The Relationship Between the Duration of Drug Use and the Bipolar Disorder Patients' Sociodemographic and Clinical Characteristics

Cengiz AKKAYA[1], Gülnihal DENİZ[2], Şengül CANGÜR[3], Selçuk KIRLI[4]

SUMMARY

Objective: The purpose of this study was to determine the duration of psychotropic drug use in the long-term follow-up of bipolar disorder (BD) patients. In addition, this study aimed to investigate their role in the daily clinical practice in association with patient sociodemographic and clinical characteristics. The overarching goal for this study was to produce results that enlighten the development of new treatment strategies.

Method: Follow-up data acquired from the Psychiatry Department of Uludag University Faculty of Medicine was used to retrospectively evaluate 151 patients diagnosed with BD. Socio-demographic data of the patients and information regarding the disease and the drugs used were analyzed.

Results: Of the patients studied, 57.0% were female with a mean age of 41.5±12.8. The mean duration of follow-up was 1985.3±1933 [median 1291 (15-9135)] days; euthymic period accounted for 86.0% of this duration. Interestingly, incompliance with the treatment triggered the switch to mania and ineffective treatment triggered the switch to depression. Medication distribution was as follows: 95.4% of the patients received antipsychotic and mood stabilizer treatments, 3.3% received only mood stabilizer treatment, and 1.30% received only antipsychotic treatment. The major findings of this study was that many sociodemographic as well as clinical manifestations including, early onset (aged ≤18 years), unmarried, first episode of mania, those with disease not showing seasonal features, psychotic symptoms, history of hospitalization, and higher number of manic or hypomanic episodes resulted in increased patient prescribed antipsychotic drugs

Conclusion: Our data suggests that antipsychotic drugs are being used more frequently and for longer durations in the treatment of BD.

Key Words: Bipolar disorder, antipsychotics, sociodemographic characteristics, drugs.

INTRODUCTION

Bipolar disorder (BD) is a mental disorder that has a negative effect on one's personal and social life due to several reasons, such as breakdown in social and professional performance, risk of suicide, alcohol/substance use, and involvement in judicial cases. It can also result in repetitive hospitalization and chronicity (Angst and Sellaro 2000, World Health Organization 2001, Baldessarini and Tondo 2008).

The prevalence rate of BD was reported to range between 0.9-1.7 percent however, the lifelong prevalence rate of the BD spectrum is 6.0% (Goodwin and Jamison 2007). The recurrence rate of BD is high despite developments in drug treatment and a better understanding of its genetic and neurobiological basis (Çakır and Özerdem 2010). According to the monitoring data of 20 years, only 24% of the patients fully recovered (Angst et al. 2005), while the 5-year recurrence rate was 73% even when drug compatibility was sufficient (Gitlin et al. 1995). In bipolar disorder treatment, mood stabilizers (MS) such as lithium and anticonvulsant drugs are used as for the treatment of the disease periods and the maintenance of general well-being (Smith et al. 2007). However, the latest monitoring studies indicate malfunctioning levels and low protection rates with MS, contrary to the expectations (Saka et al. 2001). In a study of drug prescription tendency change over time, lithium and first generation antipsychotic

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[1]Assoc., Prof.,MD., [2]MD, [4]Prof., MD., Uludağ University Medical Faculty, Psychiatry Department, Bursa, [3]Assist., Prof.,, PhD., Düzce University Faculty of Medicine, Department of Biostatistics and Medical Informatics, Düzce., Turkey.

e-mail: *cakkaya@uludag.edu.tr*

(AP) drug use was reduced, whereas anticonvulsant and second generation AP drug prescription increased (Wolfsperger et al. 2007). In recent years, some studies have shown that anticonvulsants are increasingly preferred to lithium in the protective treatment of BD (Blanco et al. 2002, Türkçapar 2003, Shulman et al. 2003, Calabrese et al. 2003, Maj 2005, Bozkurt and Karlıdere 2006). Furthermore, the effect of the MS combinations or comorbid AP drugs may be superior to single drug use (Blanco et al. 2002, Cookson 2005). Furthermore, second generation APs (except for clozapine) are now preferred as the primary drugs for the additional treatment of mania (Vacheron-Trystram et al. 2004, Perlis et al. 2006). Several studies suggest that certain APs are beneficial when used separately or in combination with other drugs in the depression period of BD (Amsterdam and Shults 2005, Thase et al. 2006, Endicott et al. 2007).

Studies in recent years have shown the changes in traditional drug use tendencies. Therefore, it is important to investigate the daily clinical practices in this regard. With a retrospective focus on patient sociodemographic and disease characteristics, the aim of the present study is to determine the duration of the patient psychotropic drug use and investigate the relationship between psychotropic drug use and daily clinical practice. The results of the present study provide guidance for new treatment strategies.

METHOD

The medical records of 151 patients, who fulfill the "Bipolar Disorder" criteria according to DSM-IV-TR (American Psychiatry Association 2001) diagnosis criteria and monitored by Uludağ University Medical Faculty Department of Mental Health and Diseases and Mood Disorders Clinic, were retrospectively investigated. The present study was approved by Uludağ University Medical Faculty, Local Ethics Committee (09.06.2009 / 2009–11/53).

