Introduction

Depression and Its Subtypes:
A Treatment Update

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Despite the considerable advance in recent years in our understanding of the course and treatment of major depressive disorder, psychiatry remains challenged by significant gaps in our understanding of the etiology of the disorder and in the adequacy of our therapeutics. Although the minority of patients seeking treatment for major depression will be refractory, the majority, despite our treatment efforts, will endure residual symptoms, continued impairment, and recurrences. For a disorder with the adverse social and health impact of major depression and a lifetime prevalence of about 15% of the population, the motivation to do better is compelling.

One particular challenge to research efforts on etiology and therapeutics of depression is the daunting heterogeneity of the disorder. Patients are heterogeneous across a variety of dimensions including the number and type of their symptoms and their age at onset of the disorder as well as the course and outcome of the disorder, its severity, comorbid conditions, treatment response, degree of impairment, familiality, and presence and nature of antecedents, just to name a few. Consider the challenge of the heterogeneity of symptoms alone. Within the category of major depressive episode as defined by DSM-IV, we identify patients as having one diagnosis, although the possible presentation of symptoms varies so widely that, within the structure provided by DSM-IV criteria, we encounter patients with diagnoses of major depression who have no individual symptoms whatsoever in common. For example, given that the disorder is defined by the presence of 5 of 9 possible symptoms, 1 patient might have depressed mood, insomnia, anorexia, suicidal thinking, and psychomotor agitation, while another patient may experience loss of interest, hypersomnia, hyperphagia, fatigue, difficulty concentrating, and psychomotor retardation. Do 2 such different presentations represent the identical pathologic entity? While the diagnostic criteria were based, in large measure, on consensus among experts and not on objective markers, they are nonetheless accepted as a reasonable attempt to establish a balance between diagnostic sensitivity and specificity and to be predictive of response to antidepressant therapies. Nonetheless, the variability of symptoms from patient to patient suggests that, within the larger category of major depression, there may be several distinct entities or subtypes.

Paralleling the heterogeneity of the disorder and its symptoms is the heterogeneity of our therapeutic armamentarium. Efficacy is established for agents that influence function of norepinephrine, serotonin, or dopamine (or combinations thereof), with impact on uptake transporters, autoreceptors, and postsynaptic receptors. For some agents, mechanisms of action are unknown. Treatments as distinct as electro-

convulsive therapy and cognitive therapy are established as efficacious. A new, potentially effective therapy is in development that antagonizes substance P receptors.

Thus, we must consider the possibility that there are distinct subtypes of depressions, and, if so, that they might respond specifically to different types of treatments. The implications of this possibility are several. In our efforts at new antidepressant drug development, we may fail to discover treatments that are specific for a subtype of depression because their efficacy is missed when studied in a heterogeneous population. Identification of subtypes of depression would be extremely informative for efforts to determine genetic predisposition to mood disorders. Moreover, recognition of specific subtypes of depression could have usefulness for predictions of course and outcome of patients seeking treatment, and, ultimately, for understanding the biology of mood disorders. One indisputable example of the clinical relevance of making diagnostic distinctions among depressives is the recognition of bipolar depression, and it is critical to consider anticycling therapy as part of the acute intervention when treating that condition.

An alternative to the hypothesis that there are distinct subtypes of depression is the possibility that a general vulnerability to mood disorders may be acquired or inherited and then simply be expressed quite variably, interacting with other individual characteristics and life experiences.

The papers compiled for this Supplement bring together information and analyses that bear on this important and evolving issue in the understanding and treatment of major depressive disorder, addressing in particular the atypical, hostile, anxious, and bipolar subtypes as well as the heterogeneity of available pharmacotherapies and the relevance of the diversity of mechanisms for treatment selection. Andrew A. Nierenberg, M.D., the Associate Director of the Depression Clinical and Research Program at Massachusetts General Hospital, Harvard Medical School, Boston, and colleagues discuss the course and treatment of atypical depression; Maurizio Fava, M.D., Director of the Depression Clinical and Research Program at Massachusetts General Hospital, Harvard Medical School, Boston, presents that group's innovative work on hostile depression (depression with anger attacks); R. Bruce Lydiard, M.D., Ph.D., Director of the Psychopharmacology and Anxiety Disorders Programs, and Olga Brawman-Mintzer, M.D., Assistant Professor of Psychiatry, at the Medical University of South Carolina, Charleston, review the issue of anxious depression; William Z. Potter, M.D., Ph.D., formerly of the National Institute of Mental Health, and currently Research Scientist at the Lilly Research Laboratories, reviews bipolar depression. Finally, Steven M. Stahl, M.D., Ph.D., from the Department of Psychiatry and the Clinical Neuroscience Research Center, University of California San Diego, addresses antidepressant mechanism of action and the selection of antidepressant therapies.