parental status, making the healthy parenthood effect a plausible explanation.

SUSANNE OKSBJERG DALTON, M.D., PH.D.
THOMAS MUNK LAURSEN, M.SCI.
LENE MELLEMKJAER, M.SCI., PH.D.
CHRISTOFFER JOHANSEN, M.D., PH.D.
PREBEN BO MORTENSEN, M.D., DR.MED.SCI.
Copenhagen, Denmark

Irritability and Depression

TO THE EDITOR: Manics are irritable. Some depressives are irritable. Ergo, some depressives are bipolar. Not necessarily true. This topic was discussed in a recent article by Giovanni B. Cassano, M.D., et al. (1).

DSM-III and DSM-IV turned diagnoses into symptom checklists. This may increase the reliability of diagnosis, but it does not follow that the symptom necessarily is associated with the diagnosis. Many diagnoses are associated with irritability or distractibility, and even more are associated with impaired concentration or insomnia. These symptoms may occur in mania, but they are so nonspecific that they cannot be said to imply mania.

Much of medicine used to be like psychiatry, i.e., without definitive diagnostic tests. Imagine diagnosing a myocardial infarction without ECGs or enzymes; a constellation of symptoms, including chest pain, diaphoresis, dizziness, irregular heartbeat, etc., suggest a myocardial infarction, but none of these symptoms alone would indicate a myocardial infarction. All occur much more frequently in other conditions.

An unfortunate (and unintended) legacy of DSM-III and DSM-IV is the attribution of diagnostic significance to nonspecific symptoms that are only diagnostically meaningful when they are part of a constellation of symptoms or a syndrome. This has led to agitated, irritable depressives being called bipolar (often "mixed") and to the overdiagnosis of bipolar disorder (analogous to the overdiagnosis of schizophrenia prior to 1970).

Undeniably, some apparent unipolar depressives will turn out to be bipolar. However, the majority of unipolar depressives will never become manic or hypomanic, even with antidepressants, and the presence of irritability, agitation, and other nonspecific symptoms associated with mania does not make these patients even a little bit bipolar.

Reference

1. Cassano GB, Rucci P, Frank E, Fagiolini A, Dell'Osso L, Shear MK, Kupfer DJ: The mood spectrum in unipolar and bipolar disorder: arguments for a unitary approach. Am J Psychiatry 2004; 161:1264–1269

JEFFREY A. MATTES, M.D.
Princeton, N.J.

Dr. Cassano Replies

TO THE EDITOR: In our recent article on the mood spectrum, we showed that in patients with carefully diagnosed recurrent unipolar depression, there is variability in the lifetime experience of manic-hypomanic symptoms and that increased scores on this manic-hypomanic component of our measure of mood spectrum were associated with a higher likelihood of suicidality and paranoia.

It is undeniable, as Dr. Mattes asserts, that the presence of irritability does not necessarily imply mania. Indeed, our conclusions were not based on individual symptoms but on a dimension that includes 60 items, of which only three could be construed to assess irritability. Therefore, although irritability is frequent, it is not the most prominent aspect of the manic-hypomanic component, which includes a range of mood, energy, and cognitive features.

Regarding the attribution of diagnostic significance to "nonspecific symptoms," our intention was not to purport that unipolar patients who have a high number of manic-hypomanic features should be relabeled "bipolar." Still, the linear relationship found between the depressive and the manic-hypomanic components in patients with both unipolar and bipolar disorder when we used a dimensional approach suggests continuity between these disorders. Moreover, we found an association between the manic-hypomanic component and suicidality and paranoia both in unipolar *and* bipolar patients. In our view, this finding has important clinical implications. The question of whether this dimensional spectrum approach will eventually lead to the identification of a distinct phenotype of unipolar patients presenting similarities with bipolar patients is still open. We are currently conducting a clinical trial that we hope will shed some light on this issue.

GIOVANNI B. CASSANO, M.D.
Pisa, Italy

Sertraline for Recurrent Major Depression

TO THE EDITOR: Jean-Pierre Lépine, M.D., and his colleagues (1) evaluated the efficacy of sertraline for the prophylactic treatment of recurrent depressive disorder. We read this double-blind, randomized study with great interest and wish to raise some concerns about the methodological issues.

The use of placebo arms in randomized, controlled trials remains a controversial issue. It has been criticized on ethical grounds. In this context, the Declaration of Helsinki demands that individual patients in a study "be assured of the best proven diagnostic and therapeutic method," even in a control group (2). This statement clearly discards the use of a placebo as a control when a "proven" treatment exists.

In this trial, the way the authors tried to establish that sertraline is more effective than placebo is misleading. Even if sertraline is worse than an existing treatment, it may still be "effective" in that it is better than no treatment (placebo). In this regard, Hill (3) pointed out that the essential medical question at issue is how the new treatment compares with the old one, not whether the new treatment is better than nothing. Similarly, Cochrane (4) stated that no new treatment should be introduced into medicine unless it has been shown in randomized, controlled trials to be superior to existing treatments or equivalent to existing treatment but cheaper or safer.

As there are drugs with proven efficacy for recurrent depressive disorders, such as lithium, we are keen to know why the authors did not try to compare the efficacy of sertraline with existing drugs. It appears that the authors were keen to reflect a drug-specific effect rather than demonstrating its relative efficacy. As readers, we would like to know why the authors carried out such a long placebo phase (2 months). The