Bipolar Disorder Treatment: An Evidence-Based Reality Check

Results from the largest treatment study of bipolar disorder ever performed, the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD), are presented in this issue by Perlis et al. The authors report that just over one-half of their bipolar patients achieved full remission during the 2-year study and that almost one-half of these recovered patients relapsed at least once before the end of the study. They conclude that "these results suggest that in spite of modern evidence-based treatment, bipolar disorder remains a highly recurrent, predominantly depressive illness." The STEP-BD data reported here are not the usual comparative assessment of treatments in a homogeneous sample of patients (i.e., an efficacy study). As a study carried out in a broadly representative sample of patients, it is an effectiveness study, and it describes a full 2 years of treatment. In addition, this study employed a "best-treatment-available" rather than a "treatment-as-usual" protocol, so I would call it an "effectiveness-plus" study. Nonetheless, the results are so similar to those observed in lithium treatment studies reported 20 to 35 years ago (1–5) that the question of whether today's best treatments available for bipolar disorder are better than older treatment begs for an answer. Although not ideal, these outcomes are better than those reported by other large effectiveness studies of schizophrenia (the Clinical Antipsychotic Trials of Intervention Effectiveness [CATIE] [6]) and of major depression (Sequenced Treatment Alternatives to Relieve Depression [STAR*D] [7]). The three studies taken together, however, underline the suggestion that modern pharmacological treatments may be no more beneficial than older ones, despite their added cost.

"Modern pharmacological treatments may be no more beneficial than older ones, despite their added cost."

The authors also report that the relapses in their sample were strongly correlated with residual symptoms of depression or mania. And they suggest that if clinicians were to target residual symptoms, the overall treatment results for bipolar patients might improve. However, given the rigorous assessment and treatment protocols of the STEP-BD, which includes both psychological and pharmacological interventions, these symptoms already were the primary targets of the clinicians. It is not at all clear therefore whether clinicians could get better results with the treatments now available to them. So what should our field do today to address the needs of patients with bipolar disorder who have residual, chronic, or relapsing symptoms?

Three articles in this issue (two by Perlis et al. and one by Lin et al.) point us toward logical places to look for help. Perlis et al. (in this issue), in a symptomatic comparison of depression in patients with unipolar and bipolar disorders, show, as have earlier studies, that many patients initially diagnosed and treated for depression later turn out to have bipolar disorder. Although not firmly established in the literature, if treatment of bipolar illness occurred earlier in its course, remission rates might improve. Indeed, patients might do better not only in symptomatic terms but also in social development. The diagnosis of bipolar disorder, which regularly begins in late adolescence (8; Perlis et al. in this issue), is often delayed for a decade (9). The illness is a significant hurdle on the path to normal adulthood, and delayed treatment can only make it harder to overcome.

A third article in this issue, by Lin et al., on the clustering of age at onset in families as a marker of genetic heterogeneity reminds us that we still do not understand this largely

genetic illness—from its origins, its molecular pathogenesis, or its pathophysiology. The sine qua non of translational research is that we must have some basic science findings in bipolar disorder to translate, i.e., to create rational treatment advances.

Because we already have modestly effective, albeit empirical, treatments for bipolar disorder, we might not have to wait for decades after genes and pathways are illuminated to develop treatments, as is contemplated for Alzheimer's and Huntington's disease. Translatable clues to the biology of bipolar disorder could make today's treatments much more effective by directing treatments to the patients who can best respond to them. The results of the STEP-BD study argue strongly that genetic, brain imaging, and neurobiological studies of bipolar disorder must be accelerated to help define who will respond best to which treatments in the long term. What seems clear from STEP-BD and the other major treatment studies is that we must provide clinicians and our patients with substantially better treatment options than are now available.

References

1. Prien RF, Caffey EM Jr, Klett CJ: A comparison of lithium carbonate and chlorpromazine in the treatment of excited schizo-affectives: report of the Veterans Administration and National Institute of Mental Health Collaborative Study Group. Arch Gen Psychiatry 1972; 27:182–189
2. Prien RF, Caffey EM Jr, Klett CJ: Prophylactic efficacy of lithium carbonate in manic-depressive illness: report of the Veterans Administration and National Institute of Mental Health Collaborative Study Group. Arch Gen Psychiatry 1973; 28:337–341
3. McCreadie RG, Morrison DP: The impact of lithium in south-west Scotland, I: demographic and clinical findings. Br J Psychiatry 1985; 146:70–74
4. Morrison DP, McCreadie RG: The impact of lithium in south-west Scotland, II: a longitudinal study. Br J Psychiatry 1985; 146:74–77
5. McCreadie RG, McCormick M, Morrison DP: The impact of lithium in South-West Scotland, III: the discontinuation of lithium. Br J Psychiatry 1985; 146:77–80
6. Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, Keefe RS, Davis SM, Davis CE, Lebowitz BD, Severe J, Hsiao JK (Clinical Antipsychotic Trials of Intervention Effectiveness [CATIE] Investigators): Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med 2005; 353:1209–1223
7. Trivedi MH, Rush AJ, Wisniewski SR, Nierenberg AA, Warden D, Ritz L, Norquist G, Howland RH, Lebowitz B, McGrath PJ, Shores-Wilson K, Biggs MM, Balasubramani GK, Fava M (STAR*D Study Team): Outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. Am J Psychiatry 2006; 163:28–40
8. McMahon FJ, Stine OC, Chase GA, Meyers DA, Simpson SG, DePaulo JR Jr: Influence of clinical subtype, sex, and lineality on age at onset of major affective disorder in a family sample. Am J Psychiatry 1994; 151:210–215
9. Lish JD, Dime-Meenan S, Whybrow PC, Price RA, Hirschfeld RM: The National Depressive and Manic-Depressive Association (DMDA) survey of bipolar members. J Affect Disord 1994; 31:281–294

J. RAYMOND DePAULO, JR., M.D.

Address correspondence and reprint requests to Dr. DePaulo, Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, 600 North Wolfe Street, Meyer 4-113, Baltimore, MD 21287-7413; jrd@jhmi.edu (e-mail).