A Comparison of Clinical Characteristics in Bipolar I Disorder and Antidepressant-Associated Mania/Hypomania

Nesrin Tomruk[1], Ömer Saatçioğlu[2], Rahşan Erim[3], Nihat Alpay[4]

[1]Clinic Ass't Chief., [2]Assoc. Prof Dr., [3]Spec. Dr., [4]Clinic Chief, Bakırköy Prof. Dr. Mazhar Osman Research and Training Hospital for Psychiatry, Neurology and Neurosurgery, Istanbul

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ÖZET

Bipolar I bozukluk ve antidepresana bağlı mani/hipomani klinik özelliklerinin karşılaştırılması

Amaç: Antidepresan tedavisi sırasında gelişen hipomani/mani klinisyenler tarafından sıklıkla gözden kaçırılmaktadır. Son gelişmelere göre, bipolarite, günümüzde geniş bir spektrum olarak kabul edilmektedir. Bipolar bozukluğu olan hastaların yaklaşık %40'ı yanlış tanı almakta ya da doğru tanı hastalığın daha ileri evrelerinde konulmaktadır. Antidepresan kullanımı ile ilişkili hipomani/mani için özgün tanı ölçütleri bulunmamaktadır. Bu hastalar bipolar spektruma dahil edilmemiştir. Bu çalışmada, bipolar I bozukluğun ve antidepresan kullanımına bağlı olarak ortaya çıkan mani/hipomaninin klinik özellikleri karşılaştırılarak farklı yönlerinin ortaya konması ve bipolar bozukluk içerisindeki yeri tartışılmıştır.

Yöntem: Bu çalışmaya, polikliniğe başvuran 84 ardışık hasta alınmıştır. Bu hastaların 40'ına antidepresan kullanımına bağlı hipomani/mani, 44'üne ise DSM-IV kriterlerine göre bipolar I tanısı konulmuştur. Tüm hastalara SCID-I ile sosyodemografik ve klinik özellikleri sorgulayan bir form uygulanmıştır.

Bulgular: Her iki gruptaki hastaların çoğu kadındı. Bipolar I grubunun akrabalarında majör depresyon oranı, antidepresan ile indüklenen mani/hipomani grubundakinden daha düşüktü. Antidepresanla ilişkili mani/hipomani, bipolar I grubu hastalarına göre, daha hafif şiddette bir bozukluk olarak saptandı.

Sonuç: Bulgularımız, antidepresan kullanımına bağlı gelişen mani/hipomaninin bipolar bozukluklar içinde ayrı bir alt grupta sınıflandırılması gerektiğini düşündürmektedir.

Anahtar kelimeler: Antidepresan, bipolar bozukluk, hipomani, mani

ABSTRACT

A comparison of clinical characteristics in bipolar I disorder and antidepressant-associated mania/hypomania

Objective: Although hypomania/mania during antidepressant treatment is not rare, it is often neglected by clinicians. As a result of the recent developments in this topic, bipolarity is now accepted as a wide spectrum. Forty percent of the patients with bipolar disorder have been misdiagnosed or diagnosed in later stages of illness. There are no specific diagnostic criteria for antidepressant-induced hypomania/mania. These patients have not been included in bipolar spectrum. In this study, we aimed to compare clinical features of BP I and antidepressant-induced hypomania/mania, and discussed bipolar spectrum disorders.

Method: In this study, 84 consecutive patients who referred to outpatient unit were selected. Forty of the patients were diagnosed as antidepressant-induced mania or hypomania, and 44 of them as BP I disorder according to DSM-IV criteria. All patients were given SCID-I and a data form which included sociodemographic characteristics and clinical features.

Results: The majority of the patients in both groups were female. The rate of major depression among the relatives of BP I group was significantly lower than antidepressant induced manic or hypomanic group. Antidepressant-associated mania or hypomania has been observed as a milder disorder compared to BP I.

Conclusions: Our results suggest that antidepressant-associated mania or hypomania should be categorized as a different subgroup in bipolar disorders.

