Düşünen Adam The Journal of Psychiatry and Neurological Sciences 2013;26:122-130
DOI: 10.5350/DAJPN2013260201

Research / Araştırma

Sociodemographic and Clinical Features of Antidepressant-Induced Hypomanic and Manic Switch in Patients with Bipolar Disorder

Gokhan Sarisoy[1], Ozan Pazvantoglu[1]

[1]Assist. Prof. Dr., Ondokuz Mayis University, Faculty of Medicine, Department of Psychiatry, Samsun - Turkey

ABSTRACT

Sociodemographic and clinical features of antidepressant-induced hypomanic and manic switch in patients with bipolar disorder

Objective: The aim of this study was to identify sociodemographic, familial, childhood and various clinical characteristics of bipolar disorder patients in whom hypomanic/manic switches had been observed during treatment with antidepressant drugs.

Methods: One hundred sixty-one patients diagnosed with bipolar disorder on the basis of DSM-IV-TR were included. The study was a retrospective chart review. The sociodemographic, familial, childhood and various clinical characteristics of patients with manic or hypomanic switches (n=41, 25.4%) observed in association with antidepressant treatment during polyclinic or ward monitoring, or patients without switches (n=120, 74.6%) were compared. Patient data were obtained from Psychiatric Association of Turkey Mood Disorders Branch patient record forms.

Results: The first disease episode in the switch group was more commonly a depressive one. Cesarean birth and enuresis nocturna were more common childhood characteristics in the switch group. No difference was determined between the groups in terms of other characteristics.

Conclusion: Physicians should be careful in terms of hypomanic/manic switch in patients whose first episode is a depressive one. Our other two findings, cesarian birth and enuresis nocturna, may be significant in terms of suggesting clues for the planning of new studies illuminating the etiology.

Key words: Bipolar disorder, antidepressant treatment, switch

ÖZET

Antidepresan tedavi ile hipomanik/manik kayma gösteren bipolar bozukluk hastalarında sosyodemografik ve klinik özellikler

Amaç: Bu çalışmanın amacı, antidepresan ilaçlarla tedavi sırasında hipomanik/manik kayma gözlenen bipolar bozukluk hastalarının sosyodemografik, ailesel, çocukluk çağı ve bazı klinik özelliklerinin saptanmasıdır.

Yöntem: DSM-IV-TR'ye göre bipolar bozukluk tanısı konan 161 hasta çalışmaya alınmıştır. Çalışma, geriye dönük dosya tarama çalışmasıdır. Poliklinik ya da servis takipleri sırasında, antidepresan tedaviye bağlı olarak manik ya da hipomanik kayma gözlenen (n=41, %25.4) ve gözlenmeyen (n=120, %74.6) hastaların sosyodemografik, ailesel, çocukluk çağı ve bazı klinik özellikleri karşılaştırılmıştır. Hasta bilgileri, bipolar polikliniğimizde kullanılmakta olan Türkiye Psikiyatri Derneği Duygudurum Bozuklukları Çalışma Birimi'nin hasta kayıt formlarından elde edilmiştir.

Bulgular: Kayma olan grupta hastalığın ilk dönemi daha sıklıkla depresif dönem olarak belirlendi. Kayma olan grupta çocukluk çağı özelliklerinden sezaryen doğum ve enürezis nokturna daha sıktı. Diğer özellikler açısından gruplar arasında fark saptanmadı.

Tartışma ve Sonuç: Klinisyenler ilk dönemi depresif dönem olan hastalarda hipomanik/manik kayma açısından dikkatli olmalıdırlar. Diğer iki bulgumuz olan sezaryen doğum ve enürezis nokturna, etiyolojiye ışık tutabilecek yeni çalışmaların planlanması için ipuçları taşıması açısından önemli olabilir.

