The Relationship Between Lifetime Hypomanic Symptoms and Activation Syndrome in Major Depressive Disorder

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SUMMARY

Objective: Activation syndrome (AS), as described by the U.S. Food and Drug Administration (FDA), comprises 10 bipolar associated symptoms which starts after antidepressant therapy. The aim of this study is to investigate whether there is a relationship between lifetime hypomanic symptoms and the development of AS in patients diagnosed with major depressive disorder (MDD).

Method: The study was conducted at Hacettepe University Faculty of Medicine Department of Psychiatry. A total of 60 consecutive outpatients diagnosed with MDD were assessed at three time points; before the initiation of antidepressant therapy (baseline), at 2nd week and at 4th week. At the initial interview the patients completed the Hypomania Checklist-32 (HCL-32) in order to assess the lifetime history of hypomanic symptoms. Barnes Akathisia Rating Scale (BARS), Hamilton Rating Scale for Depression (HAM-D), Hamilton Anxiety Rating Scale (HAM-A) and Young Mania Rating Scale (YMRS) were utilized to detect the symptoms of AS at each assessment.

Results: AS was detected in 25 (41.7%) patients. The most prevalent symptoms of AS were insomnia (31.7%), anxiety (25%) and irritability (15%). A significant difference was found in the HCL-32 scores of patients with and without AS. A moderate correlation between the number of AS symptoms and HSL-32 test scores were also determined.

Conclusion: AS development was more common among the depressed patients with lifetime history of hypomanic symptoms. Given the frequency of misdiagnosis of BPD as MDD, it would be helpful to assess the hypomanic symptoms systematically with scales similar to HSL-32 in depressive patients before prescribing antidepressant medication.

Keywords: Bipolar disorder, major depressive disorder, antidepressants, activation syndrome, hypomania

INTRODUCTION

Differential diagnosis of unipolar and bipolar depression is one of the most debated issues in psychiatry. Sixty percent of the outpatients with bipolar or associated disorders are misdiagnosed with major depressive disorder, caused mainly by incomplete anamnesis and overlooking hypomania symptoms during psychiatric examination (Hirschfeld et al. 2003, Angst et al. 2011). Indeed, hypomanic symptoms are detected more frequently in research by the use of psychometric scales. Patients often do not spontaneously refer to perceptions of possible hypomanic episodes, probably on account of the short consultation duration and also having associated hypomanic episodes with increase in their functionality (Judd et al. 2003, Vieta et al. 2009). The French National EPIDEP (Evaluating the clinical epidemiology of depression) Study showed that the incidence of BPD-II was increased from 20% to 39% when hypomanic symptoms were queried psychometrically (Akiskal et al. 2006).

It is widely accepted that the response to antidepressants in bipolarity spectrum is not optimal. Thus, overlooking

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hypomanic symptoms can adversely affect the course of the treatment. Clinicians are well aware of treatment-induced problems like anxiety, agitation, sleep problems and irritability in the first weeks of antidepressant treatments which have been described as the phenomenon of activation syndrome (AS) or "jitteriness/anxiety syndrome" (JAS), although , the debate around its definition and explanation of the underlying mechanisms have not been concluded (Culpepperer et al. 2004, Sinclair et al. 2009). In a systematic review conducted in 2009, insomnia, anxiety, irritability, increased psychomotor energy and restlessness were reported to be the most common symptoms of AS, although none of the symptoms were found to be stable (Sinclair et al. 2009). In the literature, "JAS" was used earlier than "AS" and it was denoted that caution should be taken into account during treatment of anxiety disorders with selective serotonin reuptake inhibitors (SSRI) (Baldwin et al. 2005, Harada et al. 2008, Sinclair et al. 2009).

FDA reported that, according to short-term studies, antidepressant drugs could induce suicidality in children and adolescents (FDA 2003) and warned in 2004 against the 10 possible precursor symptoms of suicide as anxiety, agitation, panic episodes, insomnia, hostility, aggressiveness, impulsiveness, akathisia and hypomania/mania, recommending evaluation of the BPD risk before starting antidepressant treatment (FDA 2004). Subsequently, this symptom cluster was called AS by clinical scientists (Culpepper et al. 2004). In 2007, FDA obligated all antidepressant drug manufacturers to use black box warnings about increased suicide risk in the first months of treatment not only for children and adolescents but also for young adults between 18-24 years of age (FDA 2007, Friedman and Leon 2007).

