

# Comparing the Effectiveness of Mood Stabilizers and Antidepressants for Bipolar Depression Treatment: a Retrospective Chart Review

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## ÖZET

İki uçlu depresyon tedavisinde duygudurum dengeleyici ve antidepresan etkilerinin karşılaştırılması: Geriye dönük bir dosya taraması

**Amaç:** Bu çalışma ile antidepresanların iki uçlu depresyonda düzelmeye üzerine etkisinin değerlendirilmesi amaçlanmıştır.

**Yöntem:** DSM-IV'e göre iki uçlu bozukluk tanısı ile özelleşmiş bir duygudurum merkezinde takip edilmekte olan hastaların en son depresif dönemleri geriye dönük olarak değerlendirilmiştir. Yalnızca duygudurum dengeleyici titrasyonu yapılan ya da her hangi bir müdahale yapılmayan 34 hasta ve antidepresan ile tedavi edilmiş 30 hasta yineleme ve düzelmeye kadar geçen süre açısından karşılaştırılmıştır.

**Bulgular:** Her iki grupta da, hastaların üçte biri depresif dönemleri sırasında duygudurum dengeleyici ilaç kullanmaktaydı. Duygudurum dengeleyici düzeyleri terapötik aralıkta olup ortalama düzeyler gruplar arasında farklılık göstermiyordu. Yineleme ve düzelmeye kadar geçen süre yönünden gruplar arası farklılık saptanmadı.

**Sonuç:** Geriye dönük yapılmış bu ön çalışmada, antidepresan ilaçlarla tedavi edilen iki uçlu depresif dönemlerin antidepresanla tedavi edilmeyenlerden daha iyi tedavi sonucu getirmediği görüldü.

**Anahtar kelimeler:** İki uçlu depresyon, antidepresanlar, duygudurum dengeleyiciler, düzelmeye, yineleme

## ABSTRACT

Comparing the effectiveness of mood stabilizers and antidepressants for bipolar depression treatment: a retrospective chart review

**Objective:** The purpose of this study was to evaluate the effect of antidepressants on recovery in bipolar depression.

**Method:** The most recent depressive episode of patients with DSM-IV Bipolar Disorder, recruited from a specialized mood disorder outpatient unit in Turkey, were evaluated retrospectively. Thirty-four patients, only received mood stabilizer titration or did not change their current treatment regimens and thirty patients, treated with an antidepressant agent were compared on rates of recurrence and time to remission.

**Results:** One third of patients in each group were taking at least one mood stabilizer during their depressive episodes. Mood stabilizer levels were similar in each group and were within therapeutic limits. There were no significant differences between groups on rates of recurrence or time to remission.

**Conclusions:** In this preliminary retrospective study, patients with bipolar depression who were treated with antidepressants did not have a better outcome than patients who received no antidepressants.

**Key words:** Bipolar depression, antidepressants, mood stabilizers, remission, recurrence

DOI: 10.5350/DAJPN2010230206

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Kabul tarihi / Date of acceptance:  
11 Haziran 2010 / June 11, 2010

## INTRODUCTION

Bipolar disorder is a common, chronic and often serious mental illness, characterized by episodic mood periods with the life time prevalence of 1-3.5% (1-4). But misdiagnosis rates should not be underestimated, because it is usually hard to detect previous mania or hypomania (5). The morbidity of bipolar disorder is high and mortality rates from

suicide are estimated to be 3 times that of the general population. The risk is also increased in patients who are in the depressed phase of bipolar illness, who have mixed states, or psychotic mania (6,7). However, there are only a few treatment choices for bipolar depression and just two of them are (olanzapine-fluoxetine combination and quetiapine; in Turkey, only quetiapine) approved by the U.S. Food and Drug Administration (FDA).

Although antidepressants are usually prescribed for bipolar depressive episodes, the effectiveness of antidepressants for people with bipolar disorder has been largely inferred from studies of unipolar depression. Calabrese and colleagues, in an International Consensus Group on bipolar depression, reported that antidepressant monotherapy continues to be the most common treatment for bipolar I depression, despite little or no evidence proving its efficacy as a treatment (8). Although early studies indicated that antidepressants may have some positive effect, several recent large-scale studies have found that antidepressants have little (if any) benefit for the treatment of bipolar disorder (9). In a large effectiveness study funded by the National Institute of Mental Health, the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD), Sachs et al. reported that adjunctive antidepressant treatment for bipolar depression neither improved depressive symptoms nor increased the risk of switch to mania (10). The aim of this study is to compare effects of mood stabilizers (MS) and antidepressants (AD) according to remission and recurrence periods among bipolar depressive patients.