Anahtar kelimeler: Bipolar bozukluk, antidepresan tedavi, kayma

Address reprint requests to / Yazışma adresi:
Assist. Prof. Dr. Gokhan Sarisoy,
Ondokuz Mayis University, Faculty of Medicine,
Department of Psychiatry, 55200
Samsun - Turkey

Phone / Telefon: +90-362-312-1919/3777

Fax / Faks: +90-362-457-6041

E-mail address / Elektronik posta adresi:
gokhansarisoy@gmail.com

Date of receipt / Geliş tarihi:
May 31, 2012 / 31 Mayıs 2012

Date of acceptance / Kabul tarihi:
June 30, 2012 / 30 Haziran 2012

INTRODUCTION

Switching during treatment of depressive period of bipolar disorder is a frequently neglected fact (1). It is not included in a specific diagnostic category. Akiskal and colleagues (2) defines this situation as bipolar disorder type III. Switching can be due to drugs as well as a natural process of the disorder. Therefore, two types of switching, spontaneous and treatment induced, are discussed. There is no consensus on the diagnostic criteria of both types of switch (3,4). According to Altshuler and colleagues et al. (5), switch caused by treatment must be evident on the first 8 weeks of treatment and it must be a change which is not observed in the history of the disorder before. Henry and Demotes-Mainard (6) reported that there must not be absence of an euthymic period between depressive and switch episodes, recovery after cessation of the drug and excluding rapid cycling patients as additional criteria. It has been argued that different types of switch can be associated with various clinical features and that manic switch phenomena may be associated with some biological factors (7,8). Manic switch is observed in 15-49% of bipolar patients who are on antidepressant treatment (3,9-14). All antidepressants can cause manic switch (5,15-20). Using a mood stabilizer is protective (3,12,13,16,21,22).

No relationship between switch phenomena and gender (13,15,21,23,24) has been reported in most of the previous studies. It was reported in only one study that switch is more frequent in women (25). Results, regarding age are contradictory (13,15,21,24). Early onset of disorder, short duration of disorder, frequent hospitalizations, history of manic switch, depression in the first episode, mixed episode, agitation, psychomotor retardation, atypical features, cyclothymic or hyperthymic temperament, serotonin gene polymorphism and low thyroid stimulating hormone (TSH) are found in patients with manic switch (7,9,11-13,16,21,23-26,29,31-33). Findings on rapid cycling, type of bipolar disorder, comorbid substance use disorder, and number of manic and depressive episodes before the switch are contradictory (9,11-13,15,21,23,24,32,34,36).

In this study, our aim was to investigate sociodemographic, familial, clinical and childhood features of bipolar patients who had hypomanic/manic switch with antidepressant treatment. Our study is the first study to investigate the association of childhood features with this issue.

MATERIALS AND METHOD

This is a chart review study which included all bipolar patients who were admitted to Ondokuz Mayıs University Faculty of Medicine Department of Psychiatry Affective Disorders Unit between January 2006 and January 2009. Bipolar disorder diagnosis was made according to DSM-IV diagnostic criteria. Sociodemographic and clinical data of the patients who had hypomanic or manic switch at least once during the antidepressant treatment of depressive episode and the patients who did not have any hypomanic or manic switch during the antidepressant treatment of their depressive episode in the three-years period were compared. There is no consensus on the criteria (particularly regarding duration) for manic or hypomanic switch induced by antidepressant treatment in the literature. In certain studies, patients who switched directly from depression to hypomania or mania in the first 6, 8, or 12 weeks of the antidepressant treatment, with no remission of the depressive episode before switch and who did not have spontaneous switch are examined (2,5,6,23,24). In our study, for duration of treatment, as suggested by Althuser and associates (5), we investigated patients who switched directly from depressive episode to manic or hypomanic episodes in the first 8 weeks of the antidepressant treatment. Besides, we also took Henry and Demotes-Mainard's (6) criteria of absence of euthymic period between the depressive episode and the switch period. The patients who had spontaneous switches are excluded from the study. All patients were diagnosed with bipolar type I or type II disorder before the initiation of antidepressant treatment. Manic switch was detected in 41 of 161 (25.4%) bipolar patients while the remaining 120 (74.6%) did not switch. Forms used in our Affective Disorder Unit are the forms of Turkish Association of Psychiatry Mood Disorders Work Group; these forms are for mood disorders patient recording the first evaluation, pre and post protective treatment periods follow-up, treatment and time algorithms.

Sociodemographic and clinical data of the patients were obtained by using these forms. Sociodemographic variables such as age, gender, years of education, employment status, socioeconomic status, and place of residency; family variables such as number of siblings, people living with the patient, presence of psychiatric disorders in first and second-degree relatives, social support; childhood variables such as pre and post-natal features, history of childhood psychiatric disorders, childhood academic and social functioning, childhood abuse; and clinical variables including age of onset of the disorder, type of first episode of the disorder, bipolar disorder type, life events prior to the first episode, severity of the first episode, postpartum features in the first episode, mean number of episodes (total, manic, hypomanic, mixed, depressive), seasonal features, hospitalizations and suicide attempts are determined and compared between the groups.

