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Research report

Association between the so-called "activation syndrome" and bipolar II disorder, a related disorder, and bipolar suggestive features in outpatients with depression

Minoru Takeshima [a,*], Takashi Oka [b]

[a] Department of Psychiatry, Kouseiren Takaoka Hospital, 5-10 Eiraku-cyou, Takaoka 933-8555, Japan
[b] J Clinic and Department of Psychiatry, Juzen Hospital, 3-30-10 Sainen, Kanazawa 920-0024, Japan

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ABSTRACT

Background: Activation syndrome (AS) is a cluster of symptoms listed by the US Food and Drug Administration as possible suicidality precursors during antidepressant treatment. We aimed to clarify whether AS is associated with bipolar II disorder (BP-II) and its related disorder, i.e., bipolar disorder not otherwise specified (BP-NOS), which are often mistreated as major depressive disorder (MDD), as well as bipolar suggestive features in outpatients with depression.
Methods: The frequency of AS, bipolar suggestive features, and background variables in consecutive outpatients with a major depressive episode (MDE) due to BP-II/BP-NOS or MDD, who were naturalistically treated with antidepressants, were investigated and analyzed retrospectively.
Results: Of 157 evaluable patients (46 BP-II/BP-NOS, 111 MDD), 39 (24.8%) experienced AS. Patients with BP-II/BP-NOS experienced AS significantly more frequently than patients with MDD (52.2% of BP-II/BP-NOS vs. 13.5% of MDD, $p < 0.01$). Univariate analysis revealed that BP-II/BP-NOS diagnosis, cyclothymic temperament, early age at onset of first MDE, psychiatric comorbidities, and depressive mixed state (DMX) were significantly associated with AS development in the entire sample. Multivariate analysis revealed that BP-II/BP-NOS diagnosis and DMX were independent risk factors for AS.
Limitations: This is a retrospective and naturalistic study; therefore, patient selection bias could have occurred.
Conclusions: Cautious monitoring of AS is needed during antidepressant trials in patients with BP-II/BP-NOS. Clinicians should re-evaluate underlying bipolarity when they confront AS. Antidepressants should be avoided for treating a current DMX beyond the unipolar–bipolar dichotomy. Prospective studies are needed to confirm these results.

1. Introduction

In 2004, the US Food and Drug Administration (FDA) issued a warning that antidepressants can increase the risk of suicidal thinking and behavior (suicidality) in children and adolescents compared with placebo in short-term studies of major depressive disorder (MDD) and other psychiatric disorders (FDA, 2013; Friedman and Leon, 2007). Furthermore, in 2007, the FDA ordered that all antidepressant medications carry an expanded black box warning incorporating information about an increased risk of suicidality in young adults aged 18–24 years, as well as children and adolescents (FDA, 2013; Friedman and Leon, 2007). The FDA listed the following symptoms of anxiety, agitation, panic attack, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), and hypomania/mania emerging during antidepressant treatment as possible suicidality precursors and recommended to consider changing the therapeutic regimen, including discontinuing the antidepressants if these symptoms were severe, abrupt in onset, or were not part of the patient's presenting symptoms (Culpepper et al., 2004; FDA, 2013). The FDA also mentioned the possibility that these symptoms could be related to underlying bipolar disorder (BP) and prompted a screen to determine if patients with depressive symptoms are at risk of BP prior to initiating antidepressant treatment (FDA, 2013).

The cluster of the above-described 10 symptoms is sometimes called "activation syndrome (AS)" (Culpepper et al., 2004). Clinicians have known for years that during antidepressant treatment some patients develop such an energized and agitated state before the improvement of their depressive mood, and that this makes them more likely to act on pre-existing suicidal impulses. Several AS symptoms, such as agitation, hostility, aggressiveness, psychomotor restlessness (and by definition mania/hypomania) could be

* Corresponding author. Tel.: +81 766 21 3930; fax: +81 766 24 9509.
E-mail address: min-take@p2.tcnet.ne.jp (M. Takeshima).

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interpreted as symptoms of dysphoric mania/hypomania. A major depressive episode (MDE) with a few concurrent manic/hypomanic symptoms, under the threshold of a mixed episode defined by the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (DSM-IV-TR), is termed a depressive mixed state (DMX) or mixed depression (Benazzi, 2007; Benazzi and Akiskal, 2001; Dilsaver et al., 2005; Sato et al., 2005). DMX has been extensively studied recently and is observed predominantly in patients with bipolar depression, particularly those with bipolar II disorder (BP-II), than in those with monopolar depression, i.e., MDD (Akiskal and Benazzi, 2005; Benazzi, 2005; Takeshima et al., 2008; Takeshima and Oka, 2013; Vieta and Suppes, 2008). This state has also recently drawn attention as one of the strongest risk factors for suicidality (Balázs et al., 2006; Undurraga et al., 2012; Valtonen et al., 2008). In line with the phenomenological similarities between AS and DMX, Akiskal and Benazzi (2006) and Rihmer and Akiskal (2006) argued that AS could be understood as antidepressant-induced DMX. Faedda et al. (2004) retrospectively analyzed 57 patients with juvenile BP who had been given an antidepressant or psychostimulant and reported that 33 of the 57 (58%) patients so exposed developed mania with a median latency of 14 days. They also reported that many symptoms corresponding to AS (anxiety 54.3%, insomnia 68.6%, homicidal ideation 5.7%, irritability 97.1%, aggressiveness 77.1%, and impulsivity 91.4%), as well as suicidality (self-injurious behavior 20.0%, suicidal ideation 14.3%, and suicide attempts 5.7%) were observed concurrently in patients who developed mania. In a multisite study, Goldberg et al. (2007) prospectively examined the outcomes of patients with bipolar depression with two or more concomitant manic symptoms who had been treated with antidepressants plus mood stabilizers in the Systematic Treatment Enhance Program for Bipolar Disorder (STEP-BD) study, and reported that treatment with antidepressants did not hasten time to recovery relative to treatment with mood stabilizers alone and led to greater manic symptom severity.