## METHODS AND MATERIALS

### Participants and study protocols

Bipolar patients (type I and II) attending the Raşit Tahsin Mood Disorders Outpatient Unit (RTMDU) of Istanbul Bakırköy Prof. Dr. Mazhar Osman Research and Training Hospital for Psychiatry, Neurology & Neurosurgery were assessed using standardized forms based on a nation-wide mood disorders follow-up program (i.e. SKIP-TURK) and all patients signed written informed consents for attending our specialized mood disorders outpatient unit.

### Data collection

Data records of 64 patients experiencing a depressive episode were evaluated retrospectively and included for the statistical analysis. Patients were

divided into two groups according to their treatment interventions for their most recent depressive episodes between April 2003- July 2007: 1) AD group (defined as patients who had received a new AD agent or were already taking AD and received to increase AD dosage); 2) Non-AD group (defined as patients who had received mood stabilizer titration or no pharmacological intervention for their most recent depressive episode). The primary outcome assessment was time to another mood episode according to clinician decision using standardized follow-up forms (11). 35.3% of patients in Non-AD group and 33.3% of patients in AD group were taking one or two MS; antipsychotic-MS combination rates were 26.5% in Non-AD group and 23.3% in AD group.

### Statistical Analysis

Statistical analysis was performed with the Statistical Package for Social Sciences (SPSS) 13 for Windows. Chi-square test was used to compare the nominal and ordinal demographic variables. Student t-test was used for comparing duration of illness of 34 patients (32 patients with bipolar type I, 2 patients with bipolar type II) in Non-AD group and 30 patients (26 patients with bipolar type I, 4 patients with bipolar type II) in AD group. Time to remission and follow-up periods were compared with student t-test. Mann-Whitney-U test was used to compare mood stabilizer levels between the groups. Kaplan-Meier analysis was applied to find the survival times of the 22 patients in MS and 15 patients in AD groups with the duration to relapse. Log rank test was applied to find the significance of differences between two groups. Differences were considered significant at  $p < 0.05$  for all tests.

## RESULTS

There were no significant differences between groups on baseline characteristics (Table 1 and Table 2). At presentation, nearly one third of the patients in each group were taking one or two mood stabilizers (MS) alone (AD group 33.2%, Non-AD group 32.3%). More than a quarter of patients in each group were taking

**Table 1: Baseline characteristics of patients**

	Non-AD group (n=34)	Non-AD group (%)	AD group (n=30)	AD group (%)	$\chi^2$	p*
Gender					0.05	0.807
Male	10	29.4	8	26.7		
Female	24	70.6	22	73.3		
Educational status					4.45	0.108
Primary	18	52.9	21	70.0		
High school	9	26.5	2	6.7		
University/doctorate	7	20.6	7	23.3		
Marital status					0.32	0.570
Married	16	47.1	12	40.0		
Single/divorced	18	52.9	18	60.0		
Occupation					2.29	0.318
Housewife	13	38.2	17	56.7		
Working/student	11	32.4	6	20.0		
Can't work/unemployed	10	29.4	7	23.3		
BP-I	32	94.1	26	86.7	1.35	0.497
BP-II	2	5.9	4	13.3		
Family history of illness					1.15	0.283
Present	17	50.0	11	43.8		
Absent/unknown	17	50.0	19	56.2		

AD: Antidepressant, BP-I: Bipolar Disorder type I, BP-II: Bipolar Disorder type II \*p>0.05 is not significant

**Table 2: Comparison of duration of illness**

Duration of illness (years)	n=64	Mean	SD	t	p*
Non-AD group	34	15.88	8.74	-0.895	0.375
AD group	30	18.17	11.17		

AD: Antidepressant, SD: Standard deviation, \*p>0.05 is not significant

MS-AP (AP=antipsychotic) or MS-AD in combination (Non-AD group 26.5%, 35.3% and AD group 23.3%, 30.0% respectively).