All patient data, including the sociodemographic and disease records, were obtained. Patients who were included in the present study were previously monitored by the same faculty member of the Mood Disorders Clinic through the same file order since 2002. During each examination, various scales were performed on the patients in the Mood Disorders Clinic in order to measure the efficiency and the side effects of the drug treatment. The duration of drug use was determined by considering the patient's statement and medical records in addition to how many days the recommended treatment was used by the patient. Whether a patient adheres to the treatment is based on the opinion of the physician who monitors the patient in accordance with the statement of the patient and his/her family. The applied treatment was regarded as effective if the patient has euthymia (Hamilton Depression Rating Scale ≤7 and Young Mania Rating Scale ≤8 points). The diagnosis and periods of the disease along with the presence of a comorbid diagnosis were determined by the physician who monitored the patient during the clinical examination and follow-ups.

The lowest doses that were recommended in the AP (olanzapine 5 mg/g, quetiapine 200 mg/g, risperidone 2 mg/g, haloperidol 5mg/g) and antidepressant prospectus were accepted as the efficient dose. The combination therapy was accepted as the use of two or more congeneric drugs together. The effective dose combined therapy was accepted as the use of all drugs in an effective dose. The periods of drug use were defined as the continuity time of each usage during the entire treatment (e.g., the effective dose combined AP period defines the period of multiple AP use in the lowest effective dose).

Statistical Analysis

Social Sciences Statistical Package Program (Statistical Package for Social Sciences-SPSS Inc., version 13.0; Chicago, IL) was used for the statistical analysis. The descriptive statistics were given as mean±standard deviation, median, frequency, minimum, and maximum. The fitness of the measured variables to the normal distribution was determined using the Kolmogorov-Smirnov test. Regarding the numeric variables, the Mann-Whitney U-test was used in the comparison of the two groups, and the Kruskal-Wallis test was used in the comparison of multiple groups. Spearman's correlation test was used to determine the correlation between the variables. Pearson's chi-square test and Fisher's exact test were used for the evaluation of the categorical variables. P values <0.05 were considered significant.

RESULTS

Eighty-six patients (57%) were female, and 65 patients (43%) were male. The mean age was 41.5±12.9 years (19–83); 68.9% of the patients were high-school and postgraduate graduates; 57.6% of the patients were married and 41.1% of the patients were employed. The age of BD onset was 26.3±9.1 years; the mean duration of disease was 15.3±10.8 years. The majority of the patients (92.1%) had no comorbid psychiatric diagnosis; the patients with comorbid psychiatric diagnosis (2.6%) had the alcohol-substance abuse as the most common additional diagnosis. There was no comorbid disease in 72.2% of the patients; hypothyroidism (7.3%) was the most common comorbid disease in patients with a comorbid disease. There were no family characteristics in 41.1% of the patients. Unipolar depression was the most frequent disease (13.9%) in the family history of the patients.

The initial stage of the disease was mania in 51.7% (n=78) of the patients, depression in 45.7% (n=69) of the patients, and mixed in 2.6% (n=4) of the patients. The mean number

of mania was 5.1±5.7 [median 4(0–52)], the mean number of depression was 4.2±5.8 [The median 3 (0–51)], the mean number of mixed episode was 0.1±0.5 [The median 0 (0–3)] and the mean number of the hypomanic episode was 1.4±4.1 [The median 0 (0–32)]. The incidence of manic attacks was 86% (n=67) in the patients who experienced mania as the initial stage, and 70% (n=51) in the patients who did not experience mania as the initial stage (p=0.017). The incidence of depressive attacks was 72% (n=50) in patients who experienced depression as the initial stage, and 57% (n=47) in the patients who do not experience depression as the initial stage (p=0.056).

During the follow-up of the patients with bipolar disorder by our institution, the ratios of rapid cycling, judicial cases, suicide attempt, electroconvulsive treatment, seasonal features, and psychotic symptoms were 16.6%, 4.60%, 6.60%, 3.30%, 43.7%, and 51.7%, respectively. According to the data from our institution, the mean follow-up period was 1985.3±1933 [median 1291 (15–9135)] days. The periods of only MS use, AD, and AP use at effective dose were respectively as follows: 358.6±735.8 [median: 13 (0–4380)], 391.3±830.5 [median: 50 (0–6417)] and 881.3±1061,6 [median: 538 (0–5873)] days. The patients had euthymia during 86.3% of the entire follow-up period; the ratios of manic and depressive periods were 5.9% and 5.0%, respectively. During the follow-up, the mean mania and mean mixed periods were 52.7±49.7 days and 77.7±88.4 days, while the mean depressive and the mean hypomanic periods were 63.9±54 days and 39.3±32.5 days, respectively.

Only 37.7% of the patients were adherent to the treatment. The manic process was the most frequent (49.2%) due to the nonadherence to the treatment, and the depressive process was the most frequent (53.6%) due to the inefficient drug therapy. One hundred forty-four (95.4%) patients received AP and MS treatments in combination, 5 patients (3.3%) received only MS treatment, and 2 patients (1.3%) received only AP treatment. Thirty-four (22.5%) patients were given additional hypnotic drugs, and 70 (46.4%) patients were given no AD drugs during the follow-up by our institution. There was no significant correlation between the age, family characteristics, suicide attempt, educational and work status, and the treatment periods (p>0.05).