Statistical Analysis

Chi-square test is used to compare categorical variables. When the expected value is lower than 5, Fisher chi-square test is used. Kolmogorov-Simirnov test is used to evaluate whether the variables obtained by measuring are normally distributed or not. We used Student t test to compare variables obtained by measuring, as compatibility for normal distribution was sustained. Variables obtained by counting are presented as percentages and variables obtained by measuring are presented as mean ± standard deviation. Logistic regression analysis was done with variables taken as independent variables throughout group comparisons; such that having the first episode in which significancy was detected in favor of the switch group, caeserean section and enuresis nocturna. For all analysis level of significance was accepted as 0.95 ($p<0.05$).

RESULTS

In our study, we detected manic switch in 41 patients (25.4%). Name, number and dose of the antidepressants that caused switch are as follows: Sertraline (n=10, 50 mg/day for 3, 100 mg/day for 4, 200mg/day for 3 patients),

Table 1: Comparison of sociodemographic features of the groups

	Switch (-) (n=120)		Switch (+) (n=41)		Statistics Value	
	n	%	n	%	χ^2/t	p
Gender						
Female	79	65.8	32	78.0	1.60	NS
Male	41	34.2	9	22.0		
Mean±SD age	38.43±13.31		38.32±14.47		0.04	NS
Mean±SD Years of Total Educattion	10.01±4.28		10.93±4.18		-1.19	NS
Employment						
Working/Student	49	40.8	14	34.1		
Unemployed		14.2	6	14.6		
Disabled		4.2	2	4.2	1.35	NS
Retired	13	10.8	7	17.1		
Housewife	36	30.0	12	30.0		
Marital status						
Married	60	50.0	23	56.1	0.24	NS
Unmarried	60	50.0	18	43.9		
Number of children	1.37±1.67		1.44±1.47		0.25	NS
Socioeconomic status						
Lower	11	9.2	1	2.4		
Middle	104	86.7	38	92.7	2.02	NS
Upper	5	4.2	2	4.9		
Place of residence						
City	80	66.7	34	82.9		
Town	23	19.3	5	12.2	4.23	NS
Village	17	14.2	2	4.9		

χ^2: Chi-square test, t: Student T test, NS: Not significant

Table 2: Comparison of familial features of the groups

	Switch (-) (n=120)		Switch (+) (n=41)		Statitical Value	
	n	%	n	%	χ^2/t	p
Number of siblings	3.11±1.99		3.44±2.02		-0.92	NS
People living with						
Parents	33	27.5	9	22.0		
Spouse, offspring	53	44.2	23	56.1		
Parents, spouse, offspring	20	16.7	3	7.3	4.42	NS
Sibling	6	5.0	3	7.3		
Partner	2	1.7	0	0.0		
Single	6	5.0	3	7.3		
Psychiatric disorders in first-degree relatives						
No	72	60.0	20	48.8	1.15	NS
Yes	48	40.0	21	51.2		
Type of psychiatric disorders in first-degree relatives						
Bipolar	30	25.0	8	19.5	0.25	NS
Unipolar	6	5.0	4	9.8	0.51	NS
Schizophrenia	4	3.3	4	9.8	1.48	NS
Other	8	6.7	5	12.2	0.62	NS
Psychiatric disorders in second-degree relatives						
No	93	77.5	29	70.7	0.44	NS
Yes	27	22.5	12	29.3		
Type of psychiatric disorders in second-degree relatives						
Bipolar	11	9.2	3	7.3	<0.001	NS
Unipolar	7	5.8	3	7.3	<0.001	NS
Schizophrenia	6	5.0	3	7.3	0.03	NS
Other	3	2.5	3	7.3	0.86	NS
Social support						
Present	108	90.0	32	78.0		
Not present	4	3.3	5	12.2	5.19	NS
Insufficient	8	6.7	4	9.8		