AS symptoms like agitation, hostility, aggressiveness, psychomotor restlessness and insomnia can also present in dysphoric mania/hypomania. A retrospective study in 2004 reported that 33 (58%) of the 57 BPD patients given antidepressants or psychostimulants in their childhood had experienced a manic episode in 14 days and showed AS symptoms at the same time (Faedda et al. 2004). In addition to mania/hypomania, AS symptoms can also be found in mixed and agitated depressive episodes.

Agitated depression is depressive episodes involving signs of stimulation and symptoms such as psychomotor acceleration, restlessness, dysphoria, irritability, acceleration in speech and thought processes, anxiety or panic episodes (Maj et al. 2003, Akiskal et al. 2005). Agitated depression can also be defined as depression with non-euphoric hypomanic symptoms. It is a matter of debate whether such depression episodes should be placed under unipolar, bipolar or mixed depressive episodes since some authors warn against increased suicidality with antidepressants in agitated depression (Maj et al. 2003, Akiskal et al. 2005, Koukopoulos et al. 2013).

According to the DSM-IV-TR criteria, manic and depressive episodes should be met at the same time for the diagnosis of the mixed type depressive episode (American Psychiatric Association 2000 -APA). On the other hand, some researchers proposed diagnosing depressive episodes accompanied by multiple mania/hypomania symptoms as mixed depressive episodes (Benazzi 2002, 2007). Akiskal et al. (2005) used the "The Hypomania Interview Guide" (HIGH-C) on 254 major depression patients, who had been free of medication for 2 weeks, and took a family history of BPD. If the number of hypomanic symptoms in a major depressive episode was more than 3, the episode was accepted as a mixed episode, whereas if HIGH-C psychomotor agitation score was higher than 2, the depressive episode was accepted as an agitated depressive episode. It was observed that 19.7% of patients had agitated depression and association was found between agitated depressive episodes and the mixed episodes. The agitated depression group was named as the pseudo-unipolar group due to the presence of non-euphoric hypomanic symptoms. The authors claimed, in line with the FDA warnings, that this situation was the result of inappropriate prescription of antidepressant medications (Akiskal et al. 2005). Takeshima et al. (2013) reported in their retrospective study that major depression patients, later diagnosed with BPD in their follow-up visits, showed higher incidences of AS symptoms. Based on these findings in the literature and the phenomenological similarities between AS and mixed depressive episodes, some authors suggest that AS should be considered as an antidepressant induced mixed episode (Akiskal et al. 2005, Akiskal and Benazzi 2006, Takeshima et al. 2013). Hence, the mixed episode diagnosis in DSM-5 was replaced with "depressive episode with mixed features " and "manic/hypomanic episodes with mixed features " in order to enable differentiating the features of mixed depressive and mixed manic episodes (APA 2014). It was denoted, however, that symptoms such as irritability, psychomotor agitation and attention problems that overlap with depression and manic episodes cannot be used to diagnose mixed episodes, which is controversial in practice as it results in the exclusion of most common symptoms of mixed episodes (Koukopoulos et al. 2013).

A number of authors posited that AS is associated with BPD and it is more common in major depression patients who present with signs of bipolarity (Akiskal et al. 2005, Akiskal and Benazzi 2006, Takeshima et al. 2013). However, up to now most of the studies were designed as cross- sectional or retrospective investigations. Based on the findings in the literature, it is legitimate to hypothesize an association

between previous hypomanic symptoms and development of AS during antidepressant treatment. This study examined the possibility of AS development during antidepressant treatment and its relation to lifetime hypomanic symptoms in outpatients with MDD.

METHOD

Sample

The study was conducted at Hacettepe University Faculty of Medicine Psychiatry Outpatient Unit between April 2015 and December 2015. Patients diagnosed with MDD and prescribed SSRI antidepressants by their psychiatrists were enrolled for evaluation. All patients gave written informed consent prior to participation. Patients who had current or lifetime diagnosis of any DSM-IV Axis- I mental disorders, except nicotine addiction and anxiety disorders, and those who had used psychotropic drugs in the previous one month, or who had been prescribed additional psychotropic drugs for the current episode were excluded.

Design of the Experiment

Patients who gave informed consent for participation in the study were examined according to the Structured Clinical Interview for DSM-IV (SCID-I) to verify the diagnosis of MDD and exclude other axis is I mental disorders. Because AS symptoms were reported mostly in the early phase of treatment (Faedda et al. 2004, FDA 2007), the patients were assessed two more times at the 2nd and the 4th weeks after the initial assessment and the start of antidepressant treatment.