The patients were grouped according to the disease onset as follows: ≤18 years, 19–29 years and ≥30 years. The duration of AP use was 1287.9±1252.2 days [median 744.5 (0–4946)] in the ≤18 years group, and 869.2±819.9 [median 570.5 (0–2920)] days in the ≥30 years group (p=0.01). There was no difference in the process of adherence to the treatment among these groups. There was a positive correlation between the age of the patients at the time of the study and the periods of MS use (r=0.165; p=0.043), only MS use (r=0.172; p=0.035), AD use (r=0.248; p=0.002), and effective dose AD use (r=0.227; p=0.005).

The duration of combined AP use was longer in single patients compared to married patients. The married patients received a longer efficient dose of combined AP, MS, AD, efficient dose AD, and efficient dose combined AD treatment. The adherence to the treatment was better in the married patients compared to the single patients. The duration of combined AP and efficient dose combined AP use was longer in the single patient group compared to the widowed-divorced patient group. There was no significant difference in the duration of treatment between the married patients and the widowed-divorced patients (Table 1).

Table 1. The descriptive values of the treatment duration according to the marital status

	Marital Status				
	Single	**Married**	**Widow/ Divorced**	**p**	**KW-χ^2**
Duration of medication Median (Minimum-Maximum)					
AP	763 (0-5873)	738 (0-7117)	488 (60-4061)	0,351	2,093
AP at effective dose	555 (0-5873)	522 (0-4339)	488 (42-4058)	0,437	1,655
Combined AP	90 (0-2167)	0 (0-3232)	0 (0-1380)	0.008a	9.652
Combined AP at effective dose	30 (0-921)	0 (0-2628)	0 (0-1047)	0.015b	8.441
MS	735 (37-5525)	1343 (0-7812)	946 (0-3981)	0.024	7.474
Combined MS	0 (0-2789)	0 (0-4733)	0 (0-2518)	0.952	0.099
MS only	0 (0-2686)	30 (0-4380)	0 (0-2496)	0.081	5.026
Combined MS only	0 (0-1291)	0 (0-1517)	0 (0-1041)	0.705	0.700
AD	0 (0-3889)	150 (0-6417)	60 (0-1119)	0.038	6.560
AD at effective dose	0 (0-3889)	146 (0-6417)	30 (0-1191)	0.046	6.176
Combined AD	0 (0-509)	0 (0-5835)	0 (0-343)	0.060	5.629
Combined AD at effective dose	0 (0-509)	0 (0-5835)	0 (0-343)	0.028	7.116
Duration of adherence to treatment	914 (53-5960)	1438 (159135)	1002 (60-4034)	0.037	6.575

All periods are presented as days.
AP: antipsychotic; MS: mood stabilizer; AD: antidepressant
pa and pb are also significant between single and widow/divorced groups.

Table 2. The descriptive values of the treatment duration according to the first episode

	First Disease Period			
	Mania	**Depression**	**p**	**MW-z**
Duration of medication Median (Minimum-Maximum)				
AP	810 (0-7117)	553 (0-4061)	0.012	-2.515
AP at effective dose	643 (0-5873)	280 (0-4538)	0.001	-3.458
Combined AP	89.5 (0-3232)	0 (0-2117)	0.001	-3.290
Combined AP at effective dose	17.5 (0-2628)	0 (0-1205)	0.002	-3.055
MS	1001.5 (0-7673)	1206 (0-7812)	0.969	-0.039
Combined MS	0 (0-4733)	0 (0-1910)	0.037	-2.088
MS only	10 (0-2360)	14 (0-4380)	0.905	-0.120
Combined MS only	0 (0-1517)	0 (0-486)	0.017	-2.392
AD	0 (0-1517)	239 (0-6417)	<0.001	-3.533
AD at effective dose	0 (0-3889)	207 (0-6417)	0.001	-3.386
Combined AD	0 (0-541)	0 (0-5835)	0.019	-2.342
Combined AD at effective dose	0 (0-541)	0 (0-5835)	0.010	-2.563
Duration of adherence to treatment	1173 (52-9135)	1214 (15-8543)	0.995	-0.006

All periods are presented as days.
AP: antipsychotic; MS: mood stabilizer; AD: antidepressant

Table 3. The descriptive values of the treatment duration according to the comorbid psychiatric diagnosis

	Comorbid Psychiatric Diagnosis			
	Yes	**No**	**p**	**MW-z**
Duration of medication Median (Minimum-Maximum)				
AP	520 (0-2034)	743 (0-7117)	0.244	-1.166
AP at effective dose	183 (0-1211)	555 (0-5873)	0.008	-2.639
Combined AP	0 (0-807)	30 (0-3232)	0.009	-2.611
Combined AP at effective dose	0 (0-779)	0 (0-2628)	0.043	-2.021
MS	926.5 (159-6585)	1026 (0-7812)	0.744	-0.327
Combined MS	0 (0-441)	0 (0-4733)	0.201	-1.280
MS only	13.5 (0-2686)	7 (0-4380)	0.701	-0.385
Combined MS only	-	0 (0-1517)	-	-
AD	673.5 (0-2648)	10 (0-6417)	0.004	-2.851
AD at effective dose	557 (0-2648)	10 (0-6417)	0.005	-2.786
Combined AD	0 (0-1221)	0 (0-5835)	0.030	-2.168
Combined AD at effective dose	0 (0-1221)	0 (0-5835)	0.023	-2.280
Duration of adherence to treatment	1159.5 (310-7345)	1200 (15-9135)	0.701	-0.385

