of response

Maintenance treatment regime	Number of patients	Number of the patients with treatment response
	n (%)	n (%)
Li monotherapy	131 (70.4)	80 (61.1)
AC monotherapy	81 (43.5)	50 (61.7)
AP monotherapy	33 (17.7)	24 (72.7)
Li + AC	43 (23.1)	21 (48.8)
Li + AP	28 (15.1)	20 (71.4)
AC + AP	47 (25.3)	38 (80.8)
Li + AC + AP	8 (4.3)	6 (75.0)

When we studied on relations between response to lithium, the most frequently used preventive treatment, and demographical features, we obtained these results. Response rate to lithium significantly varies depending on were being married, non-psychotic, to have less severe episodes, to show seasonal pattern. Nevertheless, response rate of married subjects to lithium were found to be significantly high (p=0.001); however, there was no significant difference between single or divorced subjects. Additionally, response rate to lithium of non-psychotic subjects was found significantly higher (p=0.001). Furthermore, those indicating a seasonal structure have a significantly higher response rate to lithium (p=0.001), the rate was the highest for patients with dominant episode depressive type and was followed by mix and manic episode (Table 2).

Table 2: The correlation of response to lithium with clinical features

		Patients with Response (%)	Patients non-response (%)	p
Gender	Female	79 (60.0)	52 (40.0)	0.703
	Male	82 (62.9)	49 (37.1)	
Marital status	Married	95 (72.6)	36 (27.4)	0.001*
	Single	62 (47.4)	69 (52.6)	
	Divorced	66 (50.1)	65 (49.9)	
Psychotic symptoms	Yes	69 (52.7)	62 (47.3)	0.001*
	No	116 (88.9)	15 (11.1)	
Suicide attempts	Yes	76 (57.7)	55 (42.3)	0.528
	No	81 (61.7)	50 (38.3)	
Seasonal pattern	Yes	101 (76.9)	30 (23.1)	0.001*
	No	70 (53.1)	61 (46.9)	
Dominant episode type	Manic	73 (56.0)	58 (44.0)	0.001*
	Mix	87 (66.7)	44 (33.3)	
	Depressive	101 (76.9)	30 (23.1)	
Severity of episodes	Less severe	70 (71.4)	37 (28.6)	0.062*
	Severe	70 (53.5)	61 (46.5)	

Evaluated via Pearson Chi-square test
*p<0.05: statistically significant

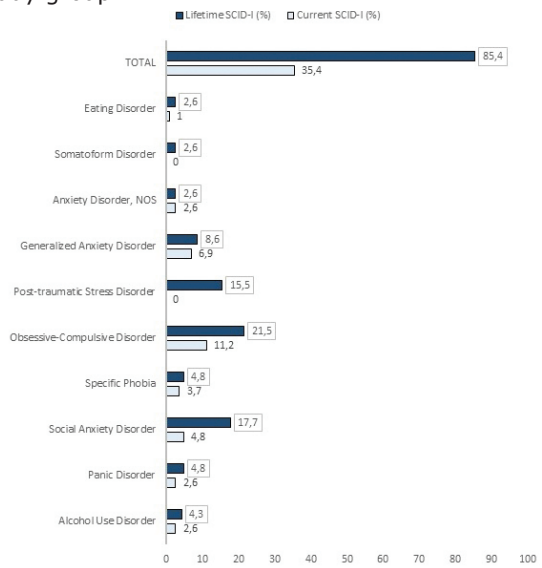
When the effect of clinical and demographic features on response rate to AC is studied, the findings given in Table 3 were obtained. Having analyzed the table, we see that response to AC by male subjects is significantly higher than female subjects (p=0.021). There is no significant difference in AC response between married and single subjects, however, both have significantly higher AC response rate against divorced subjects. AC response was found significantly low in those with suicide attempt (p=0.001). Additionally, it was observed that AC response rate was significantly higher in subjects with dominant episode mix type when compared to other two types (p=0.024). On the other hand, no significant relation between psychotic symptom, seasonal structure or episode severity and AC response rate was found (Table 3). 35.4% of bipolar patients (n=66) had presenting and 85.4% (n=159) had a lifetime comorbid psychiatric disorder. 75.5% of the patients had at least one comorbid anxiety disorder. Bipolar patients' most seen lifelong comorbidity was obsessive-compulsive disorder (40/ 186; 21.5%); followed by social anxiety disorder (33/ 186; 17.7%), post-traumatic stress disorder (29/ 186; 15.5%) and generalized anxiety disorder (16/ 186; 8.6%) comorbidity (Table 4).

