Clinical characteristics of antidepressant use and related manic switch in bipolar disorder

Tonguc D. Berkol, MD, Yasin H. Balcioglu, MD, Simge S. Kirlioglu, MD, Zengibar Ozarslan, MD, Serkan Islam, MD, Ilker Ozyildirim, MD.

ABSTRACT

الأهداف: دراسة العلاقة بين الخصائص السريرية والعلاج ومضادات الاكتئاب (AD) التي يسببها تبديل الهوس في اضطراب ثنائي القطب (BD).

الطريقة: أجريت هذه الدراسة المستعرضة في عام 2016م. تم تسجيل ما مجموعه 238 مريضًا BD تم متابعتهم لمدة 6 أشهر على الأقل في العيادة الخارجية بمستشفى هاسيكي للتدريب والبحوث في اسطنبول، تركيا. طبقنا نموذج البيانات شبه المنظمة، ومخطط المزاج، والتقييم المعين لجميع المرضى. تم استعراض ملفات المرضى بأثر رجعي وتمت مقارنة المرضى الذين يستخدمون AD في مجموعات AD–m) AD–mone) و AD–c)، ثم قسمت إلى مجموعتين فرعيتين وفقاً لوجود/غياب مبدل الهوس تحت علاج AD.

النتائج: واجه 58 (47.15%) من أصل 123 المرضى الذين تلقوا ADs على التحول الهوسي تحت العلاج مرة واحدة على الأقل. كان معدل التحول الهوسي لدى مرضى AD-m أعلى بكثير من مجموعة AD-c. ارتبط استخدام AD أكثر من 12 شهرا سلبياً مع حدوث التحول الهوسي بشكل مستقل عن العلاج الوحيد أو المشترك.

الخاتمة: تقترح دراستنا أن خطر التحول الهوسي بارز بشكل خاص في الأشهر الأولى من الاستخدام. مضادات الاكتئاب التي تستخدم في دمجها مع مثبتات المزاج (MS) قد لا تكون كافية في منع التبديل بمصطلحات أقصر. ومع ذلك، في الاستخدامات على المدى الأطول، قد تؤدي إضافة MS إلى AD إلى تقليل مخاطر التبديل.

Objectives: To examine the association between clinical and treatment characteristics and antidepressants (AD)-induced manic switch in bipolar disorder (BD).

Methods: Total of 238 euthymic BD patients, who had been followed-up for at least 6 months at the outpatient clinic of Haseki Training and Research Hospital in istanbul, Turkey, were enrolled in this cross-sectional study in 2016. Semi-structured data form, the mood chart, and the mirror-designated assessment were applied to all subjects. The files of the patients were retrospectively reviewed and the patients using ADs were compared as AD-monotherapy (AD-m) and AD-combination (AD-c) groups, then divided into 2 subgroups according to the presence/absence of manic switch under AD treatment.

Results: Fifty eight (47.15%) patients out of 123 who received ADs at least once had experienced a manic switch under AD treatment. The rate of manic switch in AD-m patients was significantly higher than the AD-c group. Independent from being monotherapy or combined treatment, AD use longer than 12 months was negatively associated with the occurrence of manic switch.

Conclusion: Our study suggests that the risk of manic switch is especially prominent in the first months of AD use. Antidepressants use in combining it with a mood stabilizers (MS) may not be adequate in preventing switches in shorter terms. However, in longer term uses addition of MS to ADs may decrease the risk of switches.

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From the Department of Psychiatry (Berkol, Balcioglu, Kirlioglu), Bakirkoy Prof. Mazhar Osman Training and Research Hospital for Psychiatry, Neurology, and Neurosurgery, from the Psychiatry Unit (Ozarslan), Arnavutkoy State Hospital, from the Department of Psychiatry (Islam), Haseki Training and Research Hospital, and from the Department of Psychiatry (Ozyildirim), Oteki Psychoterapy Center, Istanbul, Turkey.