All periods are presented as days.
AP: antipsychotic; MS: mood stabilizer; AD: antidepressant

The duration of AP, combined AP, combined AP at effective dose, combined MS and only MS were longer in patients who experienced mania as the first disease stage. Conversely, the duration of AP drugs at effective dose and all AD drugs were longer in patients who experienced depression as the first disease stage. There was no difference in adherence to treatment between the groups (Table 2).

The duration of all AD use was longer in patients with comorbid psychiatric disorder, whereas the duration of AP at effective dose, combined AP, and combined AP at effective dose were longer in patients who did not have a comorbid psychiatric disorder (Table 3). The incidence of depressive attacks was 92% in patients with comorbid psychiatric disorder (n=11), and 62% in patients who did not have a comorbid psychiatric disorder (n=86) (p=0.037). The incidence of a comorbid psychiatric diagnosis was 88% in patients who received AD treatment (n=71) and was higher compared to the other patients (p<0.001).

There was a positive correlation between the number of manic periods and the duration of all AP and MS; between the number of depressive periods and the duration of MS, combined MS, AD and AD at effective dose, and between the number of hypomanic periods and the duration of combined AP, AP at effective dose, MS and combined MS. There was no correlation between the number of mixed periods and the duration of drug use. The adherence to treatment increased with increasing number of manic and hypomanic periods (Table 4).

The duration of combined MS use was the only significant difference between the rapid cycling patients (n=25) and patients who are not rapid cycling (n=126). Rapid cycling patients used combined MS for more days (401±791.9) [median: 0 (0–2518)] compared to patients who were not rapid cycling (p=0.01). There was no difference in adherence to treatment between the groups. The duration of AP and MS

Table 4. The correlation between the treatment duration and the number of episodes

	Number of episodes							
	Manic		Depressive		Mixed		Hypomanic	
Duration of medication Median (Minimum-Maximum)	**r**	**p**	**r**	**p**	**r**	**p**	**r**	**p**
AP	0.212	0.009	0.740	0.366	-0.010	0.907	0.165	0.042
AP at effective dose	0.201	0.014	0.047	0.569	-0.009	0.913	0.108	0.188
Combined AP	0.366	<0.001	0.048	0.562	-0.006	0.943	0.455	<0.001
Combined AP at effective dose	0.300	<0.001	-0.023	0.775	-0.066	0.421	0.222	0.006
MS	0.233	0.004	0.169	0.038	-0.042	0.612	0.211	0.009
Combined MS	0.460	<0.001	0.264	0.001	0.088	0.281	0.591	<0.001
MS only	0.192	0.018	0.106	0.195	-0.104	0.202	0.147	0.071
Combined MS only	0.240	0.003	0.122	0.136	-0.042	0.611	0.145	0.076
AD	0.076	0.356	0.071	<0.001	0.028	0.735	0.029	0.725
AD at effective dose	0.080	0.329	0.442	<0.001	0.017	0.832	0.041	0.620
Combined AD	0.067	0.413	0.052	0.524	-0.018	0.824	-0.031	0.707
Combined AD at effective dose	0.064	0.435	0.041	0.616	-0.016	0.848	-0.028	0.732
Duration of adherence to treatment	0.240	0.003	0.174	0.033	-0.034	0.681	0.224	0.006

AP: antipsychotic; MS: mood stabilizer; AD: antidepressant

Table 5. The descriptive values of treatment duration according to the seasonal features

	Seasonal Features			
	Yes	**No**	**p**	**MW-z**
Duration of medication Median (Minimum-Maximum)				
AP	1056 (0-5873)	595 (0-7117)	0.011	-2.536
AP at effective dose	663.5 (0-5873)	398 (0-4538)	0.017	-2.391
Combined AP	7 (0-3232)	29 (0-2117)	0.781	-0.278
Combined AP at effective dose	0 (0-2628)	0 (0-1324)	0.852	-0.187
MS	1365 (75-7812)	868 (0-5355)	0.001	-3.404
Combined MS	0 (0-4733)	0 (0-2518)	0.781	-0.279
MS only	33 (0-2496)	0 (0-4380)	0.248	-1.156
Combined MS only	0 (0-1517)	0 (0-1291)	0.856	-0.181
AD	18 (0-6417)	90 (0-2648)	0.775	-0.285
AD at effective dose	18 (0-6417)	90 (0-2648)	0.717	-0.362
Combined AD	0 (0-5835)	0 (0-541)	0.838	-0.205
Combined AD at effective dose	0 (0-5835)	0 (0-541)	0.955	-0.057
Duration of adherence to treatment	1487 (75-8543)	915 (15-9135)	0.007	-2.699

