The current characterization of major depressive disorder is the key problem. In DSM criteria for major depressive disorder, many features of melancholia have been adopted, while allowing many nonmelancholic features. Of nine qualifying items, only five are required for major depressive disorder. This disjunctive format guarantees heterogeneity within the diagnosis. Moreover, because the melancholia specifier criteria overlap so much with the criteria for unspecified major depressive disorder, it becomes logically problematic to establish melancholia as a distinctive disorder in evaluating biomarkers or treatment specificity. When alternate criteria for melancholia versus nonmelancholic major depressive disorder are employed, differential treatment outcomes emerge. For example, the Newcastle Scale predicts ECT response (3); the meta-analysis by Perry (4) reported tricyclic antidepressants as distinctly superior to selective serotonin reuptake inhibitors; and higher ratings on the Clinical Outcome in Routine Evaluation show superior responses to antidepressant drugs and to ECT (1, pp. 160–171).

The Mallinckrodt et al. study cited by Dr. Kocsis misapplied even the limited DSM criteria for the melancholia specifier. Mallinckrodt et al. used an idiosyncratic Mini-International Neuropsychiatric Interview that does not measure the criteria central to the melancholia definition. While the usefulness of neuroendocrine markers is rejected by Dr. Kocsis, the evidence is strong that the Dexamethasone Suppression Test does differentiate ICD-8-defined melancholic and nonmelancholic depression (2). And, in challenging the argument that melancholia responds poorly to placebo, he ignores evidence presented by Brown (5).

In our view, melancholia is a distinctive syndrome clinically defined by specific and pervasive disturbances in affect, psychomotor activity, vegetative functions, and cognition—and, in a subset of patients, by psychosis. The risk of suicide is high. Tricyclic antidepressants and ECT are differentially superior treatments. To advance diagnosis-specific treatment and research, melancholia should be acknowledged as an entity, not marginalized as a secondary specifier. Given the stakes, the importance of getting the diagnosis right is considerable.

References

1. Parker G, Hadzi-Pavlovic D: Melancholia: A Disorder of Movement and Mood. Cambridge, United Kingdom, Cambridge University Press, 1996
2. Taylor MA, Fink M: Melancholia: The Diagnosis, Pathophysiology and Treatment of Depressive Illness. Cambridge, United Kingdom, Cambridge University Press, 2006
3. Carney MWP, Roth M, Garside RF: The diagnosis of depressive symptoms and the prediction of ECT response. Br J Psychiatry 1965, 111:659–674
4. Perry PJ: Pharmacotherapy for major depression with melancholic features: relative efficacy of tricyclic versus selective serotonin reuptake inhibitor antidepressants. J Affect Disord 1996; 39:1–6
5. Brown WA: Treatment response in melancholia. Acta Psychiatr Scand Suppl 2007; 115:125–129

GORDON PARKER, M.D.
Sydney, Australia
MAX FINK, M.D.
Saint James, N.Y.
EDWARD SHORTER, PH.D.
Toronto, Canada
MICHAEL ALAN TAYLOR, M.D.
Ann Arbor, Mich.
HAGOP AKISKAL, M.D.
San Diego, Calif.
GERMAN BERRIOS, M.D.
Cambridge, United Kingdom
TOM BOLWIG, M.D.
Copenhagen, Denmark
WALTER A. BROWN, M.D.
Tiverton, R.I.
BERNARD CARROLL, M.B.B.S.
Carmel, Calif.
DAVID HEALY, M.D.
Gwynedd, Wales, United Kingdom
DONALD F. KLEIN, M.D.
New York, N.Y.
ATHANASIOS KOUKOPOULOS, M.D.
Rome, Italy
ROBERT MICHELS, M.D.
New York, N.Y.
JOEL PARIS, M.D.
Montreal, Quebec, Canada
ROBERT T. RUBIN, M.D.
Los Angeles, Calif.
ROBERT SPITZER, M.D.
New York, N.Y.
CONRAD SWARTZ, M.D.
Springfield, Ill.

The authors' disclosures accompany the original editorial.

This letter (doi: 10.1176/appi.ajp.2010.10091297) was accepted for publication in September 2010.

New-Onset Psychosis and Emergence of Suicidal Ideation With Aripiprazole

TO THE EDITOR: Aripiprazole is an atypical antipsychotic approved for treatment of schizophrenia and bipolar disorder as well as use as adjunctive therapy in major depressive disorder. We report the case of an emergence of psychotic symptoms in a patient following the addition of aripiprazole to duloxetine.