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Address correspondence and reprint request to: Dr. Simge S. Kirlioglu, Department of Psychiatry, Bakirkoy Prof. Mazhar Osman Training and Research Hospital for Psychiatry, Neurology, and Neurosurgery, Istanbul, Turkey. E-mail: simgekirlioglu@gmail.com
ORICID ID: orcid.org/0000-0001-9778-6617

Patients with bipolar disorder (BD) are found to live nearly half of their lives with depressive symptoms according to naturalistic observational research onto the illness course. Despite the occurrence of manic or hypomanic episodes, it is the hallmark defining the disorder, the predominance of depressive episodes over manic symptoms causes much of the significant morbidity, more serious harm on social function, and higher burden in BD.[1] Nevertheless, treatment of bipolar depression has much less evident data and is far less optimized in clinical routine compared to the management of mania/hypomania. Although quetiapine and fluoxetine-olanzapine combination (OFC) are the 2 approved treatment options in bipolar depression, antidepressants (AD) have long been a focus of interest to challenge depressive episodes of BD.[2] However, their efficacy and safety profile in BD is the subject of a long-standing dispute based on a scientific literature.[3] Thus, the academicians endeavor to develop practice guidelines in light of relatively broad consensus.[3,4] Accordingly, AD, as both combination or monotherapy, are not recommended for bipolar depression unless the depressive episode is very severe and has a poor response to MS, or antipsychotics (AP) monotherapy is shown.[5,6] Despite the discourage from current treatment guidelines, ADs constitute 50% of all prescribed psychotropic agents in BD, and the long-term AD use is seen as high as 40% of all bipolar patients in the maintenance phase of the community health settings.[6-8] Besides, the cardinal concern with the use of AD in the treatment of bipolar depression is that it may induce a switch to hypomania/mania. The recommendations above have hardly been supported by the relevant literature. Therefore, there is a need for further comprehensive research on the topic to elucidate clinical features and outcomes related to AD use in BD. Our aim in this study was to examine the frequency of AD use in BD, and assess the association between clinical and treatment characteristics, such as types of BD, presence of adjunctive treatment, AD types, AD treatment duration, and occurrence of mood switch in bipolar patients with a view to contributing evidence for a better understanding of the AD-related mood switch in BD. In light of the previous findings of relevant studies, we have addressed 2 major hypotheses that; 1) manic switches in BD would be closely linked to AD-monotherapy; 2) shorter use of ADs is associated with the higher occurrence of manic switch.

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Methods. ***Study participants.*** This cross-sectional study was conducted in a total of 238 patients who met the diagnostic and statistical manual of mental disorders-Fifth Edition (DSM-5) criteria for BD and who had been followed-up for at least 6 months at the psychiatric outpatient clinic of Haseki Training and Research Hospital in Istanbul, Turkey in 2016.[9] All the outpatients were in euthymic phase in their current follow-up visit. Diagnosis of schizophrenia spectrum and other psychotic disorders, intellectual disability, dementia or other organic mental disorders, and neurological disorders were defined as exclusion criteria. The study was approved by the Local Ethics Committee, and written informed consents were obtained from all of the participants.

Study procedure. Semi-structured sociodemographic, clinical and medication data form. The form included demographic variables and also covered information regarding clinical features including BD type, illness duration, presence of manic switch, treatment characteristics and duration, presence of AD use and, subtype of the AD. The files of the patients were retrospectively reviewed and the data forms were filled according to the related information. Minimum one week of AD use was considered in the evaluation of AD use. The patients who used ADs were separated into 2 groups as AD-monotherapy (AD-m) and AD-combination (to MS/AP)(AD-c) to compare the medication features and, in particular, the presence of manic/hypomanic switch between these groups. Patients who experienced mood switch during AD use were compared with those who did not experience switch in order to examine the association between the presence of a mood switch and AD medication dosage and duration. Dose equivalent of antidepressants were levelled to fluoxetine 20 mg for the comparison of mean AD doses (fluoxetine 20 mg, sertraline 50 mg, paroxetine 20 mg, citalopram 20 mg, fluvoxamine 100 mg, escitalopram 10 mg, clomipramine 100 mg, amitriptyline 100 mg, venlafaxine 75 mg or mirtazapine 30 mg.[10]

The mood chart. This instrument is a graphic reflection of the illness course from the first mood episode of BD to date, which helps to monitor and respond to daily, monthly and annual mood fluctuations, manage medication adverse effects, and maintain an appropriate treatment strategy. It also allows identifying early mood

switches that may serve as precursors to episodes.[11] Types, duration, severity, psychotic features of episodes, psychiatric hospitalizations, suicide attempts, important life events, treatment modalities, duration of treatment, dosages and blood drug levels were summarized in the chart.