All periods are presented as days.
AP: antipsychotic; MS: mood stabilizer; AD: antidepressant

Table 6. The descriptive values of treatment duration according to the psychotic symptoms

	Psychotic Symptom			
	Yes	**No**	**p**	**MW-z**
Duration of medication Median(Minimum-Maximum)				
AP	934 (44-5873)	543 (0-7117)	0.002	-3.039
AP at effective dose	615 (0-5873)	377 (0-4538)	0.002	-3.039
Combined AP	95 (0-3232)	0 (0-2117)	<0.001	-4.955
Combined AP at effective dose	30 (0-2628)	0 (0-1697)	<0.001	-4.900
MS	1131.5 (0-7673)	1005 (0-7812)	0.644	-0.462
Combined MS	0 (0-4733)	0 (0-2082)	0.493	-0.685
MS only	10 (0-4380)	14 (0-4142)	0.540	-0.612
Combined MS only	0 (0-1291)	0 (0-1517)	0.510	-0.658
AD	18 (0-3889)	79 (0-6417)	0.304	-1.027
AD at effective dose	18 (0-3889)	60 (0-6417)	0.329	-0.977
Combined AD	0 (0-541)	0 (0-5835)	0.029	-2.182
Combined AD at effective dose	0 (0-541)	0 (0-5835)	0.017	-2.389
Duration of adherence to treatment	1270.5 (53-8253)	1119 (15-9135)	0.647	-0.458

All periods are presented as days.
AP: antipsychotic; MS: mood stabilizer; AD: antidepressant

use was longer in patients with seasonal features, whereas the duration of AP at effective dose was longer in patients who did not have seasonal features. The adherence to treatment was better in patients with seasonal features (Table 5). The incidence of manic attacks was 85% in patients with seasonal features (n=66), and 73% in patients who did not show seasonal features (n=62) (p=0.077).

The duration of all AP use was significantly higher in patients with psychotic symptoms, whereas the duration of combined AD use and combined AD at effective dose were higher in patients who did not have psychotic symptoms. There was no significant difference in MS use and adherence to treatment between the patients who had psychotic symptoms and patients who did not have psychotic symptoms (Table 6). The incidence of manic attacks was 94% in patients with psychotic features (n=73) and 62% in patients without psychotic features (n=45) (p<0.001). The incidence of depressive attacks was 64% both in patients with psychotic features (n=50) and without psychotic features (n=47) (p=1.00). The incidence of manic attacks was higher in the patient group with psychotic features.

Table 7. The descriptive values of treatment duration with respect to the hospitalization status

	Hospitalization			
	Yes	**No**	**p**	**MW-z**
Duration of medication Median (Minimum-Maximum)				
AP	819.5 (0-7117)	498 (15-2606)	0.005	-2.806
AP at effective dose	616 (0-5873)	207 (0-914)	0.001	-3.406
Combined AP	31 (0-3232)	0 (0-498)	0.005	-2.789
Combined AP at effective dose	5 (0-2628)	0 (0-498)	0.037	-2.081
MS	1216 (0-7812)	578 (0-4703)	0.006	-2.769
Combined MS	0 (0-4733)	0 (0-282)	0.445	-0.764
MS only	13.5 (0-4380)	0 (0-4142)	0.568	-0.570
Combined MS only	0 (0-1517)	0 (0-72)	0.365	-0.906
AD	60 (0-6417)	0 (0-1941)	0.428	-0.793
AD at effective dose	55 (0-6417)	0 (0-1941)	0.439	-0.775
Combined AD	0 (0-5835)	0 (0-343)	0.162	-1.398
Combined AD at effective dose	0 (0-5835)	0 (0-343)	0.188	-1.317
Duration of adherence to treatment	1365 (52-9135)	606 (15-4703)	0.004	-2.879

All periods are presented as days.
AP: antipsychotic; MS: mood stabilizer; AD: antidepressant

The patient with the highest number of hospitalizations was hospitalized 13 times, and the mean hospitalization number was 2.4±2.3. During the follow-up period, the mean hospitalization period was 40±55.7 days. The patient with the longest hospitalization period was hospitalized for a total of 352 days. Twenty-five out of 151 patients (16.6%) had no prior hospitalization during the follow-up, whereas the remaining 126 patients (83.4%) were treated as inpatients. The duration of all AP and MS use was significantly longer in the hospitalized group, and the treatment adherence of these patients was better compared to the outpatient group (Table 7). The incidence of seasonal features was 49% in the hospitalized patients (n=62), and 16% in the outpatients (n=4) (p=0.002). The incidence of psychotic symptoms was 55% in the hospitalized patients (n=69) and 36% in the outpatients (n=9) (p=0.08). The incidence of manic attacks was 83% in the hospitalized patients (n=104) and 56% in the outpatients (n=14) (p=0.003).

DISCUSSION

The present study is one of a few studies on the duration of psychotropic drug use in BD treatment. Most importantly, our study demonstrates that the recommendations of the treatment guidelines are implemented in the daily clinical practice at a considerably low level. The conventional clinical practice regarding BD treatment involves the use of MS, AP, or AD drugs and continuation of treatment with only MS drugs in the remission periods (Sachs 1996). However, the use of AP drugs both as AP, AD, and MS especially in recent years along with the duration of their use have increased with the discovery of second-generation APs (Wolfsperger et al. 2007). The present study retrospectively evaluated the medical records of 151 BD patients and resulted in findings that indicate an increasing use of AP drugs in BD treatment.