χ^2: Chi-square test, t: Student t Test, NS: Not significant

fluoxetine (n=9, 20 mg/day for 8, 30 mg/day for 1 patient), venlafaxine (n=6, 75mg/day for 4, 150 mg/day for 1 patient), clomipramine (n=3, 75 mg/day for all patients), fluvoxamine (n=3, 50 mg/day for 2, 100 mg/day for 1 patient), paroxetine (n=2, 20 mg/day for both patients), citalopram (n=2, 20 mg/day for 1, 30 mg/day for 1 patient), mirtazapine (n=2, 15 mg/day for 1, 30 mg/day for 1 patient), escitalopram (n=2, 10 mg/day for 1, 20 mg/day for 1 patient), mianserin (n=1, 30 mg/day), imipramine (n=1, 25 mg/day). All but two patients were on mood stabilizers when switch occurred (Valproic acid [n=16], lithium [n=16], lamotrigine [n=4], carbamazepine [n=1], valproic acid+lithium combination [n=2]). Mean duration of antidepressant use before the manic switch was 2.56±1.57 weeks (minimum:0.5, maximum:6).

There were no significant differences between the groups in terms of gender, age, years of education, employment status, number of children, socioeconomic status, and place of residence (p>0.05) (Table 1). Likewise, family variables such as number of siblings, individuals living with the patient, presence of psychiatric disorders in the first and second degree relatives and social support were not significantly different between the groups (p>0.05) (Table 2). Among the childhood features, caeserean section (p=0.027) and enuresis nocturna (p=0.034) were more common in the switch group. Other childhood features, including postnatal features (jaundice, febrile convulsions, hypoxia), history of childhood psychiatric disorders [Attention deficit hyperactivity disorder (ADHD), separation anxiety], childhood academic and social functioning, and childhood abuse were not significantly different between the groups (p>0.05) (Table 3). First episode was more frequently depression in the switch group (p<0.001). Other clinical features like type of bipolar disorder, life

Table 3: Comparison of childhood features of the groups

	Switch (-) (n=120)		Switch (+) (n=41)			
	n	%	n	%	χ^2	p
Delivery						
Caesarean section	4	3.3	6	14.6	*	0.018
Post natal						
Hypoxia	16	13.3	2	4.9	1.43	NS
Jaundice	15	12.5	8	19.5	0.72	NS
Febrile convulsions	14	11.7	2	4.9	0.91	NS
Childhood psychiatric disorders						
ADHD	6	5.0	0	0.0	0.96	NS
Enuresis nocturna	6	5.0	7	17.1	*	0.022
Seperation anxiety	7	5.8	2	4.9	<0.01	NS
Childhood academic functioning						
Poor	9	7.5	4	9.8	2.23	NS
Moderate	57	47.5	24	58.5		
Good	42	35.0	10	24.4		
Very good	12	10.0	3	7.3		
Childhood social functioning						
Poor	6	5.0	3	7.3	1.53	NS
Moderate	52	43.3	21	51.2		
Good	47	39.2	12	29.3		
Very good	15	12.5	5	12.2		
Childhood abuse						
Sexual	16	13.3	3	7.3	0.56	NS
Physical	36	70.0	15	36.6	0.35	NS
Emotional	39	32.5	18	43.9	1.27	NS

χ^2: Chi-square test, NS: Not significant, *When the expected value is lower than 5, Fischer's chi-square test is used

events prior to the first episode, severity of the first episode, postpartum features in the first episode, mean number of episodes (total, manic, hypomanic, mixed, depressive), seasonal features, rapid cycling, hospitalizations and suicide attempts were not different between the groups (p>0.05) (Table 4). Logistic regression analysis revealed that depressive first episode increased the risk of switch 4.9 times, history of enuresis nocturna increased the risk 5.4 times and caeserean section increased the risk 8.1 times (p>0.05) (Table 5).

DISCUSSION

Sociodemographic features of groups

In our study, no difference was detected between the groups with or without switch in terms of all sociodemographic variables (age, gender, marital status, socioeconomic level, number of children, total years of education, place of residency, and employment status). There are two studies in the literature, one supporting that the switch group was younger (24), the other one older (21), while two other studies did not find any difference in terms of age (13,15). Our study supported the studies which did not find any difference. In the literature, consistent with our study, most of the studies, except one study which reported switch was more common in women (25), did not determine gender differences (13,15,21,23,24). Again, consistent with our study, Saatçioğlu and colleagues (23) did not report any difference regarding marital status, level of education and socioeconomic level. In addition to the literature, we also did not find any difference in terms of number of children and place of residence. When all of these results are taken into account, it can be argued that sociodemographic features of bipolar patients who switched or did not switch due to antidepressant treatment are similar.