"Ms. L" was a 49-year-old woman with chronic depression and postoperative cellulitis following a bunion excision. She was evaluated on the medical unit. She endorsed depressive symptoms, auditory hallucinations, and suicidal thoughts. The patient had previously attempted suicide twice by drug overdose. Her most recent suicide attempt was 7 months prior. Previous responses to sertraline and citalopram were poor. At the time of assessment on the medical unit, she was receiving duloxetine (40 mg twice daily), aripiprazole (1 mg/day), clonazepam (1 mg twice daily), and amoxicillin/clavulanate (850 mg twice daily).

The patient was started on duloxetine 7 months before. Ten days prior to admission, her primary care physician had started her on aripiprazole (2 mg/day) for augmentation. She denied a history of psychotic symptoms and drug or alcohol abuse as well as a family history of psychosis.

Three days after starting aripiprazole, Ms. L reported auditory hallucinations. She was paranoid regarding her ex-husband. She described command hallucinations from the devil, who meant to harm her, and could also hear God's voice encouraging her not to listen to the devil. She experienced concurrent onset of suicidal ideation

with no plan. She was fully oriented, with no evidence of confusion. Aripiprazole was reduced to 1 mg/day, which led to amelioration of her hallucinations. However, her suicidal thoughts and paranoid beliefs persisted.

The psychiatric consultant decided to discontinue aripiprazole, leading to rapid and complete resolution of the patient's psychotic symptoms and suicidal ideation. Her ongoing depression was managed with duloxetine (60 mg twice daily).

Emergence of psychotic symptoms immediately following the addition of aripiprazole suggests a causative role of the drug in the onset of the present patient's psychosis. Furthermore, improvement in this patient's psychosis upon reduction of aripiprazole as well as complete resolution of psychosis following discontinuation further support an inference that the compound was a causal agent. The patient was not started on any other medication known to potentiate psychosis. Her antibiotic regimen was instituted 9 days after starting aripiprazole. She attained menopause approximately 1 year before, which doesn't completely eliminate her predisposition to psychosis secondary to dropping estrogen levels.

A diagnosis of major depressive disorder with psychotic features was ruled out, based on lack of prior history, temporal relationship between drug initiation and emergence of symptoms, and, most importantly, complete remission of psychotic symptoms on antipsychotic discontinuation.

The most likely explanation for this phenomenon is aripiprazole's action as a dopamine partial agonist (1, 2). Aripiprazole alleviates psychosis by interfering with dopamine transmission, but its agonist action at the D_2 receptor can intensify psychosis. There are case reports that aripiprazole worsens psychosis (3–5) and increases suicidal ideation (6), but the present case is the first, to our knowledge, in which aripiprazole apparently induced psychosis. Another possibility may be the combination of a selective serotonin reuptake inhibitor and aripiprazole, which offsets aripiprazole's dopamine-serotonin system stabilizer functioning. We recommend detailed history taking and monitoring for psychotic symptoms when using aripiprazole in the management of nonpsychotic depression.

References

1. Tadori Y, Miwa T, Tottori K, Burris KD, Stark A, Mori T, Kikuchi T: Aripiprazole's low intrinsic activities at human dopamine D_{2L} and D_{2S} receptors render it a unique antipsychotic. Eur J Pharmacol 2005; 515:10–19
2. Wood M, Reavill C: Aripiprazole acts as a selective dopamine D_2 receptor partial agonist. Expert Opin Investig Drugs 2007; 16:771–775
3. Ramaswamy S, Vijay D, William M, Sattar SP, Praveen F, Petty F: Aripiprazole possibly worsens psychosis. Int Clin Psychopharmacol 2004; 194:45–48
4. Ahuja N, Lloyd AJ: Aripiprazole and worsening of psychosis: a case report. J Clin Psychiatry 2007; 68:805–806
5. Grover S, Sharan P, Gupta N: Aripiprazole worsens psychosis: a case report. Prim Care Companion J Clin Psychiatry 2006; 8:380–381
6. Beers E, Loonen AJ, Van Grootheest AC: Suicidal ideations and suicide attempts after starting on aripiprazole: a new antipsychotic drug. Ned Tijdschr Geneeskd 2006; 150:401–402

VITHYALAKSHMI SELVARAJ, M.D.
SRIRAM RAMASWAMY, M.D.
ASHISH SHARMA, M.D.
DANIEL WILSON, M.D.
Omaha, Nebraska

The authors report no financial relationships with commercial interests.

This letter (doi: 10.1176/appi.ajp.2010.10020238) was accepted for publication in June 2010.