Bipolar Disorder and Schizophrenia: Distinct Illnesses or a Continuum?

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Bipolar disorder continues to present complex diagnostic and therapeutic challenges. Originally considered 2 separate diseases (mania and depression), bipolar disorder is now recognized to be a single disorder characterized by different subtypes and degrees of severity. Despite the availability of official guidelines, such as the DSM-IV and ICD-10, diagnosis is still problematic. Traditionally, bipolar disorder has been considered a clinical entity distinct from schizophrenia, although that assumption is being increasingly challenged. Proponents of a bipolar continuum theory support the concept of an expanded psychiatric continuum ranging from unipolar to bipolar disorders all the way to schizophrenia. This notion is supported by various independent findings. Both bipolar disorder and schizophrenia demonstrate a high degree of genetic transmissibility. Some data reported in family and twin studies suggest hereditary overlap between the 2 disorders. Gene mapping for both diseases is in its early stages, but certain susceptibility markers appear to be located on the same chromosomes. Bipolar disorder and schizophrenia also demonstrate some similarities in neurotransmitter dysfunction. As further indirect evidence of a possible association, many newer atypical antipsychotic agents approved for the treatment of schizophrenia are also proving useful for bipolar disorder. Ongoing research should aid in the understanding of bipolar disorder and foster the development of more effective treatment. *(J Clin Psychiatry 2003;64[suppl 6]:23–27)*

Bipolar disorder, one of the earliest identified mental disorders, was recognized as early as the time of Hippocrates in 400 BC. At that time, the illness was seen as encompassing 2 distinct disorders: mania and melancholia.[1] The term *manic-depressive insanity* was coined in 1921 by Kraepelin, who was instrumental in segregating the various psychotic disorders and pronouncing schizophrenia and manic-depressive disorder to be distinct syndromes.[2,3] In the years since, definitions and diagnostic criteria for bipolar disorder have continued to evolve and generate scientific debate.

DIAGNOSIS

The concept of polarity was first reflected in the American *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition (DSM-III), published in 1980. This classification system, still widely used in North America, relies on 2 primary subtypes of bipolar disorder, as described in the DSM-IV. Bipolar I is defined as 1 or more manic or mixed episodes, usually accompanied in the course of the disease by major depressive episodes. Bipolar II is characterized by recurrent major depressive symptoms and 1 or more episodes of hypomania. The DSM-IV also includes a classification for cyclothymic disorder, distinguished by chronic periods of mild hypomanic and depressive mood fluctuations.[4] In 1992, the World Health Organization modified its International Statistical Classification of Diseases and Related Health Problems (ICD)[5] to more closely reflect the classifications of the DSM. However, some important diagnostic differences between ICD and DSM-IV remain, and it is probably clinically relevant to review them.

In general, whereas the DSM-IV classifies mood disorders into 2 categories, depressive disorders and bipolar disorders, the tenth revision of ICD, ICD-10,[5] mainly used in Europe, divides affective disorders into manic episodes, depressive episodes, bipolar disorders, unipolar depressive disorder, recurrent affective disorder, and other affective disorder. The ICD-10 differentiates unipolar mania (ICD 10: F30) more clearly from bipolar disorders than does the DSM-IV, which treats unipolar mania as part of bipolar disorder due to the increased probability of more than 1 affective episode in patients with bipolar disorder.

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However, it is still controversial whether unipolar mania exists as a separate entity. Interestingly, in the ICD-10, single mixed episodes are specified in "other single mood (affective) disorders" (F38.00).

According to DSM-IV, the spectrum of bipolar disorders encompasses several classifications, from a single, manic episode (bipolar I; DSM IV: 296.0x, .4x, .40, .5x, .6x, .7x) to recurrent depression with hypomania (bipolar II; DSM IV: 296.89). This clear differentiation is not fully implemented in the ICD-10, where the diagnosis of bipolar II disorder (ICD 10: F31.80) can only be found in the appendix of the manual. Similarly, rapid cycling, which specifies the longitudinal course of bipolar disorder, is mentioned as a diagnosis in the ICD-10 appendix (F31.81), but can be an additional specification to any affective episode within bipolar I or II disorder in DSM-IV. Furthermore, cyclothymic disorder is identified as a separate diagnosis of bipolar disorders in the DSM-IV, in contrast to the ICD-10, which lists cyclothymia as a separate entity within persistent affective disorders.

