Diagnostic Instability: How Much Is Too Much?

Efforts to improve the validity of psychiatric diagnoses are necessarily iterative and, at the same time, dependent on the limitations of such approaches as family studies and phenomenological clustering techniques. The assessment of diagnostic stability is a far more direct test of validity but is rarely used because repeated and thorough diagnostic reassessments that span long periods require a stable group of investigators and considerable effort, not the least of which is that required to maintain research support for such an enterprise. The quantification of diagnostic stability and the identification of features associated with instability are also of much more practical import than are the results of family or factor analytic studies. The differences between a diagnosis of major depressive disorder, that of schizophrenia, and that of bipolar disorder are profound, not only in the pharmacopeias typically used but also in the descriptions provided to newly diagnosed individuals and their families as to what lies ahead. In this issue, Bromet et al. (1) describe an effort that stands out in a relatively scant literature on this topic in its combination of sample size, its rigor of baseline and subsequent diagnostic assessments, and its length of observation. What did they find?

Perhaps the most salient of the findings was that psychotic subjects were much more likely to move into schizophrenia, both from major depressive disorder and from bipolar disorder, than to move out; 30% who began with major depression and 15% who began with bipolar disorder were classed as having schizophrenia after 10 years. These are higher rates than those reported in early studies, and this is likely to reflect, in large part, this follow-up's greater duration. The large majority of subjects who switched status from major depressive disorder to schizophrenia did so after the 2-year follow-up, and most earlier studies were of 2 years' duration or less. Notably, other groups that followed cohorts of patients with psychotic depression to 1 year (2), 2 years (3), and 4 years (4) reported rates of shifts from major depression to schizophrenia of 0%, 1.8%, and 18.2%, respectively.

"Perhaps the most encouraging finding here...was that the group assigned to 'other psychosis' at baseline experienced by far the largest shrinkage of any group by year 10, from 118 to 35."

The elegant efforts of Bromet et al. to identify evolving antecedents of diagnostic shifts yielded few surprises. Most of the symptoms and treatment changes preceding shifts to a schizophrenia diagnosis were consistent with an emerging schizophrenic picture. Of paramount importance to a clinician caring for a patient with a first episode of psychotic depression or mania, however, are those historical and symptom descriptors that increase the likelihood of an eventual schizophrenia outcome. Here it is notable that the only baseline symptom measure that predicted a shift into schizophrenia at 2 years (5) was the Scale for the Assessment of Negative Symptoms (6). Increases in negative symptoms continued to be among the most robust portents of a change to schizophrenia throughout the 10-year interval. The only historical features to survive in a logistic regression of predictors of such a shift at 2 years were the lack of a lifetime substance abuse disorder, an insidious onset, and poor psychosocial adjustment during adolescence. The latter finding is consistent with earlier results from the cohort in the National Institute of

Mental Health collaborative depression study. In that instance, one of the few historical features predictive of chronic psychosis among individuals with a baseline diagnosis of psychotic or schizoaffective depression was a six-point rating of adolescent friendship patterns, and it did so in a strikingly stepwise fashion (7).

The likelihood of shifts from major depressive disorder to bipolar disorder is more widely appreciated and can be viewed as less fundamental than shifts from psychotic mood disorder to schizophrenia. The literature that concerns the prediction of switching between major depression and bipolar disorder is far more extensive than that for shifts to schizophrenia. Those findings have limited comparability to those of the current follow-up, though, because the baseline category of "other" supplied more new bipolar diagnoses than did the baseline diagnosis of major depressive disorder and the analyses lumped together entries to the bipolar group from all other categories. Although earlier reports found early onset, a family history positive for bipolar disorder, and the presence of psychosis itself to predict shifts from major depression to bipolar disorder, recent findings show that an admixture of manic/hypomanic symptoms within a major depressive episode is also a potent risk factor (8). Most studies that have used structured interviews for baseline diagnostic assessment were unable to access the prognostic importance of such admixtures because most modules for manic and hypomanic syndromes skip further questioning when a subject scores negatively for euphoria and irritability. Unfortunately, diagnostic assessments for the study by Bromet et al. suspended skip-outs only for the depressive module. Nevertheless, findings that associate such admixtures both with family histories of bipolar disorder (9) and with shifts into that category (10) provide support for what will probably be the only change in the DSM-5 description of major depressive disorder with relevance to diagnostic stability, the provision of a "mixed" specifier.