Sixteen of 34 patients in the Non-AD group had MS doses increased while the remainder (52.8%) received no new pharmacological intervention. In the AD group, 76.7% of patients were prescribed a new AD agent, while current daily AD doses were increased for the remainder. Follow-up periods were similar between groups for patients who did not have new episode (p=0.107, Table 3).

We compared remission and recurrence periods of patients and found that although the mean remission period was slightly shorter and the duration until next episode was longer in the Non-AD group, the difference between groups was not significant (Table 3). The most commonly prescribed antidepressant in

the AD group (70%) was a serotonin reuptake inhibitor (SSRI). Mean lithium (Li) levels in depressive episodes were 0,82meq/l and valproate (VPA) levels were 84.5 in AD group while mean levels of Li and VPA in Non-AD group were 0.74 and 82.6 respectively. 22 patients (64.7%) in non-AD group and 17 patients (56.6%) in the AD group did not experience a relapse during the retrospective follow-up period (Table 3).

Kaplan-Meier analysis was applied to find the survival times of the groups with the duration until next episode. Mean and median values were 119.66±12.25 weeks and 144.81 weeks for MS group and 117.39±10.38 weeks and 134.30 weeks for AD group, respectively. Log rank test was applied to find the significance of differences between two groups (Graphic 1) and there was no significant difference between groups in terms of time to relapse (p=0.729; p>0.05).

**Table 3: Comparison of recurrence and remission periods for MS and AD groups**

	Non-AD group (n=34)		AD group (n=30)		t / $\chi^2$	p*
	n	(%)	(weeks)	(%)		
Duration of follow-up (for patients without relapse)	22	64.7	16.5	50.0	-1.65	0.107
Relapsed during follow-up	12	35.3	15	50.0	1.41	0.235
Time to remission (mean weeks)	34	100	6.3	93.3	0.05	0.955
Type of next episode					2.88	0.236
Depression	1	2.9	4	13.3		
Mania/mixed	11	32.3	11	36.7		
No recent episode	22	64.7	15	50.0		

