Models of Bipolar Disease and Their Clinical Implications

In assessing the current state of progress in understanding the pathogenesis of bipolar disease and seeking to point to future directions, we need to think of models of disease that provide the appropriate scaffolding. In this issue, four aspects of our clinical/basic neuroscience “toolbox” that may provide important leads in our desire to push the envelope of understanding are described. All of these areas, including neuropathology (postmortem studies), neuroimaging, genetics, and molecular biology, are relatively recent additions to the toolbox of the clinical researcher. Before I comment on each of these areas individually, it is noteworthy to point to those tools that will allow us to evaluate the success of our efforts. As clinical scientists, we are searching for appropriate surrogate markers to assess prognosis, treatment response, and risks for future difficulties. Any understanding of brain circuitry and the functional components of the brain and behavior will provide important leads, but we need to pay attention to the following: these action plans do not take into account that bipolar disease is a very early-onset disorder. Indeed, in a recent survey of over 2800 patients with bipolar disease, the median age of onset was 17.5 years (E. Frank and D.J. Kupfer, personal communication, 2000). The disease has a strong developmental component, so that the early identification of subsyndromal presentations will be a vital necessity in defining phenotypes for study. In addition to the complex phenotypic description of this disorder, the next important issue is that treatment response, unlike treatment response in recurrent depression, is a constantly moving target, with change rather than constancy being the rule. Using our neuroscience toolbox for biological assessment, we assume there is persistence in each clinical phase, but this is likely a false assumption. The numerous disease transitions represent an essential challenge to the interpretation of our neuroscience investigations. We will need to develop better clinical assessment measures that allow us to take into account these variations in clinical state. Furthermore, we will need to provide better measures of functional state as well as the statistical strategies to appropriately analyze these ongoing clinical and functional changes. Another key issue in the study of bipolar disorder is taking sufficient account of both psychiatric and other medical conditions. This is particularly important because it would appear that patients with bipolar disease are not only more liable to suffer from other psychiatric conditions such as panic disorder and alcohol and drug dependency, but also suffer more frequently from concurrent medical disease, particularly cardiovascular disease. Another complication of assessment relates to psychosis and the fact that mania can occur with and without psychotic features. Because of the extensive need for improved assessment (with clear nosologic implications that would broaden current DSM-IV classification to include bipolar spectrum conditions), it is appropriate to recommend that studies utilizing any of our clinical neuroscience tools be based on standardized, systematic clinical assessment methods across sites.

Given these concerns, there are questions as to whether we will be able to use the sophisticated tools of contemporary neuropathology, neuroimaging, genetics, and molecular biology appropriately. Up to the present, the majority of neuropathologic research in psychiatry has been directed toward schizophrenia, Alzheimer’s disease, and suicide. Vawter et al (2000) review the current data in bipolar disorder and conclude that some convergence exists in the area of glial reduction, with the number and density of glia cells reduced in bipolar disorder. Second, they point to the excessive signal activity that occurs in both the cyclic adenosine monophosphate and phosphatidylinositol cascades. One cause or effect of the overactivity of this signal cascade may be found in the increased number of locus coeruleus neurons and the dramatic increases in neuropeptides in the hypothalamus in bipolar disorder.

In contrast to the neuropathology research, neuroimaging studies, including magnetic resonance imaging, magnetic resonance spectroscopy, functional magnetic resonance, positron emission tomography, and single photon emission computed tomography (SPECT), have been conducted for the past decade. From their extensive review, Stoll and colleagues (2000) tentatively conclude that there is an increase in white matter hyperintensities in bipolar patients, even when they are young. Altered levels of compounds containing choline and phospholipidicesters in basal ganglia and the frontal cortex are another finding. Blood volume studies support the observed abnormality of the cerebellum in bipolar disorder. Glucose metabolic and blood flow studies suggest decreased frontal cortical activity in depression, whether unipolar or bipolar. Finally, Stoll et al draw our attention to limitations of current studies and technical suggestions for future studies.

In a third report, Berrettini (2000) reviews family and molecular genetic studies in bipolar disorder, certainly an area of great interest. This review stresses commonalities between bipolar disorder and schizophrenia, pointing to
multiple family studies with considerable nosologic overlap, as well as molecular genetic linkage studies demonstrating common susceptibility loci. Of particular interest are four regions of the genome (18p11.2, 13q32, 22q11–13, and 10p14) where bipolar disease and schizophrenia susceptibility may overlap. In addition, independent bipolar disease susceptibility loci have been reported at 18q22, 21q21, 4p16, and 12q24.

In a fourth report, Manji and Lenox (2000) discuss signaling and potential insights for pathophysiology of bipolar disorder. They conclude that components of signal transduction pathways in brain, such as protein kinase C, may not only play a role in the pathophysiology of the disease, but also represent targets for the action of mood stabilizers (i.e., lithium and valproate). It is also suggested that psychopharmacologic research strategies have most recently identified long-term actions of these mood stabilizers in the regulation of expression of genes implicated in processes involved in neuroplasticity, neuroprotection, and even neurogenesis.

The four reviews presented at our bipolar conference (Berrettini 2000; Manji and Lenox 2000; Stoll et al 2000; Vawter et al 2000) demonstrated consistently that the Ns for individual studies were insufficient to reach firm conclusions concerning a specific finding in any of these major measurement areas. Thus, larger multisite investigations with standardized methods across sites, perhaps in the form of a bipolar neuroscience consortium, may be the most appropriate response to this ongoing dilemma. Furthermore, it would appear that little attention is being paid to cross-fertilization and collaboration among those scientists conducting genetic, neuroimaging, and neuropathology research. Studies of bipolar disorder strategies that use enriched samples are necessary. For example, one might use neuroimaging techniques in patients with bipolar disease or high-risk individuals with a strong family history of bipolar disease. In a similar fashion, one might conduct specific genetic studies on the basis of a long-term treatment response to a mood stabilizer (cf. Grof 2000). Unless some level of incentivized collective activity is reached for populations that are difficult to study in the first place, we will face continued impediments. The conclusions of these reports all argue for more patients and longer term studies. They point to the need for collaborative activity between the scientific community and advocacy groups to provide sufficient patients and families to join as partners for investigation. The potential payoffs are considerable. Such advances can generate new treatment paradigms. They may also be able to suggest the appropriate point for early intervention and methods to reduce the number of discrete episodes experienced by a patient, each of which adds to the allostatic load and increases the chances of long-term chronicity (McEwen 2000). Given the rapid technical advances, we should be able to benefit substantially from our new neuroscience toolbox over the next decade.

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References