At the initial assessment, demographic and clinical information on age, education, marital status, and comorbid diseases were questioned and also the Hypomania Check List (HCL-32) was used to detect hypomanic experiences that could not be detected by the routine psychiatric examinations (Akiskal et al. 2006). The HCL-32 is a self-report scale developed by Angst and colleagues (2005) to screen life-long hypomanic symptoms. Translation and adaptation to the Turkish language of the HCL-32 was carried out by Vahip et al. (2011) and the cut-off score was determined as 14.

In the follow-up assessments of the 2nd and 4th weeks of antidepressant treatment, the patients were tested for AS symptoms on the Young Mania Rating Scale (YMRS), the Hamilton Depression Rating Scale (HAM-D), the Hamilton Anxiety Rating Scale (HAM-A) and the Barnes Akathisia Rating Scale (BARS) in order to identify the patients who had developed AS on the basis of the 10 symptoms (named by the FDA), as detailed below:

1. Anxiety: An increase in total HAM-A score,
2. Agitation: An increase in the score of HAM-D agitation item,
3. Panic episodes: Clinical inquiry,
4. Insomnia: An increase in the score of three insomnia items of HAM-D,
5. Irritability: An increase in the score of YMRS irritability item,
6. Hostility: An increase in the score of YMRS hostility item,
7. Aggressiveness: An increase in the score of-YMRS aggressiveness item,
8. Impulsivity: Clinical inquiry,
9. Akathisia: An increase in total BARS score,
10. Hypomania/mania: An increase in total YMRS score.

Statistical Analysis

For statistical analysis, the IBM SPSS for Windows Version 22.0 was used. Continuous variables were presented by using the 'mean ± standard deviation' or the median values, while categorical variables were presented by using frequency and percentage. Chi-square test or Fischer exact test were used to estimate group differences between categorical variables. Distribution of continuous variables was checked using the Kolmogorov-Smirnov test and the Levene test was used to assess homogeneity of variances. For estimation of group differences between continuous variables, one-way analysis of variance (ANOVA) and the Welch ANOVA were used. Follow-up pairwise comparisons were made through Games Howell test. For comparison of two groups of continuous variables independent sample t-test or the Mann Whitney U test were used, depending on the distribution characteristics of the dependent variables. Association between continuous variables was determined on the Spearman correlation coefficient analysis. The level of statistical significance (two-tailed) was set at $p < 0.05$.

RESULTS

Clinical and Sociodemographic Features of the Sample

Initially, 72 adult patients diagnosed with MDD and prescribed SSRI treatment were recruited for the study. However, only 60 patients returned at the 2nd and 3rd assessments; the 12 patients, who did not return at follow-up assessments, stated their unwillingness to continue with the study when contacted.

AS was detected in 25 (41.7%) of the patients included in the study. The most frequently detected AS symptom was

Table 1. Distribution of Symptoms of Activation Syndrome

		Positive (N=25)	Negative (N=35)
Anxiety	N (%)	15 (25)	45 (75)
Agitation	N (%)	7 (11.7)	53 (88.3)
Panic episodes	N (%)	2 (3.3)	58 (96.7)
Sleep problems	N (%)	19 (31.7)	41 (68.3)
Irritability	N (%)	9 (15)	51 (85)
Hostility	N (%)	3 (5)	57 (95)
Aggressiveness	N (%)	1 (1.7)	59 (98.3)
Impulsivity	N (%)	1 (1.7)	59 (98.3)
Akathisia	N (%)	3 (5)	57 (95)
Hypomania /mania	N (%)	7 (11.7)	53 (88.3)

sleep related, while the least frequent was aggression and impulsiveness (Table 1). AS symptoms presented in 13 of the patients in the 2nd week and in 12 patients in the 4th week of antidepressant treatment. Within the group with AS symptoms (AS+), 5 patients had 1 symptom, 10 patients had 2 symptoms, 5 patients had 3 symptoms, 3 patients had 4 symptoms, one patient had 7 symptoms and 1 patient had 8 symptoms; the mean AS score (the number of AS symptoms) being 2.68 (± 1.72). There were not any significant differences in terms of gender (p = 0.748), age (p = 0.245) and other sociodemographic features between AS+ and AS- groups.