As a result of more meticulous course observations and increasing knowledge about the causes of illness, bipolar disorders are being further differentiated. Differences in the prognosis and treatment of the entire spectrum of bipolar disorders are now being observed more accurately for the first time, and future classification systems will certainly place more emphasis on these newly observed features.

The clinical usefulness of the DSM-IV classification system is hindered by several barriers. Clearly, bipolar disorder comprises core features that are easily recognizable and lend themselves to a classic bipolar diagnosis. However, in the presence of some anomaly or variant, the diagnosis becomes more difficult. Furthermore, in general clinical practice, primary care physicians are not likely to think of bipolar disorder in terms of bipolar I or bipolar II. When the classifications are used, the reliability of a bipolar II diagnosis is often poor, as hypomania is harder to recognize than full-blown mania. The characterization of hypomania includes some degree of subjective assessment on the part of the physician, and one clinician may view a patient as having bipolar II whereas the other may view the same patient as having bipolar I. This phenomenon even complicates the comparison of scientific data from independent studies if disease classification is not performed uniformly.

THE BIPOLAR SPECTRUM

Over the past 10 to 15 years, it has become accepted to view bipolar disorder as a continuum of symptom severity, ranging from features of relatively mild depression and brief hypomania to debilitating patterns of rapid cycling or frequent mania with psychotic features.[6] Further complicating diagnosis and disease classification, individual pa-

tient symptoms can vary with regard to degree of polarity, symptom severity from episode to episode, duration of episodes, and cycling frequency.[2]

BIPOLAR-SCHIZOPHRENIA CONTINUUM

In the midst of these diagnostic controversies, Kraepelin's assumption that manic-depression and schizophrenia are 2 distinct disorders is also being challenged, although many experts continue to uphold this theory. Proponents of the bipolar continuum theory support the concept of an expanded psychiatric continuum ranging from unipolar to bipolar disorder, to schizoaffective psychosis, all the way to schizophrenia. Much research continues to focus on this issue, and there is a good deal of published support for both positions.[7] Much of the evidence supporting the continuum concept is based upon genetic, biochemical, and pharmacologic findings.

FAMILY LINKAGE STUDIES

Although genetic mapping for affective disorders is far from complete, it is apparent from family linkage studies that bipolar disorder has a substantial genetic component, with possibly the highest degree of genetic loading among all major psychiatric diseases. In fact, families of patients with bipolar disorder seem to have a disproportionate frequency of mood disorders. Compelling evidence of disease concordance has been presented in studies of twins with manic-depressive symptoms.

Bertelsen et al.,[8] in a study of 69 bipolar probands from monozygotic twin pairs, found 46 co-twins with manic-depressive disorders. An additional 14 co-twins displayed other psychoses or marked affective personality disorders or had committed suicide. Similarly, in a study of 106 monozygotic twin probands with functional psychotic disorders, the concordance of mania in a co-twin was approximately 37%.[9]

It is possible that data from twin studies underestimate the concordance of bipolar disorder, as difficulties in diagnosis may cause one twin to be labeled as unipolar and the other twin as bipolar, while in fact they may be expressing different features of the disease at the time of diagnosis. Misdiagnosis and improper categorization of bipolar illness may influence data gathered among relatively younger subjects before the full clinical picture of their disease becomes apparent. Diagnosis should be more reliable after the first episode, which, in the vast majority of patients, usually occurs before the age of 30. Differences between twins can also confuse the diagnosis, particularly in situations in which one twin's case is complicated by such factors as drug abuse, neurologic insult, or extreme social adversity, while the other's is not.

In 1982, Gershon et al.[10] published findings from a study of 1254 adult relatives of patients diagnosed with

various affective disorders and those of normal controls. Lifetime prevalences of major affective disorder (including schizoaffective) were 37%, 24%, 25%, and 20% in relatives of patients diagnosed as schizoaffective, bipolar I, bipolar II, or unipolar, respectively. Lifetime prevalence was 7% in relatives of normal controls. From this and other research has arisen the theory of a continuum of genetic vulnerability, wherein different degrees of "genetic loading" can raise or lower susceptibility to various forms of affective illness. In such a model, bipolar illness may manifest itself when vulnerability is more severe (severity defined as a capacity to transmit illness within a pedigree), whereas unipolar illness may surface in cases of less severe vulnerability.[10]