Key words: Antidepressant, bipolar disorder, hypomania, mania

Address reprint requests to:
Dr. Ömer Saatcioğlu, Ataköy 9. Kısım, A5-A Blok, D:6 İstanbul - Türkiye

Phone: +90-532-416-2266

E-mail address:
osaatcioglu@yahoo.com

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INTRODUCTION

The first affective episodes of bipolar patients occur as a depressive period in 40 to 60% of patients. More than 40% of bipolar patients are first diagnosed with major depression (1). The high rate of misdiagnosis indicates that the prevalence of bipolar disorder may actually be higher and that many patients are followed up with the diagnosis of unipolar depression, instead of bipolar disorder (2). The frequency of hypomania

induced by antidepressant (AD) use in major depressive disorder was reported to be as high as in misdiagnosed bipolar patients (1,3).

Lewis and Winokur stated in 1982 (4), and Angst in 1985 (5,6), in two retrospective studies that mania arising from tricyclic antidepressant may affect the natural course of bipolar disorder. Thus, whether the hypomanic or manic switch related to antidepressants is a side effect related to antidepressant use or the determinant of bipolar course began to be disputed (3).

Howland determined, in an article published in 1996 about the emergence of a manic episode in 11 (6%) of 186 patients treated with selective serotonin reuptake inhibitors (SSRI), that hypomania or mania is encountered in the personal and/or family histories of these patients, but that bipolar disorder generally emerges after beginning of depression treatment. In the same study, he stated that the manic symptoms emerging with SSRI are of an intense type, and are likely to have psychotic features or to require supervision owing to the emerging agitation – but also respond completely to antimanic treatment (7).

No hypomanic switches were detected in 89% of large-scale studies (1). The rate of hypomanic switches related to antidepressants was considered to be as high as the rate of bipolar disorders mistakenly diagnosed as unipolar depression, and these patients actually had bipolar disorder. It was stated that this clinical picture is included under the heading of major depression in DSM-IV and that this situation must be re-evaluated in DSM-V (1).

With this study, we aim to compare the clinical features of Bipolar I (BPI) disorder and mania/hypomania emerging with antidepressants, set forth their different aspects, and contribute to discussions regarding the inclusion of the switch emerging with antidepressants within bipolar disorder.

METHOD

Patients who were referred to the Outpatient Treatment Unit of Bakırköy Prof. Dr. Mazhar Osman Research and Training Hospital for Psychiatry, Neurology and Neurosurgery, who had previously been diagnosed with mood disorder according to DM-IV diagnosis criteria, followed up with the diagnosis of "bipolar disorder-type I in remission" and previously diagnosed as "depression in remission" according to DSM-IV diagnosis criteria, who use antidepressants and who were diagnosed with manic/hypomanic switchswitch (8,9) according to Akiskal et al. during the treatment process, who were given information on and provided their consent to participation in the study were admitted to our study. A total of 84 patients were enrolled in the study: 40 manic/hypomanic switch patients and 44 bipolar disorder-type I patients. For the inclusion of patients with a history of manic/hypomanic switch switchrelated to antidepressant use, interviews were held with the patients and their relatives to ascertain that they had not had any previous hypomanic or manic episodes.

In our research of hypomanic responses to antidepressant drugs, those occurring within four to 12 weeks of the drug treatment were accepted as being of pharmacological origin (8). For this reason, eight patients were excluded from the study. Other exclusion criteria were comorbid psychiatric disorder , dementia considered to cause mood disorder, delirium, conditions with organic etiology such as other amnesic disorders, a history of epilepsy and seizures, head trauma and other neurological disorders including loss of consciousness, mental retardation, and the presence of alcohol and/or substance use. Patients who were informed about the study but declined to participate, and those below the age of 18 and over the age of 65, were excluded from the study.

First, SCID-I was administered to every patient and previous diagnoses in the follow-up process were verified. At least one control interview was held with patients included in the study after their initial admittance to the unit, to determine the course of treatment and to follow it up.

Tools

Patient Follow-up Form: This form includes the family history of illness, trauma history, information on the first episode (type and intensity of episode,

causative incident, presence of psychotic symptoms, recovery), based on the socio-demographic data and clinical features (10).

Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I): A clinical interview scale developed and structured for diagnosing Major DSM-IV Axis I diagnoses (11). A structured clinical interview was developed to increase the reliability of the diagnosis by ensuring administration of the diagnostic evaluation in a measurable manner; to increase the validity of the diagnosis by facilitating the tracking of DSM-IV diagnosis criteria; and to ensure systematic research of the symptoms. Adaption and reliability studies of SCID for Turkey were conducted by Çorapçıoğlu et al. in 1999 (12).

