Multiple Perspectives on Bipolar Disorder

By David L. Dunner, MD, FACP

It has long been recognized that bipolar disorder is a familial condition and likely has a genetic contribution to its etiology. Although studies from the early 1960s suggested that the inheritance of bipolar disorder may fit a single Mendelian dominant gene mode of transmission, subsequent studies have not only failed to find "the" gene, but have suggested that more than one gene may be involved in the pathogenesis of bipolar disorder. This month's issue of CNS Spectrums focuses on bipolar mood disorder.

Carol A. Mathews, MD, and Victor I. Reus, MD, point to the difficulties in methodology for genetic linkage studies and to where current evidence for genetic linkage exists. The recent work on the Human Genome Project and advances interfacing between those data and clinical conditions will likely lead to greater understanding of genetic contributions to bipolar disorder. How long this will take is unclear. Hopefully it will be soon considering that the rate of scientific advances in human genetics has been growing exponential recently.

Paul E. Holtzheimer, MD, and John F. Neumaier, MD, PhD, review the treatment of acute mania. One interesting facet of acute mania studies is the increasing percentage of "mixed" mania over time. In the 1950s and 1960s, when lithium was being developed as an antimanic therapy, most studies were comprised of rather prototypic manic patients, and patients with mixed mania were rare. The number of subjects required to show effects against placebo were relatively small—usually <100 subjects total. Today, the percentage of mixed mania in clinical trials is relatively high, and in some studies approaches 50% of subjects studied. The reasons for this increase are unclear, but the effect of having more difficult patients in clinical trials is to necessitate larger numbers of patients being studied. Since the Food and Drug Administration requires two positive placebo-controlled trials for approval of an agent for a specific condition, many of the recent studies have been placebo-controlled. It is clear that antipsychotic medications and many, but not all, anticonvulsants are effective in acute mania.

Po W. Wang, MD, and colleagues review the use of anticonvulsants in bipolar disorder. The use of anticonvulsants was supported by the investigations of carbamazepine and, later, divalproate sodium for the acute and maintenance treatment of bipolar disorder. Subsequently, many anticonvulsants have been studied for efficacy in bipolar disorder and, interestingly, not all are effective. Studies of gabapentin and topiramate in acute mania were negative, as were studies of lamotrigine. Lamotrigine has shown positive effects as both a maintenance treatment and an antidepressant treatment for bipolar disorder. The caveat for clinicians is that anticonvulsants may be effective for various phases of bipolar disorder, but one should await proper data prior to assuming that an anticonvulsant is effective in all four phases of treatment of bipolar patients: treatment of acute mania, treatment of acute depression, maintenance effects against mania and hypomania, and maintenance effects against depression.

In spite of treatment advances on the manic side of the bipolar disorder, many patients remain chronically ill. Dong Vo, BS, and David L. Dunner, MD, FACP, examined treatment-resistant bipolar subjects and separated those who had rapid-cycling histories (a known cause of treatment resistance) from other patients. We found no clinical factors that differentiated rapid cycling from nonrapid cycling in treatment-resistant patients. Vo and Dunner found treatment resistance in nonrapid-cycling patients was largely due to persistent depression. We would hope that these data might encourage further investigation into the treatment of bipolar depression—a largely neglected area.

Dwight V. Wolf, MD, and Karen Dineen Wagner, MD, PhD, review bipolar disorder in children and adolescents. This is, a somewhat controversial area in that many clinicians question whether the diagnosis of bipolar disorder in children is a valid diagnosis. Clearly, what is being studied as childhood mania is not the acute episodic illness characterizing adult patients, but is more like a rather chronic mixed manic state.

Increasing research into the etiology and treatment aspects of bipolar disorder will likely result in improvement in the clinical outcome for such patients.