Mirror-designated assessment. This method was used to evaluate response characteristics to the maintenance treatment of the patients.[12] The mirroring which is an unstructured self-report provided subjective additional information about the state of remission besides rating scale scores. The point that protective treatment commenced was accepted as a 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 whose several preventive treatment periods were studied, prevention period of patients were compared to similar run-in period before treatment.

Statistical analysis. In this study, the statistical analyses were conducted using IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp. The variables in the present study were examined with the Kolmogorov-Smirnov's test of normality. In addition to the descriptive statistical methods (average, standard deviation) used in the assessment of the data, the Kruskal-Wallis Mann-Whitney-U test was used to analyze non-parametric and independent t-test was used to analyze parametric data. Comparison of qualitative data was carried out using chi-square test, and Fisher's exact test, along with descriptive statistical methods for data evaluation. Results were assessed at significance $p<0.05$ level.

Results. ***Demographic and clinical features.*** Out of 238 patients, 221 had BD type I (92,86%), and 17 had BD type II (7,14%). Patients who had used ADs did not statistically differ from patients who had never used ADs in terms of gender, education, marital status, BD subtype, and age at onset of disease. The duration of illness was longer in patients who had used ADs in comparison with those who had never used ADs ($p=0.026$). Demographic and clinical variables are listed in **Table 1**.

Characteristics of AD use and treatment-induced manic switch. Fifty one point sixty eight percent (n=123) of all patients had used AD medication at least once in their lives. Among 123 patients, in 38,13% (n=47) AD use were as monotherapy, in 61,87% (n=76) were in combination. The duration of illness was significantly longer in the AD-c group ($p=0.006$). Antidepressants-type significantly differed between AD-m and AD-c groups (Fisher's exact test; chi-square Z=19.260, $p<0.001$). There was no significant difference between the groups in terms of mean AD equivalent doses (22,68 vs. 22,12 mg fluoxetine equivalent; $p=0.776$). Mean duration of AD use was significantly longer in the AD-c group in comparison with the AD-m group ($p=0.002$) (**Table 2**).

Fifty eight (47.15%) patients out of 123 who received ADs at least once had experienced a manic switch under AD treatment. The risk of manic switch in AD-m patients was significantly higher than the AD-c patients ($p=0.006$). The mean duration of AD use in patients with manic switch (5.65 months) was significantly shorter than those without a switch (13.12 months) ($p=0.004$). Independent from being monotherapy or combined treatment, AD use longer than 12 months was negatively associated with the occurrence of manic switch ($p=0.006$). The ratio of patients using ADs no more than 3 months is higher in patients with a history of manic switch compared to the patients who have not experienced switch (Z=3.298, $p<0.001$) (**Table 3**). When the patients were divided into 2 groups regarding duration of use either shorter or longer than 6 months and compared, manic switch rate showed an insignificant trend towards being higher in the group with duration of use shorter than 6 months (45,5% in <6 months vs. 22,7% <6 months) (**Table 4**).

Discussion. Antidepressants use in BD patients is seen in clinical practice in a widespread manner, while available trials providing conclusive evidence for this phenomenon is scarce.[13] In the present study, the rate of AD use at least once in bipolar patients was 51.68%, while ADs are reported to be in clinical use in 14-74% of the patients with BD.[7,14,15] Despite our patients were recruited from an academic mental health setting, our institution is also providing community mental health services, so our finding is congruent with the rates previously reported in community mental health facilities.[8]

Clinical studies regarding AD efficacy in bipolar patients are far to provide adequate support for the benefits of AD monotherapy in bipolar depression.[3,16,17] In the short-term management of bipolar depression, OFC was found more effective than olanzapine or placebo in improving depression scale scores.[18] Regarding prevention of new depressive episodes, a recent meta-analysis showed a higher efficacy of AD monotherapy and AD+MS combination compared to placebo.[6] In our study, 38.13% of the patients were

Table 1 - Comparison of patients using ADs with those not using ADs.