Statistical method

The statistical analyses in this study were made with the SPSS 11.5 program. In the statistical evaluations, the t-test was administered in independent groups in cases where parametric test assumptions were made. Before the double-edged t-test was administered, the F-test was used to determine whether the two groups were homogenous with regard to average points and whether their variances were equal. In cases where the F-test was significant, we decided that there was a significant difference between the variances of the two groups and administered the t-test with the "separate variance" calculation. Chi-square was applied in non-parametric values. In four-eye patterns, if there was an observed frequency of less than five, the Yates correction was carried out.

FINDINGS

Socio-demographic Characteristics

The average age of patients with BP I disorder (n=44) included in the study was 37.23±9.85, and 36.59±10.91 for those with a switchswitch related to antidepressant use (n=32). No statistically significant difference was detected between the two groups (t=2.65, sd=74, p=0.79). Of the patients with BP I disorder included in the study, 70% (n=31) were female and 30% (n=13) were male. Of those with a switch related to antidepressant use, 72% (n=23) were female and 28% (n=9) were male. No statistically significant difference with regard to gender distribution was detected between the two groups (χ^2=0.018, sd=1, p=0.08). Of the patients with BP I disorder (n=44), 43% (n=19) were single, 45% (n=20) were married, 2% (n=1) were divorced, and 9% (n=4) were widowed. Of patients with a switch related to antidepressant use (n=32), 18% (n=6) were single, 65% (n=21) were married, 3% (n=1) were divorced, 6% (n=2) were widowed, and 6% (n=2) lived separately from his or her spouse. No statistically significant difference was detected between the two groups (χ^2 =7.750, sd=4, p=0.101).

History of Psychiatric Disease in Family

In patients with BP I disorder, there was no history of psychiatric disease in the family in 56.8% (n=25) of patients, while there was a history of psychiatric disease in the family in 43.2% (n=19) of patients. Of patients with a switch related to antidepressant use (n=32), there was no history of psychiatric disease in the family in 43.8% (n=14) of patients, and there was a history of psychiatric disease in the family in 56.2% (n=18) of patients. No statistically significant difference was detected between the two groups (χ^2=1.27 sd=1, p=0.26). When examining the breakdown of psychiatric diseases present in the patient's family, for patients with BP I disorder the diagnosis of 15.8% (n=3) of psychiatric diseases in the family was unknown, 42.1% (n=8) had bipolar disorder, 5.3% (n=1) had a diagnosis of major depression, 26.3% (n=5) had a psychotic disorder, 5.3% (n=1) had anxiety disorder, and 5.3% (n=1) had alcohol and/or substance abuse/dependency. For patients in the group with a switch related to antidepressant use, the diagnosis of psychiatric disease in the patient's family of 11.1% (n=2) was unknown, 38.9% (n=7) had a diagnosis of bipolar disorder in his or her family history, 38.9% (n=7) had major depression, 5.3% (n=1) had anxiety disorder, and 5.3% (n=1) had alcohol and/or substance abuse/dependency. No history of psychotic disorder was detected in this group. No statistically

Table 1: Comparison of some clinical variables between groups

		DIAGNOSIS				
		BP I	Mania/hypomania related to antidepressant use			
		n (%)	n (%)	χ2	sd	p
Psychiatric disease in family history	Absent	25 (56.8)	14 (43.8)	1.27	1	0.26
	Present	19 (43.2)	18 (56.2)			
	Unknown	3 (15.7)	2 (11.2)			
Diagnosis of psychiatric disease in family history	Bipolar disorder	8 (42.1)	7 (38.9)	9.75	5	0.08
	Major depression	1 (5.3)	7 (38.9)			
	Psychotic disorder	5 (26.3)	0			
	Anxiety disorder	1 (5.3)	1 (5.5)			
	Alcohol and substance use	1 (5.3)	1 (5.5)			
Accompanying disease	Absent	33 (75)	27 (84.3)	0.98	1	0.32
	Medical disease	11 (25)	5 (15.7)			
Trauma	Absent	36 (81.8)	25 (78.1)	0.16	1	0.69
	Present	8 (11.2)	7 (21.9)			
Type of trauma	Sexual	-	1 (14.2)	1.36	2	0.51
	Physical	6 (75)	5 (71.6)			
	Both	2 (25)	1 (14.2)			
Life incident	Absent	17 (38.6)	5 (15.6)	4.77	2	0.092
	Present	26 (59.2)	26 (81.2)			
	Insufficient information	1 (2.2)	1 (3.2)			
Intensity	Mild	1 (2.2)	3 (9.4)	27.56	2	<0.001
	Moderate	8 (18.2)	23 (71.8)			
	Severe	35 (80.6)	6 (18.8)			
	None	0	14 (43.8)			
Recovery with drugs	By itself	2 (4.1)	1 (3.1)	45.95	4	<0.001
	With antipsychotic	2 (4.1)	0			
	With antidepressant	4 (9.1)	13 (40.6)			
	Antipsychotic+Mood regulator	36 (82.7	4 (12.5)			