Table 3: The correlation of response to anticonvulsants with clinical features

		Patients with Response (%)	Patients non-response (%)	p
Gender	Female	46 (56.8)	35 (43.2)	0.021*
	Male	60 (74.1)	21 (25.9)	
Marital status	Married	53 (65.4)	28 (34.6)	0.001*
	Single	54 (66.7)	27 (33.3)	
	Divorced	27 (33.3)	54 (66.7)	
Psychotic symptoms	Yes	49 (60.5)	32 (39.5)	0.325
	No	55 (67.9)	26 (32.1)	
Suicide attempts	Yes	20 (24.7)	61 (75.3)	0.001*
	No	56 (69.1)	25 (30.8)	
Seasonal pattern	Yes	47 (58.0)	34 (41.9)	0.420
	No	52 (64.2)	29 (35.8)	
Dominant episode type	Manic	46 (56.8)	35 (43.2)	0.024*
	Mix	61 (75.3)	20 (24.7)	
	Depressive	47 (58.0)	34 (41.9)	
Severity of episodes	Less severe	49 (60.5)	32 (39.5)	
	Severe	51 (62.9)	30 (37.0)	0.746

Evaluated via Pearson Chi-square test
*p<0.05: statistically significant

Table 4: Rates of axis-I psychiatric comorbid diagnosis in study group



4. Discussion

The ultimate aim of long-term treatment in bipolar disorder is the prevention of episodic relapse. In general, our findings coincide with the recommendations of recent guidelines for the long-term treatment of bipolar disorder. Lithium monotherapy was the most frequently appealed preventive treatment by the patients enrolled in this study (by 70,4% of patients) and it was followed by respectively anticonvulsant monotherapy (43,5%) and combined treatment of anticonvulsant and antipsychotic (AC and AP) (25,3%), lithium and anticonvulsant combination treatment (Li and AC) (%23,1). The lithium metal has been in clinical practice for more than a half century, as a best-established maintenance treatment option in bipolar disorder, owing to convincing evidence from a plenty of randomized-controlled trials. A meta-analysis of five placebo-controlled lithium monotherapy maintenance trial (n=770) demonstrated the drug's reducing effects on relapse risks of mania (by 38%) and depression (by 28%) (Vieta et al., 2008). Lithium is also still the only proven anti-suicidal agent (Geddes & Miklowitz, 2013). As expected, response rate to AC monotherapy of patients with suicide attempt history was found lower in our study. In spite of the given superiority of lithium compared to all other medications, AC drugs can be the first option for patients who have not sufficiently responded to lithium treatment, or got serious side effects or have not accommodated to lithium treatment, or those clinically expected to respond better to other mood stabilizers. For instance, lithium showed strongest antimanic properties, unlike AC agents, particularly lamotrigine, appeared to be more effective for prevention of depressive episodes (Popovic et al., 2012). Valproate and lithium were considered to be the only agents in terms of preventing all three types of episodes (manic, depressive and mixed) (Joas et al., 2017). Trials comparing the efficacies of combined treatment and monotherapies in bipolar disorder is scarce in the literature. Combination treatments were suggested in case of non-responsiveness to monotherapy, however, synergistic mechanisms of mood-stabilizers remained unclear. In an open-label trial with 330 bipolar patients, combination of lithium plus valproate was more likely to prevent mood episodes than valproate monotherapy, with no confirmed difference to lithium monotherapy (Geddes et al., 2010). In our unit, the first option was seemed to be lithium among other mood stabilizers and we prioritize monotherapies, which interprets our findings.

61.1% of patients received lithium treatment was responsive to the treatment. In a meta-analysis, it was found out that 30% of patients had recurrence of episodes whilst prevention with lithium (Davis, Janicak, & Hogan, 1999). In this meta-analysis, it was also reported that there was no difference between lithium and carbamazepine maintenance in terms of recurrence risk. In a double-blinded placebo controlled study, lithium and divalproex were compared in terms of prevention results. In this study, both active medications were found effective than placebo, but divalproex was reported to be more effective than lithium to prolong recurrence (Bowden et al., 2000). In our study, it was observed that lithium and AC monotherapies have similar preventive efficiency and this condition generally comply with the literature.