HCL-32 scores of 33 (55%) of the patients were over while scores of 27 were under the threshold value of 14.

After the initial assessment, all patients were put on antidepressant medications including sertraline(n = 26, fluoxetine (n = 14), escitalopram(n = 7), paroxetine(n = 4),; duloxetine(n = 4), bupropion (n= 2), citalopram (n = 2) and agomelatine (n = 1). None of the medications was associated with AS. When the antidepressants were divided in two groups as the SSRIs and the non-SSRIs, significant association between these groups and AS (p = 1) was not demonstrated.

The Association between Activation Syndrome and HCL-32 Scores

When compared, the incidence of having HCL-32 scores above the threshold value of 14 was significantly higher in the AS + group than in the AS - group (χ^2 = 12.623, p < 0.001, Table 2).

When the patients were divided into three groups as the AS-, the AS+ at the 2nd week and the AS+ at the 4th week, the total HCL-32 score of the 3 groups differed significantly (F = 19.31, p < 0.001; Table 3). Pairwise comparison with Games Howell test showed that the intergroup differences were

Table 2. Distribution of Baseline HCL-32 Scores of the Patients With and Without Activation Syndrome

		HCL-32 scores below scale threshold	HCL-32 scores above scale threshold	Total	χ^2	p*
AS positive	N	**23**	**12**	**35**	12.623	0.001
	%	85.2	36.4	58.3		
AS negative	N	**4**	**21**	**25**		
	%	14.8	63.6	41.7		
Total	N	27	33	60		

*Yates corrected chi-square

Table 3. Distribution of Baseline HCL-32 Scores of the Patients With and Without Activation Syndrome Detected in the Second and Fourth Weeks After Starting Antidepressant Therapy

	HSL-32 score						
	N	Mean	Std. Dev.	Min.	Max.	F*	p*
AS negative	35	12.69	5.89	3	26	19.31	0.001
AS positive at the 2. Week	13	19	4.92	7	27		
AS positive at 4. week	12	20.83	2.97	16	25		
Total	60	15.68	6.30	3	27		

*One way Anova Test

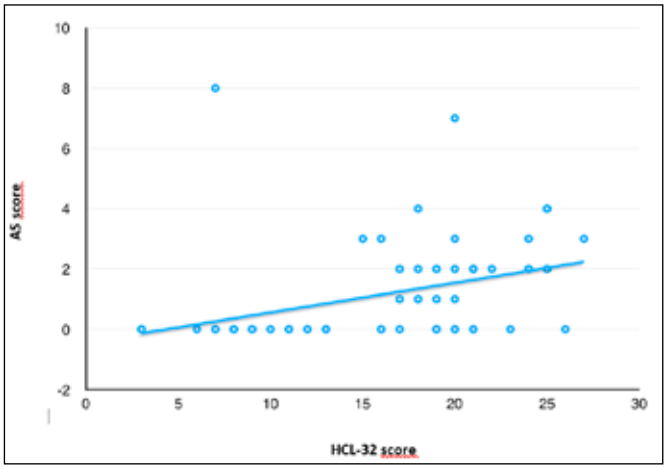

Figure 1. Association Between HCL-32 Scores and AS Scores (Spearman's rho: 0.522, p<0.001)

driven by the differences between the AS - and the AS+ scores at the 2nd (p = 0.003) and the 4th week (p < 0.001), but not by the difference between the AS + scores at the 2th and 4th weeks (p = 0.503).

The AS scores (number of AS symptoms) of the AS+ group with the HCL-32 total score above the threshold score of 14, were significantly higher as compared to the AS+ with HCL-32 scores under the threshold value (Mann-Whitney U test, z = -3.323, p = 0.001).

The association between HCL-32 scores and AS scores was tested and a significant moderate positive correlation was found (Spearman's rho = 0.522, p < 0.001, Figure 1).

When AS symptoms were analysed separately, the HCL-32 total scores were found to be significantly elevated in the AS+ patients with increased anxiety scores (t=-2.997, p=0.005), increased sleep disorders (t=-4.462, p< 0.001), increased irritability scores (t = 2.845, p = 0.006) and increased mania/hypomania scores (t:2.045, p= 0.045) as compared to the AS+ patients who did not show the same symptoms.