significant difference was detected between the two groups (χ^2=9.75, sd=5, p=0.08) (Table 1).

Comorbidities

Evaluated in terms of accompanying disease, 75% (n=33) of the group with BP I disorder had no additional medical condition and 25%% (n=11) had an additional medical condition. In the group with a switch related to antidepressant use, 84.4%% (n=27) had no additional medical disease, while 15.6%% (n=5) had one. No statistically significant difference was detected between the two groups (χ^2=0.98, sd=1, p=0.32) (Table 1).

Trauma and Its Type

When a comparison is made in terms of trauma, no trauma was detected in 81.8 %% (n=36) of patients with BP I disorder, while 18.2 %% (n=8) had a history of trauma. Of those with trauma history, 75% (n=6) had physical trauma and 25% (n=2) had both physical and sexual trauma. Of patients with a switch related to antidepressant use, no trauma was detected in 78.1%% of patients, while sexual (14.3%, n=1), physical (71.4%, n=5), and sexual and physical (14.3 %%, n=1) trauma was detected in 21.9 % (n=7). The presence of trauma among both groups (χ^2=0.16, sd=1, p=0.69) and type of the trauma (χ^2=1.36, sd=2, p=0.51) was not statistically significant different (Table 1).

Characteristics During Onset of the Disorder

Life Incident

When the two groups are evaluated with regard to the presence of a simultaneous life incident during

the emergence of the disease, of the patients with BP I disease (n=44), 39% (n=17) had no simultaneous life incident during the emergence of the disease, while a simultaneous life incident was detected in 60% (n=26) and 2% (n=1) did not give sufficient information in this respect. Of patients with a switch related to antidepressant use, no simultaneous life incident was seen during the emergence of the disease in 15% (n=5), while 81% (n=26) had a simultaneous life incident, and 3% (n=1) did not give sufficient information in this respect. No statistically significant difference was detected between the two groups (χ^2=4.770, sd=2, p=0.092) (Table 1).

Intensity

When the two groups were evaluated with regard to intensity of the first episode, in the group with BP I disorder (n=44) the first episode was evaluated as "mild" in 2% (n=1), "moderate" in 18% (n=8) and "severe" in 80% of patients. In patients with a switch related to antidepressant use, the first episodes were evaluated as "mild" in 9% (n=3), "moderate" in 72% (n=23), and "severe" in 18% (n=6) of cases. A statistically significant difference was detected between the two groups (χ^2=27.563, sd=2, p=0.001) (Table 1).

Recovery according to drug type

In the first episode, when treatment ensuring patient recovery were evaluated, 4% (n=2) of patients in the group with BP I disorder recovered by themselves, 4% (n=2) by using antipsychotics, 9% (n=4) by using antidepressants, and 82% (n=36) with combined treatment. Among patients with a switch related to antidepressant use, 44% (n=14) were not able to recover, 3% (n=1) recovered by themselves, 41% (n=13) by using antidepressants, and 12.5% (n=4) by using antipsychotic+mood stabilizers. A statistically significant difference was detected between the two groups (χ^2=36.047, sd=2, p=0.001) (Table 1).

DISCUSSION

In our research, no statistically significant difference with regard to gender distribution was found between patients groups with BP I disorder or a switch related to antidepressant use. The ratio of females was higher in both groups. However, bipolar disorder is reported to be encountered equally in males and females (13). And while the ratio of males is reported to be higher among patients with a switch related to antidepressant in some studies, others report the ratio of females to be higher (3,15).