Antipsychotics have emerged with their short-term efficacy in the management of bipolar disorder, particularly symptomatic control in the courses of episodes. The number of publications indicating that AP agents may be effective for bipolar disease has increased recently (M Tohen, Chengappa, Suppes, Baker, & Ate, 2004; Mauricio Tohen et al., 2003, 2005). Second-generation or atypical antipsychotic drugs, particularly quetiapine and olanzapine, have studied as maintenance treatment options in bipolar disorder. These drugs were recorded with their influential antimanic outcomes, without discrediting lithium dominancy in the maintenance treatment (Yatham et al., 2013). Their efficacy in the treatment of depressive episodes is variable, with the best-known effectiveness of quetiapine (Geddes, Burgess, Hawton, Jamison, & Goodwin, 2004). Some has considered atypical antipsychotics as the most potent agents in acute mania, and reasonably defended continuation of these agents after remission from acute episodes (Yatham et al., 2013). Nevertheless, further comprehensive randomized-controlled trials are needed to establish solid evidence for mood-stabilizing effects of AP drugs with their long-term clinical outcomes in bipolar disorder. On the other hand, opinions suggesting that AP including combined treatments provide more positive results than monotherapies do have, gained importance in recent years (Muzina & Calabrese, 2005). Parallel to the regarding literature, according to our findings it is remarkable to highlight that AP monotherapy among monotherapies and AC+AP prevention among combined options showed the highest rational prevention success.

In our study, lithium monotherapy was more effective for patients with non-psychotic, to show seasonal pattern and have less severe episodes. However, response rate to AC monotherapy of patients with suicide attempt history was found lower. It can be possible to receive more positive results by giving priority to appropriate treatments for patients considering this data. Epidemiological clinical studies demonstrated greater comorbidity of other axis I disorders, particularly anxiety disorders, in bipolar disorder. Nevertheless; clinical, sociodemographical and therapeutic differential aspects of these comorbidities had not been sufficiently shown (Tamam & Ozpoyraz, 2002). Several studies have found that, half of the bipolar patients had at least one anxiety disorder (McElroy et al., 2001; Zutshi, Reddy, Thennarasu, & Chandrashekhar, 2006). Our study showed 75% comorbid anxiety disorder in bipolar disorder, which was higher than concerned literature knowledge. According to SCID-I monitoring in our study, most prevalent comorbid diagnosis was obsessive-compulsive disorder (21.5%), which was higher than in other national study (Koyuncu, Tükel, Özyıldırım, Meteris, & Yazıcı, 2010). This greater comorbidity might be attributed to our long-term-followed and complex study population. Comorbid alcohol and substance use disorders were speculated to be frequent in bipolar disorder (Cardoso et al., 2016). Current study showed lower ratios of these disorders in study group, which might be related to cultural and social determinants, and higher numbers of female patients.

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This study included several limitations. Duration of remission criteria was not included in this study. At least two months of symptomatic recovery is generally accepted as remission in bipolar disorder, despite most of the studies regarding maintenance treatment investigated 1-5 years of remission state 17. Mirror-design evaluation have been used in several preceeding studies but its subjective nature may be criticised for causing confounding results. Axis II disorders were generally mentioned not to have impact over treatment adherence and prognosis in remitted bipolar disorder. However, comorbid borderline personality disorder in bipolar disorder was reported with poor clinical outcomes (Vieta et al., 2001). We had not evaluated axis II disorders, which might limit our findings regarding clinical outcomes of maintenance treatment. We diagnosed alcohol and substance use disorders with SCID-I, did not evaluate any substance in urine. The retrospective evaluation of our patients was checked and controlled by information gathered not only from patients, but also from their relatives. The medical records were also used, and as most of the patients had been followed up by our department for a long time, the data is frequently updated. All these attempts tried to reduce the probable effects of the limitations of the retrospective design of our study.

5. Conclusion

To determine how the response to preventive treatment alters as associated with patients' clinical features can be helpful for selection of a more rational medication. Lithium and AC monotherapies were the most frequently used options to prevent bipolar disorder. However, monotherapies remain incapable for many patients that consequently requires combination therapies. In particular, it is possible to receive more solid results with combined preventions containing AP agents. However, synergistic mechanisms of combined drugs remained with uncertainty. The responsiveness was more successful for the patients taking lithium prevention who show seasonal features, have no psychotic symptom and dominant depressive polarity. Determination of appropriate long-term treatment strategy is crucial in bipolar disorder. Apart from the choice of best efficient drug, side-effects and tolerability of the treatment should also be considered. For this reason, with the consideration of clinical features and eligible treatment options, individualized medication ought to be administered for each patient. In order to select more appropriate prevention treatment, studies evaluating effects of patients' clinical features on treatment responses may be helpful.

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