A Case of Major Depressive Disorder With Mixed Features: Diagnostic and Treatment Issues

To the Editor: Manic symptoms are common in patients with major depressive disorder (MDD) with the prevalence of mixed depression approaching that observed for pure MDD in some studies.[1,2] Compared with patients who have pure depression, those with mixed depression have higher rates of comorbid anxiety disorders, substance use disorders, and suicidal behavior.[3,4] While there is increasing evidence that unrecognized bipolar disorder might be a contributing factor to antidepressant resistance in individuals with depression,[5,6] it is not clear whether intraepisodic presence of manic symptoms as in mixed depression is also associated with resistance to antidepressant therapy. We describe the successful management of a patient with treatment-resistant depression in whom the chronic use of antidepressants may have led to induction of mixed features and increased risk for suicide.

Case report. Mr A, a 60-year-old happily married father of 2 children, was referred to our mood disorders clinic by his psychiatrist for assessment and management of chronic treatment-resistant depression. At his first visit to our clinic, he reported current symptoms of depression including sad mood, diminished interest, insomnia, psychomotor agitation, indecisiveness, and feelings of worthlessness. A history of discrete hypomanic or manic episodes was denied, but both the patient and his wife noted the intraepisodic presence of pressured speech, increased goal-directed activity, flight of ideas, and irritability during depression. With the exception of occasional brief periods (less than 2 weeks) of partial improvement, he reported persistence of depression over the last 5 years. Due to concerns regarding his safety, Mr A had been hospitalized 5 times during the previous year and a half and had cumulatively spent 8 months in the hospital. He had made 2 serious suicide attempts: one with carbon monoxide poisoning and the other with a deep laceration to his throat. A family member had interrupted a third attempt by carbon monoxide inhalation.

Mr A had failed to respond to adequate trials of bupropion 350 mg, mirtazapine 45 mg used alone or adjunctively with methotrimeprazine 50 mg, zopiclone 7.5 mg, temazepam 30, and flurazepam 15 mg. He had 2 courses (total of 28 treatments) of bilateral electroconvulsive therapy (ECT). Cumulatively, he had 60 sessions of individual cognitive-behavioral and psychodynamic therapy with a psychologist and a psychiatrist in combination with pharmacotherapy. Previous treatment also included attendance at a day program 5 days a week for 6 weeks. Mr A did not find psychotherapy helpful but noted transient improvement following trials of ECT and antidepressants.

Regarding past psychiatric history, he recalled having symptoms of anxiety when he was 7 or 8 years old, but first sought professional help when he developed symptoms of depression in his early thirties. He was prescribed diazepam 5 mg daily that he took intermittently for 1 year. There were brief recurrences of depression over the next 15 years, but these episodes did not interfere with his level of functioning at home or at his workplace. There was no history of alcohol abuse or use of illicit drugs. Family history was positive for depression in his 2 sisters. His father had anger attacks and may have abused alcohol.

Laboratory investigations including complete blood count and thyroid functioning showed normal results. The Structured Clinical Interview for *DSM-IV-TR* Axis I Disorders, Research Version, Patient Edition (SCID-I/P)[7] indicated a current diagnosis of chronic, severe MDD without psychotic features and anxiety disorder not otherwise specified. A magnetic resonance imaging of the head was normal.

We concurred with the previous SCID-I/P diagnosis of MDD and anxiety disorder not otherwise specified; however, following the publication of the *DSM-5*, the diagnosis was revised to MDD with mixed features and anxious distress. At his initial visit to our clinic, Mr A was taking nortriptyline 50 mg, methotrimeprazine 25 mg, quetiapine 200 mg, venlafaxine 150 mg, and zopiclone 15 mg a day for at least 3 months. Due to the lack of sustained response to antidepressant treatment and the high risk of suicide, we added lithium carbonate 600 mg to his drug regimen. The dose was eventually increased to 1,050 mg, which produced a serum level of 0.82 mmol/L. Within a month of starting lithium, the depression worsened, necessitating another hospitalization. During the 3-week hospital stay, Mr A was treated with ECT (9 treatments). He initially responded to ECT but became depressed 9 days after ECT was discontinued. Lamotrigine was added following the completion of ECT. As the lamotrigine dose was increased to 75 mg, he experienced new onset of intrusive song lyrics. Lamotrigine was discontinued, and the obsessive sensations disappeared. As the depressive symptoms persisted, the quetiapine dose was increased to 300 mg, but he was unable to tolerate it due to restless legs syndrome that interfered with his sleep. A trial of pramipexole 0.5 mg was initiated that proved to be ineffective. Next, clonazepam 2 mg at night was added to relieve the restless legs syndrome. This addition enabled us to optimize the quetiapine dose to 600 mg. As Mr A continued to have residual symptoms of depression, we decided to taper off venlafaxine.

Mr A's current medications include lithium 1,050 mg (0.77 mmol/L at his last outpatient visit), quetiapine 600 mg, and clonazepam 2 mg daily. He has been free of mood and anxiety symptoms for nearly 3 years, and he has not made a suicide attempt or required a psychiatric hospitalization in 6 years. No hypomanic or manic episodes have emerged during the follow-up. His level of functioning has improved such that he has been doing volunteer work. Over the past 2 years, he has been seen in follow-up every 3 months.

This case raises some challenging unanswered questions. First, were antidepressants simply ineffective or did they actually contribute to treatment resistance? It has been suggested that the prolonged use of antidepressants in some predisposed individuals could cause worsening of depression.[5–10] This was most likely the case in Mr A, because there was only minimal improvement following the addition of lithium and optimization of quetiapine, but there was immediate and sustained remission following the discontinuation of venlafaxine.

Second, did the use of antidepressants contribute to suicide attempts? There was no history of suicide attempts prior to the initiation of antidepressants. Yet, it should also be noted that mixed depressive episodes and rapidly fluctuating cycles are associated with increased suicide attempts. A detailed review of the chart and interviews with Mr A about his mental state around the times of suicide attempts revealed worsening of manic symptoms including insomnia, racing thoughts, agitation, and irritability. Moreover, on both occasions, there had been an increase in the dose of antidepressants just prior to the suicide attempts.

Given the serious consequences of failing to identify mixed features, it is imperative that patients with MDD, particularly those with treatment-resistant depression or those who are at

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high risk for suicide, be routinely evaluated for concomitant hypomanic symptoms. Treatment data on mixed depression are generally derived from subanalyses or post hoc analyses of studies that have included patients with both manic and depressive episodes. However, there are no data on the management of mixed depression. Due to the paucity of specific data, treatment decisions should be made on a case-by-case basis, taking into consideration family history, the illness course, comorbid psychiatric symptoms/disorders, severity of the disorder, treatment response, safety issues, and patient preference. Patients who fail repeated antidepressant trials should be considered for cautious tapering of these drugs and initiation of mood stabilizers.

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Verinder Sharma, MBBS
vsharma@uwo.ca
Rudy Bowen, MDCM
Priya Sharma, MD

Author affiliations: Departments of Psychiatry (Drs V. Sharma and P. Sharma) and Obstetrics and Gynecology (Dr V. Sharma), Western University, London, Ontario; Perinatal Clinic, St Joseph's Health Care, London, Ontario (Dr V. Sharma); and Department of Psychiatry, College of Medicine, University of Saskatchewan, Saskatchewan (Dr Bowen), Canada.

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