When both groups are evaluated with regard to age, the average age of patients with BP I disorder and those with a switch related to antidepressant use is close. In the study by Akiskal et al., the average age during bipolar transition (from depression to mania) was 32.3 (8). In a study conducted by Wada et al. on the manic/ hypomanic switch development during treatment of acute unipolar depression with antidepressants, the average age of the group with a switch was 48.8±12.3 (between 26 and 78 years old) (14). Akiskal et al. found in a study comparing spontaneous hypomania and mania developing with antidepressant that the average age of those developing mania with antidepressants was lower (16).

When patients are compared in terms of their clinical features, even though there is a higher rate of a family history of psychiatric disease in those with a switch related to antidepressant use, no significant difference was found between the two groups. This situation is similar to findings among the patient group included in the study by Akiskal et al. (16). In a study conducted by the American Mental Health Institute on mood disorders, the prevalence of bipolar or unipolar disorders was determined as 25 % in relatives of individuals with bipolar disease and 20 % in relatives of individuals with unipolar disease, which was three times more than the normal distribution. Therefore, an increase in the psychiatric disease ratio in the families of patients is an expected situation and the findings can be considered to conform with the literature (17).

When the distribution of family history of psychiatric disorders examined (first degree relatives), the rate of bipolar disorder was high in both groups. This rate is higher in those with a switch related to antidepressant use. Some family studies support the theory that

bipolar and unipolar probands in family history can exhibit moderate and severe forms of the disease. In a three-year prospective study including children or siblings of 68 bipolar patients, bipolarity symptoms were observed in more than half of these children. Family factors can be significant in differentiating high disposition for spontaneous mania or mania related to antidepressant use (18).

Moreover, major depression was detected distinctly more often in the family histories of patients with a switch related to antidepressant use. This is in line with the study in which Blacker et al. evaluated bipolar proband against unipolar proband for unipolar-bipolar depression and showed that bipolar patients had a higher rate of subthreshold bipolar disorder history compared to depression. It is probable therefore that clinical pictures developing with subthreshold bipolar symptoms and diagnosed as major depression may have been encountered in the immediate families of these patients as well (18,19).

With regard to trauma, patients with BP I disorder were not different from patients with a switch related to antidepressant use. In both groups, the majority of patients had no history of trauma. Among those with a history of trauma, the fact that there was physical trauma in both groups was remarkable. In our research, the fact that trauma history was based on information obtained from the person was an important constraint. The unavailability of a source similar to our research regarding trauma made it impossible for us to make a comparison to other studies.

The presence of a simultaneous life incident during the emergence of the disease was high in both groups. Even though genetic and biological infrastructure is essential in emergence of the disease, some studies revealed that psychosocial stressors play a triggering role in the timing of the disease (13). Our data also tends to support these studies, for both groups. But the fact that no significant difference was found between the two groups is in line with the comparison (16) made by Akiskal et al.

In our study, the course determinants included in DMS-IV were used to predicting the episodes in terms of severity. When the two groups are evaluated in terms of severity of the first episode, the first episode was evaluated as 80% severe in patients with BP I disorder, while the first episode of patients with a switch related to antidepressant use was evaluated as 72% moderate severity. Our data related to intensity complies with the study in which Stoll et al. (15) compared spontaneous mania and mania related to antidepressant use. Goldberg et al. compared patients with a switch related to antidepressant use with spontaneous mania patients and found that the first episode is of moderate severity in the group with a switch related to antidepressant use (18).

When the two groups were evaluated about recovery according to drug type, recovery in the group with BP I disorder generally occurred following treatment that included both mood stabilizer and antipsychotic treatment, while in patients with a switch related to antidepressant use, given that the first episode is depression, antidepressant treatment is the treatment enabling recovery, as expected. Moreover, 44% of patients with a switch related to antidepressant use were not able to recover after the first episode. This result supports the view that the antidepressant treatment administered during the episode due to a misdiagnosis of depression can be related to the development of hypomanic/manic switch (14-16,20).

Important constraints on our study include in particular a lack of comparison with a control group, lack of tracking findings, limited number of cases, which is important for clinical features, and the fact that the diagnosis criteria for a switch related to antidepressant use are still controversial.

In this study, when the clinical features of a switch related to antidepressant use were evaluated, they were observed to exhibit different features than BP I disorder. Our opinion is that the switch related to antidepressant use must be classified under the diagnosis "mood disorder caused by substance use" in DSM-IV and ICD 10 and be included under a different sub-group within bipolar disorder, considering the nature and development features of the switch. Prospective, comparative, follow-up based studies to be conducted in this field will provide more information.

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