Variables	Using ADs (n=123)	Not using ADs (n=115)	Z/χ^2	*P*-value
	n (%)			
Gender				
Female	84 (68.29)	74 (64.35)	0.257[a]	0.613
Male	39 (31.71)	41 (35.65)		
[+]***Education***				
Primary	25 (20.33)	21 (18.26)	2.486[a]	0.500
High school	40 (32.52)	48 (41.74)		
College	54 (43.90)	44 (38.26)		
None	4 (3.25)	2 (1.74)		
[++]***Marital status***				
Married	48 (39.02)	55 (47.83)	4.303[a]	0.116
Single	51 (41.46)	48 (41.74)		
Divorced	24 (19.51)	12 (10.43)		
Diagnosis				
Bipolar I	111 (90.24)	110 (95.65)	1.869[a]	0.171
Bipolar II	12 (9.76)	5 (4.35)		
[+++]Age (SD)	42.98 (11.8)	39.17 (13.2)	2.308[b]	0.021*
[+++]Age at onset of illness (SD)	24.1 (8.0)	23.1 (8.7)	0.353[b]	0.724
[+++]Duration of illness (SD)	18.46 (9.8)	15.8 (8.5)	2.226[b]	0.026*

AD - antidepressants, NS - not significant (p>0.05), SD - standard deviation. Chi Square with Yates Correction, [+]Fisher Exact Chi Square,[++]Chi Square, [+++]Mann Whitney U Test, [a]X^2 value, [b]Z value. *p<0.05 - statistically significant

Table 2 - Comparison of the treatment characteristics between AD-m and AD-c groups.

Treatment characteristics	AD-m	AD-c	$t/Z/\chi^2$	*P*-value
	n (%)			
Patients (n)	47/238 (19.74)	76/238 (31.93)		
Manic switch				
Present	30 (63.82)	28 (36.84)	7.440 [a]	0.006
Absent	17 (36.18)	48 (63.16)		
[+]***AD-type***				
SSRI	29 (61.7)	48 (63.16)	19.260 [a]	<0.001*
TCA	15 (31.9)	5 (6.58)		
Venlafaxine	0 (0)	6 (7.89)		
Mirtazapine	3 (6.4)	17 (22.37)		
Combined agent				
Lithium		56 (73.7)		
AC	-	16 (21.1)	-	-
AP		4 (5.2)		
Mean dose (SD), (mg)				
[++++]SSRI	20.98 (5.3)	22.87 (9.87)	1.208 [b]	0.229
[+++]TCA	118.76 (78,65)	116.55 (96.76)	1.221[c]	0.889
Venlafaxine	-	93.7 (37.5)		-
[+++]Mirtazapine	42.76 (12.65)	38.17 (14.76)	1.522[c]	0.064
[++++]MED	22.68 (10.87)	22.12 (10.43)	0.284[b]	0.776
[++++]Age (SD)	40.29 (11.98)	42.56 (12.39)	0.999[b]	0.319
[+++]Age at onset of disease (SD)	25.13 (7.93)	24.85 (7.9)	0.998[c]	0.841
[+++]Duration of disease (SD)	14.99 (8.15)	19.87 (10.76)	2.512[c]	0.006*
Mean duration (months)	5.43 (6.79)	12.65 (15.43)	3.090[c]	0.002*

Chi Square, Chi Square with Yates Correction, [+]Fisher Exact Chi Square,[++]Chi Square, [+++]Mann Whitney U test, [++++]Student t Test, a Chi Square, [b]t value, [c]Z value. AD - antidepressant, SSRI - selective serotonin reuptake inhibitors, TCA - tricyclic antidepressants, AC - anticonvulsant, AP - antipsychotic, MED - mean equivalent dose, NS - not Significant (p>0.05). *p<0.05 statistically significant

Table 3 - Comparison of the patients with and without manic switch.