DISCUSSION

To the authors' best knowledge, this study is the first study that examined the relationship between previous hypomania symptoms and AS. In the four-week long prospective natural study, lifetime hypomania symptoms were assessed with the HCL-32 scores collected at the first (baseline) control and the AS criteria named by the FDA were detected on validated psychometric scales used at the 3 assessment times. It is important to emphasize that only patients who were free of any psychotropic drugs at least for one month before the initial assessment and prescribed only one medication from the antidepressant classes were included in the study. Thereby, a possible effect of other psychotropic medications on the emergence of AS symptoms was eliminated. AS was detected in 25 (41.7%) of the patient sample. Incidence of AS depends on the number of symptoms investigated, the methods used to determine AS, duration of the observation, diagnoses on the patients included in the study and the types and doses of the antidepressant agents used. In the medical literature, the incidence of AS was reported to range between 4% and 65% (Sinclair et al. 2009). Harada et al. (2008) reported the incidence of AS as 4% in their retrospective study, while in a subsequent prospective study in 2014, they reported an incidence of 7% for JAS determined on the basis of the same criteria. JAS incidence among the MDD diagnosed patients was determined to be 11.1% and JAS was found to be associated with MDD (Harada et al. 2014). In both studies of 2008 and 2014, determination of the AS incidences was based on clinical evaluations only; and psychometry was not used to assess the changes after the initial condition. Symptoms detected in the initial stage were not accepted as AS in the subsequent evaluations, whereby, the clinical worsening of the symptoms were not taken into account. Also, information was not given on other medication used during the antidepressant therapy. In the 2014 study, patients using benzodiazepine as additional medication were reported. All additional treatments can obliterate the AS symptoms and would result in low incidence of AS. Takeshima et al. (2013) reported an incidence of 24.8 % for AS in their retrospective study. However, patients prescribed additional psychotropic medications in addition to antidepressant treatment were included in the study. Additionally, the retrospective method of their study might have hindered the detection of some AS cases.

In the current study, the most frequently observed AS symptom of was sleep disorder (31.7%) followed by increased anxiety scores (25%). Incidence of sleep problems induced by antidepressant medications can vary depending on the type of antidepressant medication (Alberti et al. 2015). In a study with adolescents, the incidence of SSRI induced sleep problems was reported to be as high as 54% Emslie et al. 2006). Hu et al. (2004) controlled treatment side effects in their MDD patients by phoning after 75-105 days following the start of antidepressant treatment. Sleep problems and anxiety were reported by 22.4% and 19.2% of patients, respectively. Likewise, Harada et al. (2014) reported sleep problems as the most frequent JAS symptom. Furthermore, Perlis and colleagues (2007) reported that sleep problems (30.6 %) were the most frequent and unexpected side effect after fluoxetine treatment. All of these findings suggest that even though the reported incidence variation depend on differences of study designs, sleep problems are frequently induced by antidepressant treatment, and especially by the SSRIs.

During the current study, 7 (11.7 %) patients were detected to have developed mania/hypomania on the basis of the

YMRS scores. As mentioned in the introduction section, up to 60% of the outpatients with BPD or associated spectrum disorders are misdiagnosed as major depressive disorder cases (Hirschfeld et al. 2003). Previous studies pointed out that hypomanic symptoms, which patients do not often mention spontaneously, can be detected better in studies using specific psychometric tools (Akiskal et al. 2006). Thus, it is plausible that high rates of mania/hypomania found in the 4-week long follow-up period can be the result of detecting even the subtle symptoms by using the YMRS, which could have been missed by clinical inquiry only.

The HCL-32 scores of 33 (55 %) patients were above the scale threshold value of 14. In a combined study carried out in 29 different centers, 256 (57.4%) of 466 treatment-resistant MDD patients had a score ≥ 12, accepted as positive for hypomanic episode screening (Francesca et al. 2014). In another study, hypomanic episodes estimated with HCL-32 were reported in as much as 43.9 % of treatment-resistant MDD patients, while the incidence of hypomanic episodes was %30.5 in non-treatment resistant patients (Dudek et al. 2010). Xin et al. (2015) reported an incidence of 26.8 % of lifetime hypomanic episodes assessed with the HCL-32 in a population of 1176 MDD patients. Hence, when MDD patients are screened with the HCL-32, hypomanic symptoms are reported to be higher than that by clinical examination alone, though the incidences of symptoms can change depending on the inclusion criteria, size of the sample and design of the study.