Perhaps the most encouraging finding here, though not discussed, was that the group assigned to "other psychosis" at baseline experienced by far the largest shrinkage of any group by year 10, from 118 to 35. This is a reminder both that much diagnostic uncertainty resolves with time and that a small but substantial group will continue to be enigmatic.

For investigators seeking to identify biomarkers or genotypes, the results here for schizophrenia seem reassuring. For bipolar and major depressive disorders, it should be remembered that all subjects had psychotic features at study entry and that such features substantially raise the risk for an eventual diagnosis of schizophrenia or, in the case of major depressive disorder, a diagnosis of bipolar disorder. Most efforts to study the biology of bipolar or major depressive disorder do not confine samples to those with psychotic features and so can assume lower rates of eventual diagnostic change. Investigators who do focus on major depression with psychotic features, though, would do well to reconsider the inclusion of subjects who have had an insidious onset, persistently prominent negative symptoms, and poor adolescent social functioning.

References

1. Bromet EJ, Kotov R, Fochtmann LJ, Carlson GA, Tanenberg-Karant M, Ruggero C, Chang S-W: Diagnostic shifts during the decade following first admission for psychosis. Am J Psychiatry 2011; 168:1186–1194
2. Amini H, Alaghband-rad J, Omid A, Sharifi V, Davari-Ashtiani R, Momeni F, Aminipour Z: Diagnostic stability in patients with first-episode psychosis. Australas Psychiatry 2005; 13:388–392
3. Salvatore P, Baldessarini RJ, Tohen M, Khalsa HM, Sanchez-Toledo JP, Zarate CA Jr, Vieta E, Maggini C: McLean-Harvard International First-Episode Project: two-year stability of ICD-10 diagnoses in 500 first-episode psychotic disorder patients. J Clin Psychiatry 2011; 72:183–193
4. Whitty P, Clarke M, McTigue O, Browne S, Kamali M, Larkin C, O'Callaghan E: Diagnostic stability four years after a first episode of psychosis. Psychiatr Serv 2005; 56:1084–1088
5. Schwartz JE, Fennig S, Tanenberg-Karant M, Carlson G, Craig T, Galambos N, Lavelle J, Bromet EJ: Congruence of diagnoses 2 years after a first-admission diagnosis of psychosis. Arch Gen Psychiatry 2000; 57:593–600
6. Andreasen NC: Scale for the Assessment of Negative Symptoms (SANS). Iowa City, University of Iowa, 1983
7. Coryell W, Keller M, Lavori P, Endicott J: Affective syndromes, psychotic features, and prognosis, I: depression. Arch Gen Psychiatry 1990; 47:651–657

8. Fiedorowicz JG, Endicott J, Leon AC, Solomon DA, Keller MB, Coryell WH: Subthreshold hypomanic symptoms in progression from unipolar major depression to bipolar disorder. Am J Psychiatry 2011; 168:40–48
9. Maj M, Pirozzi R, Magliano L, Fiorillo A, Bartoli L: Agitated "unipolar" major depression: prevalence, phenomenology, and outcome. J Clin Psychiatry 2006; 67:712–719
10. Zimmermann P, Brückl T, Nocon A, Pfister H, Lieb R, Wittchen HU, Holsboer F, Angst J: Heterogeneity of DSM-IV major depressive disorder as a consequence of subthreshold bipolarity. Arch Gen Psychiatry 2009; 66:1341–1352

WILLIAM CORYELL, M.D.

From the Department of Psychiatry, Carver College of Medicine, University of Iowa, Iowa City. Address correspondence to Dr. Coryell (william-coryell@uiowa.edu). *Editorial accepted for publication August 2011 (doi: 10.1176/appi.ajp.2011.11081191).*

Dr. Coryell reports no financial relationships with commercial interests.