Demographic Features

According to the sociodemographic features of the patients included in the present study, the majority of the patients were adults, high school, and postgraduate school graduates. They had easy access to a tertiary healthcare facility and complied with regular polyclinic follow-ups. Similarly, the literature findings indicate that BD patients have a higher socioeconomic level compared to the other psychiatric disorder groups (Güleç and Köroğlu 2007). In the present study, the majority of the patients did not have a comorbid psychiatric diagnosis and the comorbidity with highest incidence was alcohol-substance abuse. According to the literature, the prevalence of substance use in BD is 5% (Winokur et al. 1998), whereas the prevalence of lifelong substance use is 14-45% (Feinman and Dunner 1996, Winokur et al. 1998, Suppes et al. 2001). The risk factors for drug abuse include male

gender, low education level, and comorbid other axis-I disorders (Sherwood Brown et al. 2001). Interestingly, the rate of alcohol use in Turkey is relatively low (Özpoyraz et al. 1998). In the present study, the low incidence of alcohol-substance abuse may result from the fact that alcohol is not considered as a welcomed substance, 57% of the patients were female, and the patients had a relatively high educational level. This finding is consistent with the studies in Turkey that report relatively low levels of alcohol-substance-associated problems in BD patients (Akkaya et al. 2012). In addition, the lack of a structured interview such as Structured Clinical Interview for DSM Disorders may be the underlying reason for low rate of comorbidity.

When the medical comorbidities of our patients were examined, hypothyroidism was the most frequent medical comorbidity of the patients in this study. It is worth noting that lithium treatment is still the first option in the treatment of bipolar patients and has been shown to cause subclinical and clinical hypothyroidism (Lee et al. 1992, Deodhar et al. 1999, Kusalic and Engelsmann 1999, Frye et al. 1999, Johnston and Eagles 1999).

In this study, the suicide rate was 6.6% in the study group. The lifelong suicide rate of patients with BD diagnosis ranges between 25-56% (Jamison 2000, Slama et al. 2004, Valtonen et al. 2005) but, suicide is known to be affected by social, cultural, and religious features (Braun and Nichols 1997, Maharajh and Abdool 2005). In addition, it has been stated that drug addiction increases suicide risk (Krishnan 2005). As emphasized in the literature, the low suicide rate in the present study can be explained due to the lower suicide attempt rates in Islamic countries (Lester 2006), sociocultural structure, and low addiction rates (Jamison 2000).

According to the family histories of our patients, unipolar depression was the most frequent disease in the family histories. The rate of any given psychiatric disease was approximately 57.8% in the family histories of BD patients (Gökbulut 2008), while this rate was shown to be 14.8% for unipolar disorder (McInnis 1997). In this aspect, the family history features of our patient group are consistent with the literature.

Clinical Features and Treatment

In the present study, the manic stage was the first disease period of more than half of the patients. However, there are contradictory studies in the literature. Despite the studies reporting that depression is the first disease stage in more than half of the patients (Angst and Sellaro 2000), a similar study to the present one determined the manic stage as the first disease period in 65.7% of the patients (Çoşkun 2008). The frequency of the disease periods in the present study (Akiskal 2007) and longer mixed episode duration (Secunda et al. 1985, Keller et al. 1986) are consistent with the literature.

In the present study, AP and MS drugs were used in the treatment of 95.4% of the patients, while only MS drugs were used in 3.3% of the patients. It is well-known that the recurrence rates are higher in BD, despite MS drugs being used in sufficient doses (Gitlin et al. 1995, Fava 1999). The presence of residual mood symptoms, despite the MS drugs being administered at a sufficient dose, may cause the patients to be administered with additional psychotropic drugs. In fact, the inability to secure temperament stabilization pushes the clinicians to search for alternative approaches. In addition, clinicians attempt to stabilize the temperament of BD patients or try to reduce the recurrence rate by using AP drugs (Blanco et al. 2002, Sachs et al. 2004, Yathman et al. 2004, Cookson 2005, Sachs et al. 2006, Uzun and Doruk 2006). According to a study that was carried out in 2001, 51% of the patients used other psychotropic drugs in addition to MS drugs (Kara Özer et al. 2001). Today, monotherapy is strongly recommended in the management of psychiatric disorders in almost all treatment guidelines. However, this recommendation is not put into daily clinical practice and multiple drug use is employed for almost all patients (Yazıcı et al. 2009). The conventional notion for BD states that the disease course involves recovery periods and that the functionality of an individual fully restores to the normal level in these periods. On the other hand, there are studies reporting residual symptoms in the recovery periods as well as functional loss in the chronic progression of the disease (Martinez-Aran et al. 2004, Malhi et al. 2007). In the present study, the very low ratio of the patients with only MS use and extended use of multiple drugs can be explained by these findings.