In our study significant differences were found between the patients with and without AS separated into two groups on the basis of the HCL-32 total score being above or below the scale threshold score of 14. Patients who developed AS had significantly higher HCL-32 scores. FDA warnings on the relationship of AS symptoms with BPD and the necessity of assessing hypomania/mania symptoms before starting antidepressant therapy are not supported by conclusive evidential data. However, as stated earlier, diagnosis of BPD and associated disorders can be delayed. It is known that up to 10 years may pass before correct diagnosis could be made when patients get inappropriate pharmacotherapies headed by the antidepressants which adversely affect the course of the disease (Geller et al. 2001).

Koukopoulos et al. (2007) examined the clinical records of 1026 MDD patients to estimate the cases of agitated and mixed depressive episodes. Patients with motor agitation were diagnosed as 'agitated depression', while particular criteria were defined for mixed depression such as nervousness, acceleration in the thought process, irritability, lack of retardation symptoms, talkativeness, bursts of weeping, labile mood and sleep disorders. According to these criteria, they detected mixed depression in 33% of the patients and claimed that 66% of these cases were associated with antidepressant medications. Similarly, Sani et al. (2014),using the same criteria to scan clinical records, detected 219 mixed episode cases and reported that 111 of these were the outcome of antidepressant therapy. They argued that these antidepressant caused mixed episode cases had a severer course of the disease. They claimed that diagnosis of BPD-II was a positive marker for the occurrence of mixed episode depression after antidepressant therapy and that their description of the symptoms were more comprehensive and better for identification of the mixed symptoms given in the DSM-V for depressive and manic episodes.

Even if there is not a consensus on their definition, the characteristics given for agitated and mixed types of depression are present in AS. Symptoms of agitation, irritability, sleep problems, mania/hypomania and the increased anxiety are common features of these clinical events. Given the relationship between AS and HCL-32 scores shown by this study, AS can be proposed to be a mixed episode induced by antidepressants.

In the current study, as in previous studies by others, detection of one of the 10 clinical symptoms that FDA (2004) used in describing AS was taken as AS diagnosis (Takeshima and Oka 2013). However, detection of multiple AS symptoms may result in a more severe clinical course. In the current study sample, the number of AS symptoms and HCL-32 scores showed a moderate positive correlation. This finding suggests that previous hypomania symptoms may not only be associated with the development AS but also with the severity of the AS.

The separate analyses of single AS symptoms demonstrated that patients who showed an increase in anxiety scores had higher HCL-32 scores in comparison to those without an increase in anxiety scores after antidepressant treatment. A similar pattern of results was seen for sleep problems, irritability or mania/hypomania symptoms. When HCL-32 scores were used as dual variables above and below the threshold value of 14, only AS patients with sleep problems had significantly elevated HCL-32 scores. In a study carried out with healthy volunteers, HCL-32 total score correlated with seasonality, and the scores on the HCL-32 subscales irritability and risk taking behavior were found to correlate with seasonality and sleep disorders (Baea et al. 2014). Sani et al. (2014) validated their own criteria, inclusive of sleep problems, for diagnosis of mixed type depression after investigating its relationship with some of the symptoms of BPD course. In the study presented here, as with its use as a continuous variable, when the HCL-32 score was used as a binary variable, those patients with scores above the cutoff point after antidepressant therapy had significantly higher incidence of sleep disorders suggesting an association with BPD.

AS was associated with suicidality in some studies and the warning by the FDA and (Hammad et al. 2006). In this study,

an increased score on the HAM-D suicidality subscale was seen only in 3 patients and two of these patients developed AS.

One of the limitations of the current study is the small sample size. For that reason, the inferential statistical analysis could not be made for some of the AS criteria, and nonparametric tests were used for some of the analyses. Furthermore, the small sample size may also explain why some clinical phenomena that were previously associated with AS in the literature were not found to be related to AS in the current study.

The current study hypothesized that lifetime hypomanic symptoms are associated with the development of AS during antidepressant treatment. Accordingly, AS incidence after antidepressant treatment was found higher in patients who had more lifetime hypomanic symptoms. Considering the misdiagnosis incidences of BPD as MDD in outpatient clinics, it should be kept in mind that antidepressants may induce AS. To avoid this unwanted outcome, MDD patients should be screened with specific psychometric scales such as the HCL-32 to assess lifetime hypomanic symptoms. Furthermore, AS cases should be examined in detail and systematically to exclude BPD. Adjustment of the treatment accordingly can be beneficial for cases of AS and the long-term prognosis of the disease.

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