Treatment characteristics	Manic switch present (n=58)	Manic switch absent (n=65)	t/Z/χ^2	*P*-value
	n (%)			
[+]*AD-type*				
SSRI	33 (42.85)	44 (57.15)	3.642[a]	0.314
TCA	8 (40.00)	12 (60.00)		
Venlafaxine	2 (33.33)	4 (66.67)		
Mirtazapine	4 (20.0)	16 (80.00)		
Duration of AD use				
≤3 months	9 (100)	0 (0)	12.083[a]	0.006*
3-6 months	17 (44.7)	21 (55.3)		
6-12 months	13 (46.4)	15 (53.6)		
>12 months	19 (39.6)	29 (60.4)		
[+]*Combined agent*				
Lithium	21 (37.5)	35 (62.5)	2.422[a]	0.302
AC	4 (25.0)	12 (75.0)		
AP	0 (0)	4 (100)		
Diagnosis				
Bipolar I	47 (42.35)	64 (57.65)	0.002[a]	0.964
Bipolar II	5 (41.66)	7 (58.34)		
Mean dose (SD), (mg)				
[++++]SSRI	22.98 (9.4)	21.73 (8.76)	0.600[b]	0.550
[+++]TCA	103 (97.99)	118 (103)	0.439[c]	0.330
[+++]Venlafaxine	75 (-)	100 (43)	1.095[c]	0.273
[+++]Mirtazapine	32.86 (6.88)	30.22 (18.76)	0.276[c]	0.782
[++++]MED	22.68 (9)	22.12 (12)	0.290[b]	0.772
Mean duration (months)	5.65 (6.34)	13.12 (14.36)	2.878[c]	0.004*

Chi Square, Chi Square with Yates Correction, [+]Fisher Exact Chi Square,[++]Chi Square, [+++]Mann Whitney U test, [++++]Student t Test, [a]X^2 value, [b]t value, [c]Z value, AD - antidepressant, SSRI - selective serotonin reuptake inhibitors, TCA - tricyclic antidepressants, AC - anticonvulsant, AP - antipsychotic, MED - mean equivalent dose, NS - not Significant (p>0.05), *p<0.05 statistically significant.

Table 4 - The relationship between the durations of AD treatment and manic switch.

Duration of use	Manic switch present (n=58)	χ^2	*P*-value
	n (%)		
<6 months	26 (44.8)	4.379	0.112
6-12 months	13 (22.4)		
>12 months	19 (32.8)		

Chi Square, AD - antidepressant

using AD monotherapy. As we considered lifelong AD use, patients who experienced a depressive first episode may have AD without additional medications before a diagnosis of BD was reached. This factor may contribute to a trend towards an increased rate of AD use without additional drugs in comparison to the above mentioned studies.

Antidepressant-induced mood switch is the main concern for AD use in bipolar patients. The previous study has strongly suggested that AD monotherapy is related with acute manic episodes.[19] There is a controversial evidence whether concurrent MS treatment has a protective effect on mood switching; however, AD monotherapy has a higher risk of new mood elevation compared to MS monotherapy.[6,20,21] Among MS, lithium is the most common preventive monotherapy option in BD and has the strongest effect on the prevention of mood switch during the use of ADs.[22,23] However, in the present study, lithium or other MS use combined with the AD was not found effective on the emergence of manic switch. Manic switch was not observed in any of the 3 patients using AD+AP combination. At this point, MS are not adequately preventive against switches associated with AD, especially in the first month. However, if MS decrease manic recurrences during the natural course of BD, it is still not clear to what extent they decrease switches that may be associated with ADs. Liu et al,[6] suggested no significant difference between AD using bipolar patients (AD-m/AD-c) and placebo in inducing manic/hypomanic episodes with a pooled relative risk of 1.21. In our study, manic switch was observed in 47.15% in patients with AD use. In an evaluation, it was reported that rates of switch with AD use may be found lower in randomized-controlled studies due to selection of a special patient group (exclusion of

concomitant diagnosis which is known to increase the risk of manic switch with AD use) while naturalistic studies depending on clinical sampling may find higher rates.[24] In this respect, our findings from a naturalistic sample on manic switch are similar to others in the literature.