Overall, the estimated lifetime risk of bipolar disorder in a first-degree relative of a bipolar patient ranges from 40% to 70% in monozygotic twins to 5% to 10% in all other first-degree relatives. Despite this clear genetic linkage, the mode of transmission appears to be far more complex than simple Mendelian inheritance, possibly involving several genes, genomic imprinting, and mitochondrial inheritance. It remains unclear why out of similar pedigrees some patients may be affected only by mild depression, whereas others develop a complete manic-depressive profile. However, it has been theorized that the large variation in bipolar symptom profiles suggests that nongenetic factors, such as environmental and developmental factors, have a strong influence in disease expression.[6]

COMPARISON OF BIPOLAR DISORDER AND SCHIZOPHRENIA

In 1988, Gershon et al.[11] studied 237 relatives of 48 patients with schizophrenia or schizoaffective disorder. Relatives of patients with schizoaffective disorder had an increased incidence of bipolar disorder; an increase was not seen in relatives of patients with schizophrenia. Conversely, Angst et al.[12] found a slightly elevated morbidity risk for schizophrenia (1.9%) and schizoaffective disorder (1.5%) among first-degree relatives of patients having bipolar disorder. Other familial and twin studies have reported concordance and overlap between the 2 illnesses.[13]

Epidemiology

Despite differences in clinical characteristics, etiology, and treatment strategies, schizophrenia and bipolar disorder share certain epidemiologic characteristics, such as age at onset, lifetime risk, course of illness, worldwide distribution, risk for suicide, gender influence, and genetic susceptibility.[14] Both illnesses exhibit similar etiologic risk factors, such as an excess of winter-spring births, abnormal dermatoglyphics, and a probable excess of perinatal complications.[15] Bipolar disorder, however, may be more prevalent among higher socioeconomic groups, whereas higher rates of schizophrenia are associated with

urban births and minor physical congenital defects. According to one theory, there may be a subset of bipolar cases that represents a unique disease entity, while many cases fit into a "bipolar-schizophrenia" continuum.[15]

The now-recognized diagnosis of schizoaffective disorder, which by definition falls between schizophrenia and mood disorders, tends to add support for the continuum theory of these mental illnesses.[16] It could be argued that if the Kraepelinian dichotomy between affective disorders and schizophrenia is legitimate, the occurrence of intermediate variations, such as schizoaffective psychosis, should be quite rare. To the contrary, the prevalence of schizoaffective disorder has been reported to range from 5.7% in adult psychiatric patients to 8% in psychotic patients.[7]

Neuroanatomy

Various structural abnormalities have been found in imaging studies of patients with bipolar disorder or schizophrenia, although none has yet provided any clear answers regarding a possible relationship between the 2 disorders. Two studies using magnetic resonance imaging found indications of bilateral amygdala enlargement with no change in the hippocampus in bipolar patients.[17,18] In contrast, the amygdala and other focal areas of the brain have been found to be reduced in schizophrenic patients.[17,19]

One of the more consistent findings among patients with bipolar disorder is an enlargement of the lateral and third ventricle.[20,21] Nasrallah et al.,[22] using computerized tomography scans, found significantly larger ventricles in both manic and schizophrenic subjects compared with control subjects. Ventricle size was associated with cerebellar atrophy, observed more commonly in manic patients, but not associated with cerebral atrophy, which was more common in schizophrenia patients.

The prefrontal cortex, in particular, exhibits changes in bipolar disorder. Functional neuroimaging studies in patients with bipolar disorder and depression have shown decreased metabolism compared with normal controls in the prefrontal cortex.[23,24] A decrease in neuronal and glial cell density associated with glial hypertrophy in prefrontal area 9 was reported from necropsy findings taken from patients with bipolar disorder compared with those taken from controls. These findings resemble those in major depressive disorder but not schizophrenia.[25]

Genetics

Molecular genetic studies continue searching for chromosome linkage in bipolar disorder and schizophrenia. Certain potentially relevant gene loci have been identified in bipolar disorder, including 12q24, 18p11, 18q22, 4p16, 21q21, 22q11, and Xq26, although specific genes have not yet been consistently implicated.[6,26] At least 2 of these regions, 18p11 and 22q11, may also be linked to schizophrenia, suggesting a possible genetic overlap between the 2 disorders.[26]

Pathophysiology

Early investigations of the underlying pathophysiology of bipolar disorder centered around a theory of imbalance between cholinergic and catecholaminergic neuronal activity, an idea based on the known antimanic properties of centrally active cholinergic agonists.[6] However, it has become apparent that this complex disorder is likely mediated through multiple neurotransmitter pathways and biological interactions.[27] Several neurotransmitters, including norepinephrine, dopamine, glutamate, and γ-aminobutyric acid (GABA), have been implicated in bipolar disorder to some degree, at least during symptomatic episodes.

