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Letter to the Editor

Are antidepressants mood destabilizers?

To the Editors

The risk-benefit profile of antidepressants in bipolar disorder (BD) remains controversial. Although antidepressants are the most commonly used initial treatment for bipolar depression in the US, it has been repeatedly demonstrated that they can worsen BD promoting rapid cycling and mood instability (Ghaemi, 2012).

The assumption that all depressive conditions respond similarly to antidepressants might lie behind the reported overuse of antidepressants in bipolar depression. The introduction of the broad Major Depressive Disorder (MDD) category in the DSM-III (Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition) – which considered different varieties of depression (such as recurrent depression and neurotic depression) as if they were a single and homogeneous entity – has supported this assumption (Amerio et al., 2014). Despite their widespread off-label use for bipolar depression – excluding the combination of fluoxetine–olanzapine – no antidepressant in monotherapy is approved by the Food and Drug Administration for use in BD (McIntyre et al., 2013).

We present the case of a young BD patient who was treated with different classes of antidepressants maintained for a long period of time. The patient is a 31-year-old Caucasian married woman with positive family history for bipolar disorder. She had no previous history of manic episodes. At the age of 24 she presented decreased appetite, insomnia, feelings of inadequacy, and anhedonia. She had depressed mood and recurrent thoughts of death. These symptoms met the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th Edition) criteria for major depressive episode; the patient was treated with sertraline 150 mg/day, and symptomatology improved.

After 6 months on sertraline 150 mg/day, she developed a manic episode. Her therapy was modified to valproate 1000 mg/day (serum level 75 μg/ml) and olanzapine 20 mg/day. Olanzapine was gradually decreased with mood stabilization.

One year later she presented depressed mood, diminished interest in almost all activities, feelings of guilt, and loss of energy. Citalopram 20 mg/day was added to her valproate treatment, and symptomatology improved.

In the following 12 months, citalopram and valproate were maintained and she experienced two depressive episodes lasting 3 months each. Citalopram was discontinued and treatment was modified to amitriptyline 150 mg/day and valproate 1000 mg/day. In the following year she had four depressive episodes lasting 2 months each without full interepisode recovery.

Treatment was again modified to lithium 900 mg/day (serum level 0.7–0.9 mEq/L) and valproate 1000 mg/day, and complete remission of bipolar symptoms for the following 2 years was reported.

A task force of the International Society for Bipolar Disorders has recently confirmed that all antidepressants can worsen BD by inducing mania or mood instability with higher risk for mania with tricyclic antidepressants (TCAs) (Pacchiarotti et al., 2013). In particular, as suggested by recent studies, the greater likelihood of developing mood instability for patients treated with antidepressants seems to be associated with genetic variants of the promoter region of the serotonin transporter (5-HTT) gene (Luddington et al., 2009).

The case we presented suggests that in BD patients old generation antidepressants speed up the recurrence of short depressive episodes while new generation antidepressants promote a smaller number of mood episodes that last longer. Polypharmacy with two mood stabilizers is more effective than the combination of an antidepressant and a mood stabilizer, in contrast to common clinical belief.

As reported in the literature, well-designed randomized controlled trials (RCT) have shown the inefficacy of antidepressants in the treatment of bipolar depression, both in acute and maintenance phases (Ghaemi, 2012). With regard to acute efficacy, the largest RCT conducted on bipolar depression showed that the use of adjunctive antidepressant medication to mood stabilizers was ineffective and not superior to a mood stabilizer plus placebo (Sachs et al., 2007). With regard to maintenance efficacy, even new generation antidepressants, like serotonin reuptake inhibitors (SRIs), showed no symptomatic benefit, along with depressive episode prevention or enhanced remission rates (Ghaemi et al., 2010).

Because complete response to a single mood stabilizer only occurs in about one-third of BD patients, polypharmacy with mood stabilizers, including second-generation antipsychotics and novel anticonvulsant agents, appears to be the most promising approach for long-term prevention of mood episodes in BD, including depressive episodes (Ghaemi, 2012).

Both data from experimental settings and observational clinical experience suggest that antidepressants do not prevent depressive episodes in BD and they do not have maintenance efficacy; physicians should avoid long-term treatment with antidepressants in BD as they are largely ineffective and commonly harmful.

Competing interests: Dr. Amerio, Dr. Odone, and Dr. Marchesi report no conflicts of interest. Dr. Ghaemi has provided research consulting to Sunovion and Pfizer, and has obtained a research grant from Takeda Pharmaceuticals. Neither he nor his family members hold equity positions in pharmaceutical corporations.

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