Table 4: Comparison of the groups for some clinical features of bipolar disorder

	Switch (-) (n=120)		Switch (+) (n=41)		Statistical value	
	n	%	n	%	χ^2/t	p
Age of onset of disorder	3.11±1.99		3.44±2.02		-0.92	AD
First episode						
Elevation (mania+mixed+hypomania)	87	72.5	17	41.5	11.55	<0.001
Depression	33	27.5	24	58.5		
Bipolar type						
I	105	87.5	15	12.5	<0.01	NS
II	36	87.8	5	12.2		
Life event in the first episode						
Yes	98	81.7	22	18.3	0.38	NS
No	31	75.6	10	24.4		
Severity of first episode						
Mild	8	6.7	2	4.9	1.41	NS
Moderate	46	38.3	20	48.8		
Severe	66	55.0	19	46.3		
First episode postparum features (n=111)						
Yes	2	2.5	1	3.2	<0.01	NS
No	78	97.5	30	96.8		
First episode psychotic features						
Yes	66	55.0	54	45.0	0.61	NS
No	19	46.3	22	53.7		
Pre-switch						
Mean number of episodes (total)	5.56±5.24		6.39±6.48		-0.83	NS
Number of manic episodes	2.32±2.49		2.66±3.64		-0.67	NS
Number of depressive episodes	2.87±5.98		3.39±5.81		-0.48	NS
Number of hypomanic episodes	0.83±2.24		0.49±1.24		0.94	NS
Number of mixed episodes	0.02±0.16		0.06±0.25		1.00	NS
Seasonal Features						
Yes	37	30.8	11	26.8	0.08	NS
No	83	69.2	30	73.2		
Rapid cycling						
Yes	3	2.5	2	4.9	0.06	NS
No	117	97.5	39	95.1		
Hospitalization	1.10±2.15		1.22±1.72		-0.32	NS
Suicide attempt						
Yes	30	25.0	11	26.8	<0.01	NS
No	90	75.0	30	73.2		

χ^2: Chi-square test, NS: Not significant

Table 5: Determination of the variables predicting the hypomanic/manic switch in bipolar disorder (results of logistic regression analysis)

	B	SE	Wald	df	p	Exp (B)
First episode depression	1.61	0.47	14.88	1	<0.001	5.00
Enuresis nocturna	1.66	0.65	6.49	1	0.011	5.42
Caesarean section	2.10	0.74	8.20	1	0.004	8.19

Familial features of groups

We did not detected any difference between the groups regarding number of children, family members living with the parents, psychiatric disorders in first and second degree relatives and social support. One study argued that history of bipolar disorder was more common in the switch group (7), while another study, consistent with our results, did not find more frequent history of familial bipolar disorder (24). Nasrallah and et

al. colleagues reported that psychiatric disorders were more common in the first degree relatives of the patients with manic switch (26), and Saatçioğlu and associates (23) reported more frequent major depression. Results of our study are not consistent with these studies. In our study, we did not find any difference in the frequency of psychiatric disorders in general and bipolar disorder, unipolar disorder and schizophrenia in first-degree relatives. New studies are required to make this issue more clear.