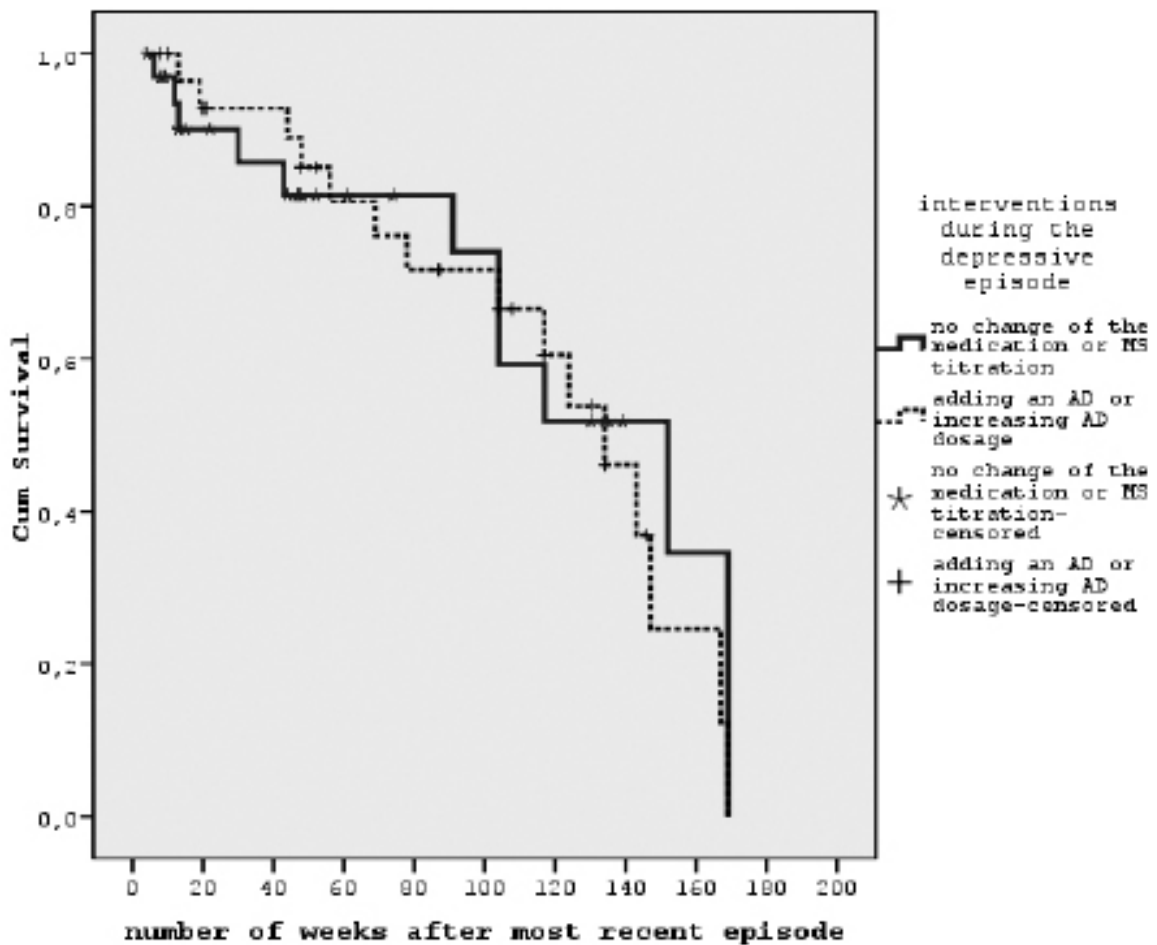
\*p>0.05 is not significant

\*Time to remission for two patients were not clarified

## DISCUSSION

Our results are consistent with the growing body of literature indicating that ADs do not make any difference

on the length of bipolar depressive episode (12-14). The Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study found that antidepressants neither improved treatment response



**Graphic 1: Comparison of duration until next episode with Log Rank test**

nor caused manic switches (10). Also, Frankle et al. evaluated the role of antidepressants during bipolar depression retrospectively in a smaller sample size. They reported similar results (15). While commonly used antidepressants, serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), and tricyclic antidepressants (TCAs) are approved by FDA for treatment of unipolar depression, no antidepressants have, as yet, been approved by the FDA for use in the depressive phase of bipolar disorder. Hence, their efficacy and safety in the treatment of bipolar depression are relatively unknown, and their use for this purpose is based largely on indirect inference from studies in unipolar depression (16). Furthermore, all major reviews and guidelines for bipolar depression recommend mood stabilizers (usually lithium or valproate) rather than an antidepressant as the first-line treatment for bipolar depression (17-20). Ghaemi et al. emphasized mood stabilizers for the treatment of bipolar depression and indicated that most patients will require two or three mood stabilizing agents taken together (21). Recently, in a meta-analysis, Ghaemi et al. reported that there was a minor beneficial effect of including an AD, with about 27% lower overall risk of long-term recurrences of depression. On the other hand, there was a 72% increase of risk of new episodes of mania (including hypomania and mixed states). In conclusion, it is indicated that the available research findings pertaining to long-term effects of AD treatment in BPD do not necessarily reflect current

experience and are far from adequate to guide rational therapeutics (22).

There are several limitations in this study. First, patients are selected from a homogenous data pool and data were evaluated retrospectively, even though we used a semi-structured form (11) for the clinical interviews. Second, most of the patients had bipolar type 1 diagnosis and we have just a few (n=6, 9.3%) bipolar type 2 patients in this study. The results may not be reflecting the whole bipolar spectrum. Third, sample size is relatively small. However, study is naturalistic and also patients were followed regularly by each clinician in a specialized mood disorders outpatient unit.

## CONCLUSIONS

Although, antidepressants are commonly prescribed for the treatment of bipolar depression, there is not clear data indicating the efficacy of antidepressants in bipolar patients. Also, risk of manic switch must be considered while treating bipolar depressive episode with antidepressants. In this preliminary retrospective study, patients with bipolar depression who were treated with antidepressants did not have a better outcome than patients who received no antidepressants. Clinicians should consider the antidepressant effects of mood stabilizers, particularly lithium. Clearly, additional prospective studies are required to investigate the usefulness of antidepressants in bipolar depression further.

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