The use of AD drugs in bipolar depression is still controversial. Given that these drugs can cause mania, hypomania, mixed mood episodes, and rapid cycling, the guidelines recommend using these drugs carefully. There is increasing data against the use of AD drugs in the literature. The use of AD drugs in short- or long-term BD treatment has been shown to be ineffective or to have a limited effect. The combination of AD with MS drugs may cause manic switches (Ghaemi 2008). Similarly, the lack of AD drug addition to the treatment of 46.4% of the patients during their follow-up may be an indicator of concern regarding the use of AD drugs in BD. Another study, which was carried out in Turkey, shows that clinicians are hesitant to use AD drugs in BD despite the treatment guidelines (Altınbaş et al. 2011).

The disordered drug adherence in BD treatment is another major problem and nonadherence to treatment has been observed in 42% of the patients (on average) according to the literature (Perlick et al. 2004, Parikh et al. 1997). In the present study, nonadherence to treatment was observed in more than half of the patients. This triggered the manic stage most prevalently, whereas ineffective drug treatment triggered the depressive stage the most.

Genetic factors have been shown to play a critical role in early-onset BD. The frequency of periods with psychotic features and mixed periods, comorbid situations, the frequency of lifelong panic disorder, alcohol-substance abuse, and suicidal behavior are higher in early-onset BD (Schurhoff et al. 2000, Yildiz and Sach 2003). Early-onset disease has shown a worse prognosis, which is associated with the chronic structure of the disorder, resistance to MS, and high comorbidity (Biederman et al. 2000, Craney and Geller 2003). In this study, the duration of AP drug use was higher in the ≤18 year's group compared to the ≥30 year's group. This situation, as expected, may be explained by the early onset in BD as an indicator of poor prognosis (Perlis et al. 2004, Ernst and Goldberg 2004). As a matter of fact, the inability to provide protection with lithium and the use of AP drugs in BD correlates with poor prognosis (Saka et al. 2001). It is suggested that psychiatric diseases that are onset during adolescence negatively affect the patients' development. In addition, it becomes difficult for these patients to adopt social roles, and thus, the patients become prone to more severe mood disorders in the later stages of their lives (Boylan et al. 2004, Wozniak et al. 2002). Despite the studies stating a lack of a correlation between psychotropic drug use and age in BD (Levine et al. 2000), a positive correlation between age and the duration of MS drugs, only MS drugs, AD drugs, and AD drugs at the effective dose were observed in the present study. In other words, the duration of AD and MS drugs increase with increasing age. This may be related to depressive attacks that are more dominant in the clinical picture or the presence of comorbid psychiatric disorders during the course of the disease.

Despite studies reporting the absence of a correlation between treatment and marital status in BD (Levine et al. 2000), marriage is known to indicate a good prognosis in BD (Keck et al. 1998). In this study, the treatment adherence in married patients was better compared to single patients. In addition, the duration of MS, AD, AD at the effective dose, and combined AD at the effective dose were significantly higher in married patients. The longer duration of AD drug use in married patients is consistent with the literature findings indicating a higher possibility of depression incidence in married couples.

The false diagnosis is high for patients who experience depression as the first disease period. Moreover, there is a risk of a manic switch depending on the AD drug use (Chun and Dunner 2004, Tomruk et al. 2010). In the present study, the duration of AP and MS drug use was longer in patients who experienced mania as the first disease period, whereas the duration of AD drug use was longer in patients who experienced depression as the first disease period. In addition, the frequency of manic attacks was higher in patients who experienced manic attacks first, while the frequency of depressive attacks was higher in patients who experienced depressive attacks first. We observed that the first disease period was a factor affecting the duration of drug use and disease course. Thus, it can be speculated that the disease onsets may affect the disease course over the long term. It can be stated that the patients with disease onset mania experience manic attacks and mood fluctuations more frequently. Thus, the duration of the combined drug is longer especially for AP and MS drugs. The long-term AD drug use of the patients with disease onset depression is possibly correlated with a more dominant clinical presentation.

It is known that the association between BD and anxiety disorder is common. Furthermore, the incidence of a comorbid anxiety disorder is higher in BD patients compared to the general population (Bauer et al. 2005). The incidence of lifelong anxiety disorder in patients diagnosed with BD ranges between 24-93% (Kessler et al. 1997, Pini et al. 1997, Henry et al. 2003). Boylan et al. (2004) reported that at least one comorbid anxiety disorder was present in 55.8% of 138 BD patients and more than one comorbid anxiety disorder was present in 31.8% of these patients. According to a clinical study in Turkey, the incidence of a lifelong comorbid anxiety disorder in 70 BD-I patients who were in the recovery period was 61.4% and the incidence of multiple anxiety disorder was 38.6% (Tamam and Özpoyraz 2002). As expected, the duration of AD drug use was significantly higher in patients with comorbid psychiatric diagnosis. Another factor affecting this situation is the increased frequency of depressive attacks in patients with a comorbid psychiatric disorder. In this case, the presence of a comorbid psychiatric disorder in BD is a predictor for depressive attacks and longer use of AD drugs.