Childhood features of groups

To our knowledge there is not a study in the literature which investigates the childhood features of bipolar patients who switched due to antidepressant drugs. In our study, we found that ceaseraen section and enuresis nocturna were more common in the switch group. Logistic regression analysis revealed that ceaseran section risk increased 8.1 and enuresis nocturna risk increased 5.4 times, respectively. However, since our sample size was small, these results must be supported by other studies using larger samples with calculated effect sizes. Postnatal features such as jaundice and febrile convulsions, other childhood disorders such as ADHD and separation anxiety disorder, academic and social functioning, sexual, physical and emotional abuse were not significantly different between the groups. Enuresis nocturna is a developmental disorder generally seen in children (sometimes it can continue in adulthood) with genetic liability. Lei and associates (38) suggested maturational lag or no maturation in prefrontal cortex circuits in this disorder, while Bosson and colleagues (39) implied retinal-hypothalamic-cortical pathway maturational problems. Hallioğlu and associates (40), reported that in EEG, decreased left dominant temporal and bilateral frontal cortex alpha activity along with increased delta activity were evident and that these findings indicated cerebral maturation problems in the corresponding cerebral regions. Freitag and colleagues (41), reported more pronounced central nervous system maturational lag in enuretic children with positive family history. It is not clear whether ceasearen section has any deleterious effects on brain maturation and neurodevelopment. However, brain maturation continues during the 37-40th weeks of gestation, which is the ceaseraen section period. In this period, particularly interneuronal connections and extensions increase, dendritic differentiation and myelinisation continues (42). It is not clear whether the possible cerebral maturational lag due to enuresis nocturna and ceasearean section continues into adulthood. We did not find any study on this issue in the literature. Salvadore and colleagues (8) argue that, anomalies in catecholamine levels, increased postreceptor sensitivity, upregulation of neurotropic and neuroplastic factors, HPA axis and circadian rhythm anomalies and sleep deprivation might be associated with manic switch phenomena. Whether the possible anomalies on cellular level due to cerebral maturation lag has an impact on the mentioned systems and possible relationship with the switch phenomena can be an interesting point for further research.

Clinical features of groups

In our study, we found that the first episode was more commonly depression in the group with manic switch. Results of the logistic regression analysis indicated that depressive first episode increases the risk of switch 4.9 times. This finding is consistent with the results of previous studies (21,27,28). In the literature, it has been reported that disease onset is earlier in the manic switch group (9,12,16,26). In our study, while the mean age was higher in the switch group this was not statistically significant. There are conflicting results in the literature regarding rapid cycling (21,23,24,32) bipolar type (9,11,13,21,24,32,34), number of pre-switch manic episodes (11-13,15,21,24) and depressive episodes (15,23). In our study, we did not find any differences in terms of rapid cycling, bipolar type, number of pre-switch manic episodes and depressive episodes between the groups. Future studies with larger samples are required to clarify these issues. In our study we did not find any difference on seasonal features and suicide attempts. These findings are consistent with the literature (21,23). Truman and associates (24), reported more hospitalizations in the

switch group. However, we did not find any difference between the groups regarding hospitalizations. In addition to the literature, we did not find any differences between the groups for life events prior to the first episode, severity of first episode, and postpartum and psychotic features in the first episode. When the results reported above are taken as a whole, the two most consistent clinical features in the bipolar patients with manic switch appeared to be early onset of disorder and depressive first episode.

In conclusion, clinicians must be alert for hypomanic/manic switch in patients with depression in the first episode. Our other two results (ceaserean section and enuresis nocturna) may be important for future studies which can enlighten the etiology.

There are several limitations of our study. This is not a population based study; it was conducted on patients who were referred to a tertiary health center. Other important limitations included not being a prospective study, using a relatively unreliable method for chart review and not calculating a sample size based on power analysis.