Several neurobiological and pharmacologic findings provide further evidence that schizophrenia and bipolar disorder may not be completely unique disease states. Many neurotransmitter abnormalities identified in bipolar disorder resemble those associated with schizophrenia, further supporting the continuum theory. For example, one of the foremost neurotransmitters implicated in schizophrenia pathology is dopamine, and most antipsychotic medications possess some degree of antidopaminergic effect.[28] The administration of amphetamine to individuals with schizophrenia has been shown to provoke excess dopamine release and precipitate schizophrenic behaviors, suggesting a labile dopamine system.[29]

Similar research has not yet been conducted in patients with bipolar disorder, although dopamine agonists have been found to precipitate mania in these patients. However, abnormalities in dopaminergic activity have been noted in bipolar disorder, including decreased concentrations of the dopamine metabolite homovanillic acid in the cerebrospinal fluid of depressed patients.[6] The administration of L-dopa has been found to precipitate mania in a nonbipolar individual and even shorten the manic-depressive cycle length in a bipolar patient.[30–32] Amphetamine and cocaine intoxication may lead to manic-like symptoms. Altered serotonergic activity has also been noted in both schizophrenia and depression, with a slightly less clear role in bipolar disorder.[27,33,34] It is possible that neurotransmitter disruptions in bipolar disorder, especially of the dopamine and serotonin pathways, are an active phenomenon of the disease but may not actually play an etiologic role.

Hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis has been documented in bipolar disorder, in which the presence of increased HPA activity has been correlated with depression, mixed manic states, and occasionally classic manic episodes. Results of a study of patients with major depression suggest that HPA-axis hyperactivity constitutes a primary dysfunction leading to compensatory abnormalities in the serotonergic, and possibly other, neurotransmitter systems.[27,35] Hyperactivation of the HPA axis and resulting elevations in glucocorticoid levels have even been suggested to play a role in hippocampal cell death and atrophy in animal models.[27] HPA-system abnormalities have also been demonstrated in schizophrenia, although the degree of dysfunction appears to be less than that observed in bipolar disorder.[36]

The presence of similarities in neurotransmitter irregularities between bipolar disorder and schizophrenia may account for the finding that some newer atypical antipsychotic agents, such as olanzapine, risperidone, and quetiapine, have been found useful in the treatment of patients with bipolar disorder. The antimanic activity of olanzapine and risperidone is attributed to blockade of dopamine D_2 receptors and antagonism of other monoaminergic receptors. Both olanzapine and risperidone have higher antiserotonergic ($5-HT_{2A}$ receptor) potency than quetiapine, which has pharmacologic antagonism at multiple sites in the central nervous system, including serotonergic, dopaminergic, histaminic, and α-adrenergic receptors. Although all 3 atypical antipsychotics mentioned above were originally studied and marketed for the treatment of schizophrenia, olanzapine is now approved for the treatment of bipolar mania, and preliminary studies have reported efficacy for risperidone, quetiapine, ziprasidone, and aripiprazole in patients with bipolar disorder.[37–42] It is interesting to note that from 1999 to 2001, more than 70% of prescriptions written for atypical antipsychotic drugs were for conditions other than schizophrenia, including bipolar disorder.[43]

SUMMARY

A conceptual case can be made for a relationship between schizophrenia and bipolar disorder. If each of these disorders is an etiologically heterogeneous syndrome, a single etiology could result in different phenotypes at the clinical level but with a shared etiology at the genetic, biochemical, or physiologic levels. If each syndrome is the result of multiple effects of a single gene (pleiotropic), e.g., change in phenomenology over time such that clinical features differ over time, subsets of persons with clinically diagnosable schizophrenia or bipolar disorder may in fact have the same illness at the etiologic level. For example, both iron deficiency anemia and vitamin B_{12} deficiency have symptoms of pallor, fatigue, and tachycardia. B_{12} deficiency can initially appear to be iron deficiency anemia, but, when fully developed, can include psychotic features and other localized neurologic findings.

In summary, the Kraepelinian dichotomy between bipolar disorder and schizophrenia may be gradually succumbing to a theory of disease overlap and continuum. Regardless of which theory eventually proves to be accurate, the most pressing clinical need is to find safe and effective treatments for these disorders. The emerging data regarding potential biological and chemical similarities between the 2 disorders will not only aid in the understanding of these very complex diseases but, most importantly, should bring us closer to the development of optimal management strategies.

Drug names: aripiprazole (Abilify), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), ziprasidone (Geodon).

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