The present study showed that the duration of AP drug use increased with the increasing number of manic and hypomanic periods, whereas the use of AD drug use increased with an increasing number of depressive periods. With the exception of the mixed episode, it was shown that increased frequency of other episodes resulted in the elevated duration of MS use. The increase in the duration of AP and/or combined use of MS with a heightened number of manic periods is expected. Likewise, the elevated frequency of the manic episode indicates that the disease is progressing to rapid cycling, which requires multiple drug use due to the insufficient response to treatment. A similar situation holds for increasing hypomanic attacks. It is expected that increasing incidences of depressive attacks increase the duration of AD drug use. To combat this, MS drugs are used in combination to prevent these attacks.

Rapid cycling in bipolar disorder is a known indicator of a poor prognosis (Perlis et al. 2004, Ernst and Goldberg 2004). In the treatment of acute mania, 70-80% of the patients who receive lithium monotherapy have a good response, whereas the response rate decreases in the presence of mixed periods, rapid cycling, psychotic mania, substance abuse, and cerebral

pathologies (Schou 1997). Valproate was effective in 60% of the patients (on average) who had rapid cycling BD, mixed periods, late-onset mania, and mania with comorbid organic diseases (Emrich and Wolf 1992). When used alone or combined with lithium, valproate was effective in rapid cycling patients (Calabrese and Delucchi 1990). Carbamazepine, on the other hand, was used in patients who do not respond to lithium, rapid cycling's, patients with dysphoric mania, and patients who do not have a family history of mood disorders (Ballenger and Post 1980). In this study, it is not surprising that the rapid cycling patients used combined MS drugs for more days compared to non-rapid cycling.

Seasonality is defined as seasonal changes having an elevated level of affecting the mood of an individual. The incidence of depression is considered to be higher during winter in patients who show a dysphoric response to stressful events and high levels of neuroticism (Osher et al. 2000). In the present study, the duration of AP and MS drugs was longer in patients who showed seasonal features, whereas the duration of AP drug use at the effective dose was longer in patients who did not show seasonal features. The adherence to treatment was better for patients who showed seasonal features. This observation may be associated with elevated neuroticism in these patients. The lower adherence to treatment in patients who did not show seasonal features may be the underlying reason for preferring high-dose AP drugs for disease management.

The dominant nature of psychotic features, mixed periods and rapid cycling negatively affect the response to lithium treatment. Lithium is the first choice for BD patients who do not have mood-incongruent psychotic symptoms and who do not have comorbidities, and continues to exist as the "gold standard" in BD treatment (Tondo et al. 2001). In the present study, the duration of all AP drug use was significantly longer in patients who had psychotic symptoms compared to the patients who did not have psychotic symptoms. The duration of combined AD drug use was longer in patients who did not have psychotic symptoms compared to the patients who had psychotic symptoms. There was no significant difference in MS drug use and adherence to treatment between the patients who had psychotic symptoms and patients who did not have psychotic symptoms. This observation may indicate that the presence of a psychotic symptom has no effect on the preference of MS drugs.

Patients who experience severe attacks frequently hospitalized, and do not have comorbid personality disorder diagnosis show better adherence to drug treatment.] Young adults and patients who perceive manic/hypomanic period better and are more sensitive to side effects show poorer adherence to the drug treatment. As a result of a two-year follow-up study, Markar and Mander (1989) reported that there was no difference in the hospitalization rates between patients who received lithium treatment and patients who did not. Gitlin et al. (1995) reported that recurrence was observed in a shorter period in patients who used a greater number of drugs at higher doses compared to patients who used fewer drugs at lower doses. According to the study by Goldberg et al. (1995), the general functionality levels of the patients who used only lithium were better compared to other patients. They were hospitalized less frequently, while the patients who used lithium in combination with AP drugs had a significantly worse outcome. This was interpreted as the protection provided by lithium treatment deemed successful in BD, and these patients may represent a BD subgroup with a good prognosis. According to a study carried out in Turkey, there is a correlation between the number of previous hospitalizations and MS drug use (Karaoğlan Kahiloğulları et al. 2008). According to the findings of the present study, patients who were hospitalized had a significantly longer duration of AP and MS drug use, had a higher incidence of seasonal features, had better adherence to treatment, and were usually hospitalized within the manic period.

LIMITATIONS

The patients included in this study consisted of patients with easy access to a tertiary healthcare facility and complied with regular polyclinic follow-ups. Thus, the study group may not fully reflect all BD patients in society. The study's retrospective design and the administration of the study at a single center are among the limitations of the present study. Therefore, it is appropriate to evaluate the results of the present study by considering these limitations. Considering the lack of a similar study regarding this topic and the guiding features of the study resulting in the clinical practice, we believe that the present study is valuable as a preliminary study.

CONCLUSION

The present study retrospectively evaluated the frequency and the duration of drug use in patients being monitored with BD and showed that the frequency and the duration of AP drugs increased in the long-term treatments. Bipolar disorder has been considered as a disorder that shows recovery at certain periods, in which functionality returns to normal levels. Despite strong recommendations for monotherapy for the treatment of all psychiatric disorders in the present treatment guidelines, the sole use of mood stabilizers for monitoring BD in the recovery periods is nothing more than a myth. However, the use of a combined drug approach (although not recommended) continues to exist as a common approach in the clinical practice. Therefore, considering these data, we believe that it is necessary to regulate the expectations regarding the disease definitions or the success of medicinal treatment.

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