REFERENCES

1. Wehr TA, Goodwin FK. Can antidepressants cause mania and worsen the course of affective illness? Am J Psychiatry 1987; 144:1403-1411.
2. Akiskal HS, Bourgeois ML, Angst J, Post R, Möller H, Hirschfeld R. Re-evaluating the prevalence of and diagnostic composition within the broad clinical spectrum of bipolar disorders. J Affect Disord 2000; 59 (Suppl.1):5-30.
3. Licht RW, Gijsman H, Nolen WA, Angst J. Are antidepressants safe in the treatment of bipolar depression? A critical evaluation of their potential risk to induce switch into mania or cycle acceleration. Acta Psychiatr Scand 2008; 118:337-346.
4. Visser HM, Van Der Mast RC. Bipolar disorder, antidepressants and induction of hypomania or mania. A systematic review. World J Biol Psychiatry 2005; 3:115-124.
5. Altshuler LL, Post RM, Leverich GS, Mikalauskas K, Rosoff A, Ackerman L. Antidepressant-induced mania and cycle acceleration: a controversy revisited. Am J Psychiatry 1995; 152:1130-1138.
6. Henry C, Demotes-Mainard J. Avoiding drug-induced switching in patient with bipolar depression. Drug Saf 2003; 26:337-351.
7. Goldberg JF, Truman CJ. Antidepressant-induced mania: an overview of current controversies. Bipolar Disord 2003; 5:407-420.
8. Salvadore G, Quiroz JA, Machado-Vieira R, Henter ID, Manji HK, Zarate CA Jr. The neurobiology of the switch process in bipolar disorder: a review. J Clin Psychiatry 2010; 71:1488-1501.
9. Goldberg JF, Whiteside JE. The association between substance abuse and antidepressant-induced mania in bipolar disorder: a preliminary study. J Clin Psychiatry 2002; 63:791-795.
10. Ghaemi SN, Rosenquist KJ, Ko JY, Baldassano CF, Kontos NJ, Baldessarini RJ. Antidepressant treatment in bipolar versus unipolar depression. Am J Psychiatry 2004; 161:163-165.
11. Altshuler LL, Suppes T, Black DO, Nolen WA, Leverich G, Keck PE Jr, Frye MA, Kupka R, McElroy SL, Grunze H, Kitchen CM, Post R. Lower switch rate in depressed patients with bipolar II than bipolar I disorder treated adjunctively with second-generation antidepressants. Am J Psychiatry 2006; 163:313-315.
12. Boerlin HL, Gitlin MJ, Zoellner LA, Hammen CL. Bipolar depression and antidepressant-induced mania: a naturalistic study. J Clin Psychiatry 1998; 59:374-379.
13. Henry C, Sorbara F, Lacoste J, Gindre C, Leboyer M. Antidepressant-induced mania in bipolar patients: identification of risk factors. J Clin Psychiatry 2001; 62:249-255.
14. Joffe RT, MacQueen GM, Marriott M, Robb J, Begin H, Young LT. Induction of mania and cycle acceleration in bipolar disorder: effect of different classes of antidepressant. Acta Psychiatr Scand 2002; 105:427-430.
15. Bottlender R, Rudolf D, Strauss A, Moller HJ. Antidepressant-associated maniform states in acute tretament of patients with bipolar-I disorder. Eur Arch Psychiatry Clin Neurosci 1998; 248:296-300.
16. Tondo L, Vasquez G, Baldessarini RJ. Mania associated with antidepressant tretament: comprehensive meta-analytic review. Acta Psychiatr Scand 2010; 121:404-414.
17. Akiskal HS. External validating criteria for psychiatric diagnosis: their application in affective disorders. J Clin Psychiatry 1980; 41:6-15.
18. Nolen WA, Bloemkolk D. Treatment of bipolar depression, a review of the literature and a suggestion for an algorithm. Neuropsychobiology 2000; 42 (Suppl.1):11-17.
19. Post RM, Altshuler LL, Leverich GS, Frye MA, Nolen WA, Kupka RW, Suppes T, McElroy S, Keck PE, Denicoff KD, Grunze H, Walden J, Kitchen CM, Mintz J. Mood switch in bipolar depression: comparison of adjunctive venlafaxine, bupropion and sertraline. Br J Psychiatry 2006; 189:124-131.

20. Peet M. Induction of mania with selective serotonin re-uptake inhibitors and tricyclic antidepressants. Br J Psychiatry 1994; 164:549-550.

21. Serretti A, Artioli P, Zanardi R, Rossini D. Clinical features of antidepressant associated manic and hypomanic switches in bipolar disorder. Prog Neuropsychopharmacol Biol Psychiatry 2003; 27:751-757.

22. Bottlender R, Rudolf D, Strauss A, Möller HJ. Mood-stabilisers reduce the risk of developing antidepressant-induced maniform states in acute treatment of bipolar I depressed patients. J Affect Disord 2001; 63:79-83.

23. Saatcioglu O, Erim R, Tomruk N, Oral T, Alpay N. Antidepressant-associated mania or hypomania: a comparison with personality and bipolarity features of bipolar I disorder. J Affect Disord. 2011; 134:85-90.

24. Truman CJ, Goldberg JF, Ghaemi SN, Baldassano CF, Wisniewski SR, Dennehy EB, Thase ME, Sachs GS. Self-reported history of manic/hypomanic switch associated with antidepressant use: data from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). J Clin Psychiatry 2007; 68:1472-1479.

