

Conclusions

Bipolar Disorder: Origin, Recognition, and Treatment

A. John Rush, M.D.

It is evident from the articles presented in this supplement to *The Journal of Clinical Psychiatry* that bipolar disorder is the result of a complex interaction of genetic, medical, environmental, and social factors. Further research is required to determine the exact origins of bipolar disorder. A need also remains for further clinical research that will lead to improvements in the early, accurate diagnosis and effective treatment of this disease.

Bipolar disorder is associated with very high levels of morbidity and mortality. Patients may present with symptoms ranging from mild depression or hypomania to severe or rapid-cycling forms of acute mania or major depressive episodes with concomitant psychosis. Individuals with a history of substance abuse or thyroid disturbances, as well as postpartum women, appear to have a higher risk of developing bipolar disorder. Certain anxiety and personality disorders also occur more frequently in individuals with bipolar disorder.

Traditionally, lithium carbonate has been used as a first-choice short- and long-term therapeutic strategy for bipolar disorder. However, long-term use of lithium may result in functional impairment, and a high rate of patient noncompliance has been noted. The anticonvulsants carbamazepine and divalproex have been considered as alternative treatment choices; however, several clinical trials suggest that monotherapy with carbamazepine is of limited use for long-term prophylaxis. Although divalproex is generally better tolerated than either lithium or carbamazepine, its use in maintenance therapy may not normalize function in many patients. Combination therapy with lithium or divalproex, together with a number of other medications, although successful in some patients, may not achieve remission in others. It may even lead to residual symptoms or recurrent manic and depressive episodes.

Antidepressants, although effective in the treatment of major depressive disorder, may be less successful for many patients with bipolar disorder. Furthermore, they may be associated with a switch from depression to mania or hypomania.

Conventional antipsychotics, such as haloperidol, may be effective in controlling acute manic episodes, but they also carry a high side effect burden and are generally less preferred than the newer atypical antipsychotics, which have been shown to be at least as effective as conventional agents but with fewer associated adverse events.

Results from both placebo-controlled and open-label trials suggest that atypical antipsychotics may have long-term mood-stabilizing effects useful for maintenance therapy. Evidence to date, although not based on direct comparison, suggests that quetiapine is as effective as other atypical antipsychotics in the treatment of acute mania, but has a lower incidence of extrapyramidal symptoms. Quetiapine is also associated with minimal weight gain over the long term and placebo-level prolactin-induced sexual side effects. Quetiapine may therefore offer the best efficacy and tolerability profile of the available antipsychotic agents for acute manic episodes, but long-term studies are required to extend this finding to maintenance therapy for bipolar disorder.

Although the terms *response* and *remission* have not been well defined in the context of bipolar disorder, the treatment goal in most North American specialty clinics is complete and sustained remission whenever possible, similar to the approach taken in the modern management of patients with depression. Realistic management goals may have to be limited to obtaining and maintaining acute symptom control and suicide prevention as episodes occur. In most cases, this approach will require some degree of maintenance pharmacotherapy.

Some evidence suggests an overlap between bipolar disorder and schizophrenia, based on genetic and physiologic similarities. Likewise, atypical antipsychotics, which are used for the treatment of schizophrenia, are also proving effective for the management of bipolar disorder. A better understanding of the similarities and differences of these 2 diseases should lead to more effective treatment strategies for both.

Although several pharmacologic options are available for the treatment of bipolar disorder, optimal treatment remains a major unmet need. Atypical antipsychotics have considerable potential both as first-line and subsequent treatment options in the management of bipolar disorder due to their improved tolerability and side effect profile, which should enhance both patient compliance and acceptance.

From the University of Texas Southwestern Medical Center, Dallas.

The roundtable discussion "Bipolar Disorder: From Clinical Research to Therapeutic Intervention" was held June 30, 2001, in Berlin, Germany, and supported by an unrestricted educational grant from AstraZeneca Pharmaceuticals, L.P.