It is recommended to terminate the AD treatment in 3-6 months after full remission of bipolar depression due to increased risk of mood switch and cycle acceleration.[4,25] In contrast, some studies reported that depressive recurrences occurred sooner following the earlier termination of AD medication.[26] We determined that AD use longer than 12 months was negatively associated with the manic switch independent of being monotherapy or combined treatment. The main explanation in this discrepancy may be that manic switches related to early AD initiation period in patients with unipolar depression.[27] In this case, manic switches related to early AD use may not be considered as a part of the natural course of the illness and may be accepted as caused by ADs. Manic switches related to AD use were pointed out to be associated with the medication if it is seen in the first 2 months of use, after which time switches could hardly be associated with AD use.[15] This approach seems to be in concordance with the findings we discussed above. However, the duration of the occurrence of a manic switch that may be associated with AD use can be increased up to 6 months.[27] It is advised that maintenance treatment with the adjunct AD may be considered if a patient relapses into a depressive episode after stopping AD treatment.[3] One-year depressive recurrence risk was higher in use shorter than that of 6 months, while there was no significant difference between these groups regarding manic recurrence risk.[25] Eventually, it was determined that mood switches tend to occur particularly in the first 6 months of the AD treatment in BD. Therefore, resuming AD treatment after 6 months is relatively safe and effective for the prevention of depressive recurrences if there is no previous history of AD-induced mood switch. In our study, the duration of AD use was found to be significantly shorter in patients with a manic switch compared to those without manic switch, which is a natural reflection of discontinuation of ADs in the manic switch occurrence.

In our study, the most frequently used AD group is the SSRIs (sertraline among SSRIs). This is in accordance with those reported in the literature.[28] In choosing AD, SSRIs or monoamine oxidase inhibitors rather than TCAs are favoured because a risk ratio of 2.92 was found for TCAs compared to other ADs in inducing mania.[29] The second most frequently used drug is TCAs (frequently clomipramine) in patients taking AD monotherapy and mirtazapine taking AD as adjunction. Recent studies reported venlafaxine is more frequently associated with manic switches in comparison with bupropion and sertraline.[3,30] In a review, switch rates of 15-27% with SSRIs, 40% with TCAs and approximately 20% with new generation antidepressants were reported.[15] Our findings are in accordance with the findings of this review, except for higher switch rates associated with SSRIs (44,1%). The switch rates may be lower in this study due to AD+MS combination that was used by most of the patients.[31] A lower rate of the manic switch was observed in AD-c group compared to AD-m group. According to our findings, AD+MS use in bipolar patients may be important in preventing manic switches.

Before concluding, there is a need to mention some of the limitations of this study. The cross-sectional study design with a retrospective file review may be considered as a major limitation for this study. Another limitation is the absence of a control group that could shed light for evaluating whether manic switch during AD use is due to AD use itself or is a part of the natural course of the disease, which is shared in many other studies on this issue. In addition, depressive recurrences were not evaluated in our study. Assessment of depressive episodes would guide us to interpret our results more accurately to define the natural course of the disorder. Many studies evaluating AD use in bipolar patients consider limited periods of time while assessment of longer periods is more important. Long-term follow-up studies including a large sample of patients are required; nevertheless, such studies are hard to complete in practice. As an alternative, studies may be carried out with retrospective evaluations obtained by patient interviews as we have carried out. Although all of the subjects were in euthymic phase, duration of remission criteria was not included in the study. This limitation is a result that in many studies a standard duration have not been defined to be regarded remission. Mirror-designated assessment has been frequently used in studies of patients with bipolar disorder; however, its subjective nature may be criticised for leading confounding results.

In conclusion, our study has shown that approximately half of the patients with BD use AD in at least one period of their lives, and nearly half of them experience manic switches. The risk of a switch is especially prominent in the first month of AD use, and AD use with MS may not be adequate in preventing

switches in shorter terms. However, longer terms of using AD+MS may decrease the risk of switches. The answer to the question whether switches occurring during AD use are the part of the natural course of illness or is associated with ADs is not elucidated. Controlled studies are required to take into consideration the natural course of the illness and comparing patients who do and do not experience a switch during AD use regarding sociodemographic, clinical and biological characteristics. Such studies would support the validity of our findings.

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