These findings seem to lend credence to the association between BP and AS. However, no study has directly examined whether AS actually develops more frequently in patients with bipolar depression than in those with MDD during antidepressant treatment. In outpatient clinical practice, misdiagnosis of BP-II and its related disorder, i.e., BP not otherwise specified (BP-NOS) in the definition of DSM-IV-TR as MDD occurs rather often (Angst et al., 2011; Hantouche et al., 1998; Hirschfeld et al., 2003), because hypomanic episodes are usually brief and often experienced as pleasant periods of improving function (Akiskal and Benazzi, 2005; Judd et al., 2003; Vieta and Suppes, 2008). Therefore, patients with BP-II/BP-NOS would be more often exposed to antidepressants than those with bipolar I disorder (BP-I). Furthermore, MDD with bipolar features, which occupies a territory between BP-II/BP-NOS and MDD in the affective spectrum, is a recent concern in the psychiatric field. Through a comprehensive literature review, Ghaemi et al. (2001) heuristically proposed "bipolar spectrum disorder," which is defined as MDD with several of the following 11 bipolar suggestive features: family history of BP in first-degree relatives, hyperthymic temperament, early age at onset of first MDE (<25 years), recurrent MDEs ($>$ three times), brief MDE (<3 months), psychotic features, atypical features, postpartum depression, antidepressant-induced mania/hypomania, antidepressant "wear-off," and lack of response to three antidepressant treatment trials. Several studies have shown that cyclothymic temperament, which shows biphasic fluctuations in mood, thoughts, and behavior with brief intervals, is tightly related to bipolarity (Hantouche et al., 1998; Mechri et al., 2011), and Akiskal and Pinto (1999) proposed to consider MDE superimposed on this temperament as bipolar spectrum (bipolar $II_{1/2}$). Others have emphasized that patients who present DMX are much closer to BP-II than to unipolar major depression from a family history and treatment response perspective (Benazzi, 2007; Vieta and Suppes, 2008). The association between such bipolar features and AS is also not well understood. We here attempted to clarify whether BP-II/BP-NOS diagnosis and the abovementioned bipolar suggestive features are associated with FDA-listed AS thorough a retrospective analysis of outpatients with depression who were naturalistically treated with antidepressants.

2. Patients and methods

2.1. Study setting and subjects

The study setting of the first author (MT) is an outpatient service and consultation–liaison psychiatry service in a general hospital and that of the second author (TO) is an outpatient private psychiatry practice. Almost all patients were referred by non-psychiatric doctors in MT's setting, whereas patients voluntarily visited or were referred by psychiatric or non-psychiatric doctors to TO's setting. These settings are generally the first or second line of treatment for depression, i.e., non-tertiary care, in the Japanese medical system. The sample included consecutive patients suffering from MDE due to BP-II, BP-NOS, or MDD as defined by DSM-IV-TR, who first visited from September 2010 to December 2012, could be observed for at least 4 weeks and were treated with antidepressants at least once during the follow-up period from the first visit to January, 2013. Treatment was determined and performed naturalistically, with the aim to use mood stabilizers or atypical antipsychotics first and to avoid monotherapy with antidepressants in patients with BP. Patients whose data concerning bipolar suggestive features described below could not be obtained for reasons such as premature withdrawal from follow-up were excluded from analyses. Patients with severe mental retardation or dementia, pervasive developmental disorders, schizophrenia and related psychotic disorders, borderline personality disorder, and serious physical illnesses such as a terminal state of malignant neoplasms were also excluded to avoid confounding the evaluation of clinical pictures.

2.2. Diagnostic procedure

Diagnoses were made by MT or TO (with 24 and 17 years clinical experience studying and treating mood disorders, respectively) according to DSM-IV-TR, based on extensive clinical interviews with the patient and their significant others as much as possible and supplemented by all available information provided by referring clinicians and past records. A change in the diagnosis could be made with further interviews regarding history, information from other institutions, or observations of symptoms and signs during the follow-up period. According to DSM-IV-TR, patients exhibiting hypomania only during periods of treatment with causative agents such as antidepressants were regarded as patients with MDD and not as patients with BP. Patients were diagnosed with BP-NOS if they had experienced at least one MDE in addition to hypomanic symptoms that lasted <4 days, as specified in DSM-IV-TR.

2.3. Data collection

All data were obtained at routine psychiatric examinations and treatments. The data collected for patient characteristics were sex, age at first visit, psychiatric comorbidities, and proposed bipolar suggestive features. We collected the following nine items as bipolar suggestive features: hyperthymic temperament, cyclothymic temperament, family history of BP in first-degree relatives,