25. Keck PE Jr, Corya SA, Altshuler LL, Ketter TA, McElroy SL, Case M, Briggs SD, Tohen M. Analyses of treatment-emergent mania with olanzapine/fluoksetine combination in the treatment of bipolar depression. J Clin Psychiatry 2005; 66:611-616.

26. Nasrallah HA, Lyskowksi J, Schroeder D. TCA-induced mania: differences between switchers and nonswitchers. Biol Psychiatry 1982; 17:271-274.

27. Ghaemi SN. New treatments for bipolar disorder: the role of atypical neuroleptic agents. J Clin Psychiatry 2000; 61 (Suppl.14):33-42.

28. Perugi G, Micheli C, Akiskal HS, Madaro D, Socci C, Quilici C, Musetti L. Polarity of the first episode, clinical characteristics, and course of manic depressive illness: a systematic retrospective investigation of 320 bipolar I patients. Compr Psychiatry 2000; 41:13-18.

29. Bottlender R, Sato T, Kleindienst N, Strauss A, Moller HJ. Mixed depressive features predict maniform switch during treatment od depression in bipolar I disorder. J Affect Disord 2004; 78:149-152.

30. Frye MA, Helleman G, McElroy SL, Altshuler LL, Black DO, Keck PE Jr, Nolen WA, Kupka R, Leverich GS, Grunze H, Mintz J, Post RM, Suppes T. Correlates of treatment-emergent mania associated with antidepressant treatment in bipolar depression. Am J Psychiatry 2009; 166:164-172.

31. Maj M, Pirozzi R, Magliano L, Bartoli L. The prognostic significance of "switching" in patients with bipolar disorder: a 10-year prospective follow-up study. Am J Psychiatry 2002; 159:1711-1717.

32. Mundo E, Walker M, Cate T, Macciardi F, Kennedy JL. The role of serotonin transporter protein gene in antidepressant-induced mania in bipolar disorder: preliminary findings. Arch Gen Psychiatry 2001; 58:539-544.

33. Bottlender R, Rudolf D, Strauss A, Moller HJ. Are low basal serum levels of the thyroid stimulating hormone (b-TSH) a risk factor for switches into states of expansive syndromes? Pharmacopsychiatry 2000; 33:75-77.

34. Himmelhoch JM, Thase ME, Mallinger AG, Houck P. Tranylcypromine versus imipramine in anergic bipolar depression. Am J Psychiatry 1991; 148:910-916.

35. Bond DJ, Noronha MM, Kauer-Sant'Anna M, Lam RW, Yatham LN. Antidepressant-associated mood elevations in bipolar II disorder compared with bipolar I disorder and major depressive disorder: a systematic review and meta-analysis. J Clin Psychiatry 2008; 69:1589-1601.

36. Manwani SG, Pardo TB, Albanese MJ, Zablotsky B, Goodwin FK, Ghaemi SN. Substance use disorder and other predictors of antidepressant-induced mania: a retrospective chart review. J Clin Psychiatry 2006; 67:1341-1345.

37. Özerdem A, Yazıcı O, Tunca Z, Oral ET, Vahip S, Kurt E, Tırpan K. Establishment of Computerized Registry Program for Bipolar Illnes in Turkey: SKİP-TÜRK. J Affective Disord 2004; 78 (Suppl.1):86.

38. Lei D, Ma J, Du X, Shen G, Tian M, Li G. Altered brain activation during response inhibition in children with primary nocturnal enuresis: a fMRI study. Hum Brain Mapp 2011; 33:2913-2919.

39. Bosson S, Holland PC, Barrow S. A visual motor psychological test as a predictor to treatment in nocturnal enuresis. Arch Dis Child 2002; 87:188-191.

40. Hallioğlu O, Ozge A, Comelekoglu U, Topaloglu AK, Kanik A, Duzovali O, Yilgor E. Evaluation of cerebral maturation by visual and quantitative analysis of resting electroencephalography in children with primary nocturnal enuresis. J Child Neurol 2001; 16:714-718.

41. Freitag CM, Röhling D, Seifen S, Pukrop R, von Gontard A. Neurophysiology of nocturnal enuresis: evoked potentials and prepulse inhibition of the startle reflex. Dev Med Child Neurol 2006; 48:278-284.

42. Kapellou O. Effect of caesarean section on brain maturation. Acta Paediatr 2011; 100:1416-1422.