Comorbidity of Mood and Anxiety Disorders: The Rule, Not the Exception?

For decades, mood and anxiety disorders were considered distinct and unrelated groups of disorders. In retrospect, from almost every vantage point—including preclinical and clinical laboratory studies (1, 2), careful clinical observation, and standardized methods to evaluate both symptomatic and syndromal overlap (3)—this "separist" view is not supported by the available data. Indeed, we now know that patients with major depression invariably show either syndromal comorbidity of one or another anxiety disorder or clinically significant severity of anxiety symptoms. Indeed, in patients with major depression and patients with generalized anxiety disorder, there is a strong positive correlation between measures of severity of both depression and anxiety symptoms, as assessed by the Hamilton Depression Rating Scale and the Hamilton Anxiety Rating Scale, respectively. Finally, the efficacy of major psychotropic drugs—including paroxetine, venlafaxine, sertraline, and fluvoxamine (4)—and perhaps potential new agents such as corticotropin-releasing factor 1 receptor antagonists (5) and substance P receptor antagonists (6) in the treatment of depression and a broad spectrum of anxiety disorders (e.g., generalized anxiety disorder, panic disorder, social anxiety disorder, and posttraumatic stress disorder) is well established.

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The elucidation of the pathophysiology of complex major medical disorders and their subtypes and the development of the best treatments for them have been accomplished by a remarkable panoply of disciplines, ranging from preclinical disease models and clinical pathophysiology to epidemiology and genetics. With the achievement of the sequencing of the human genome, molecular genetic studies now provide the hope for identification of the contribution of particular genes in the development of these disorders; eventually, the nature of the gene products might actually inform the field about novel treatment options.

Two reports in this issue of the *Journal* are examples of the contributions of epidemiology and genetics in elucidation of hitherto unrecognized characteristics and subtypes of complex psychiatric disorders. We have previously witnessed the power of such studies in our field. Two prominent examples come to mind: 1) the seminal study by Weissman and colleagues (7), based on the Epidemiologic Catchment Area (ECA) study, documenting the remarkably high rate of suicide attempts in patients with panic disorder and comorbid axis I conditions, including major depression, and 2) the study by Kendler and colleagues (8) that confirmed and extended previous observations of the preeminent role of trauma early in life in the vulnerability to major depression in adulthood.

One of the two reports in this issue of the *Journal* uses data from the National Institute of Mental Health (NIMH) Bipolar Disorder Genetics Initiative. MacKinnon et al. conducted a follow-up to their previous study in which they had reported an unusually high prevalence rate of panic disorder in 57 families with high rates of bipolar disorder. MacKinnon et al. concluded in their earlier study that there might be a genetic subset of patients with bipolar disorder who had comorbid panic disorder. Indeed, families at high risk of panic disorder showed linkage to markers on the long arm of chromosome 18, but families of probands without panic disorder did not. The study reported in this issue of the *Journal* sought to address questions about panic attacks and panic disorder as a phenotypic marker of the genetic heterogeneity of bipolar disorder.

The NIMH Bipolar Disorder Genetics Initiative provided 203 families with 966 first-degree relatives. Families of probands with both panic disorder and panic attacks were included, yielding a single group defining a variable for familial panic risk. The risk of a family member being diagnosed with panic disorder if the proband with bipolar disorder had panic was calculated. The results were striking. More than 90% of individuals with panic disorder also had an affective disorder, and panic was present in 17% of the relatives with recurrent affective disorder compared with 3% of the relatives without recurrent major affective disorder. MacKinnon et al. concluded that familial bipolar disorder is a risk for panic disorder and suggested that subsequent molecular genetics studies further illuminate this association.

The second report in this issue, by Rotondo and colleagues, is such a study—a case-control association study of the genetic polymorphisms of three monoamine neurotransmitter system candidate genes, catechol-*O*-methyltransferase (COMT), serotonin transporter (5-HTT), and tryptophan hydroxylase (TPH), in patients with bipolar disorder with and without lifetime panic disorder. The study included 127 healthy volunteers and 111 patients with bipolar disorder, 49 with and 62 without comorbid panic disorder. Polymorphisms were analyzed from blood leucocyte DNA. Remarkably, the patients with bipolar disorder without panic disorder showed significantly higher frequencies of the COMT Met158 and the short 5-HTTLPR alleles and genotypes. Thus, 40% of the patients with bipolar disorder without comorbid panic disorder were MET158/MET158 homozygotes associated with low COMT activity.

Taken together, these results suggest that bipolar disorder with and without comorbid panic disorder represent distinct genetic forms of this mood disorder. These findings raise fascinating questions. Do these two groups differ in course of illness, vulnerability to comorbid medical disorders such as coronary artery disease, and treatment response? Pharmacogenomic studies in these patient populations will undoubtedly shed light on the treatment response issue.

We have, indeed, come a long way from recognizing the common comorbidity of mood and anxiety disorders to defining biological-based subtypes of mood disorders according to the presence of panic disorder, and we are beginning to uncover their genetic underpinnings. With the advent of techniques to image gene expression in vivo, we may soon be able to determine such polymorphisms in the CNS of our patients and assess their effects on the function of the serotonin transporter protein and other elements that regulate neurotransmission.

References

1. Butler PD, Nemeroff CB: Corticotropin-releasing factor as a possible cause of comorbidity in anxiety and depressive disorders, in Comorbidity in Anxiety and Mood Disorders. Edited by Maser JD, Cloninger CR. Washington, DC, American Psychiatric Press, 1990, pp 413–435
2. Gulley LR, Nemeroff CB: The neurobiological basis of mixed depression-anxiety states. J Clin Psychiatry 1993; 54(Jan suppl):16–19
3. Wittchen HU, Zhao S, Kessler RC, Eaton WW: DSM-III-R generalized anxiety disorder in the National Comorbidity Survey. Arch Gen Psychiatry 1994; 51:355–364
4. Nemeroff CB: Depression and comorbid anxiety. Primary Psychiatry 1997; 4:53–67
5. Gutman DA, Owens MJ, Nemeroff CB: Corticotropin-releasing factor antagonists as novel psychotherapeutics. Drugs of the Future 2000; 25:923–931
6. Stout SC, Owens MJ, Nemeroff CB: Neurokinin(1) receptor antagonists as potential antidepressants. Annu Rev Pharmacol Toxicol 2001; 41:877–906
7. Weissman MM, Klerman GL, Markowitz JS, Ouellette R: Suicidal ideation and suicide attempts in panic disorder and attacks. N Engl J Med 1989; 321:1209–1214
8. Kendler KS, Thornton LM, Gardner CO: Stressful life events and previous episodes in the etiology of major depression in women: an evaluation of the "kindling" hypothesis. Am J Psychiatry 2000; 157:1243–1251

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