

## Psychopharmacology for the Clinician

*The information in this column is not intended as a definitive treatment strategy but as a suggested approach for clinicians treating patients with similar histories. Individual cases may vary and should be evaluated carefully before treatment is provided. The patient described in this column is a composite with characteristics of several real patients.*

### Identification and management of cryptic bipolarity in patients with TRD

A 32-year-old woman with recurrent major depressive disorder was referred for management of treatment-resistant depression (TRD), having failed to respond to 2 adequate antidepressant trials for the index episode. The depressive episode was characterized by symptoms of sad mood, anhedonia, increased appetite, hypersomnia, poor concentration, psychomotor retardation and fatigue. The symptoms were severe enough to have caused substantial functional impairment despite adherence to prescribed medications. She denied a prior history of manic or psychotic symptoms. There was no history of obsessions or compulsions, but she had experienced occasional panic attacks. The family history was unknown, as she was adopted at birth. Physically, she was healthy, and recent blood work confirmed normal thyroid function.

There was a history of poor response to several trials of antidepressants including 40 mg of fluoxetine (8 wk), 200 mg of sertraline (6 wk) and 225 mg of desipramine (6 wk). She was currently taking 300 mg of bupropion, 375 mg of venlafaxine, 750 mg of lithium, 50 mg of quetiapine and 2 mg of clonazepam (as needed). For the index episode, she received 300 mg of bupropion (8 wk) followed by the addition of 225 mg of venlafaxine. Her condition improved somewhat with bupropion, but she experienced a loss of response after 4 weeks. On titration of the venlafaxine dose, psychomotor agitation, racing thoughts, irritability, distractibility, insomnia and suicidal ideation developed, and lithium and quetiapine were added. She had similar symptoms with desipramine for a previous episode. She refused a trial of electroconvulsive therapy.

The patient was suspected to have TRD

with a bipolar diathesis. Clues to the bipolar nature of depression included a history of atypical symptoms of depression, emergent manic symptoms following the use of antidepressants, poor response to prior antidepressants and a loss of antidepressant response. Venlafaxine, and then bupropion, were slowly tapered off. Even though the antidepressants were withdrawn over several weeks, she experienced symptoms of antidepressant discontinuation syndrome, including worsening of insomnia and agitation. The quetiapine dose was optimized to 150 mg and the lithium dose remained unaltered. At the higher dose of quetiapine, she no longer needed clonazepam, which was discontinued. The patient has remained free of depressive or hypomanic symptoms for about 2 years.

This patient's case demonstrates the challenges of managing TRD in contemporary clinical practice. Reasons for poor response to antidepressant therapy include treatment nonadherence, inadequate dose and duration of antidepressant treatment, comorbid anxiety or substance use disorders and concomitant psychotic symptoms.<sup>1,2</sup> A recent study suggests that about 40% of patients with a history of major depression had a history of subthreshold mania.<sup>3</sup> Bipolarity may be more prevalent among patients with "unipolar" TRD.<sup>4,5</sup> A diagnostic re-evaluation should be the first step in the management of TRD. Attention to the cross-sectional symptomatology and the longitudinal illness course is important to clarify the diagnosis. Depressed patients should be routinely screened for subthreshold manic symptoms before the initiation of antidepressants. Variability in clinical presentation of depressive mixed states and the lack of consensus about their diagnostic criteria makes their detection difficult. Use of antidepressants in individuals with a

bipolar diathesis may convert the typical presentation of hypersomnic, retarded depression into an agitated, anxious mood state with accompanying insomnia and racing thoughts. Patients taking drugs like neuroleptics and benzodiazepines that have a preferential effect against manic symptoms may no longer experience hypomania resulting in a clinical state dominated by depressive symptoms. Therefore, it is important to be aware of the illness course before and after the introduction of antidepressants.

Patients with TRD with a clear bipolar diathesis should be managed with mood stabilizers.<sup>5,6</sup> Antidepressants should be tapered off slowly with close monitoring for symptoms of antidepressant discontinuation syndrome. For patients taking antidepressants and mood stabilizers, discontinuation of antidepressants and continued treatment with mood stabilizers may be effective in alleviating depression. Others may require optimized doses of mood stabilizers. Whereas polypharmacy may be unavoidable, every effort should be made to keep the overall number of medications used to a minimum. In general, the same guidelines used for bipolar depression should apply to the management of bipolar TRD.<sup>7</sup>

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