Rediscovering the Bipolar Spectrum

Bipolar Spektrumunun Yeniden Keşfi

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ABSTRACT
The classification and diagnosis of mood disorders have been the subject of much debate over the last 150 years and remain extremely important for contemporary psychiatric practice. Although the DSM (Diagnostic and Statistical Manual) and ICD (International Classification of Diseases) classifications of major depression and bipolar disorder have been very helpful for research and practice, recent work suggests that it may be appropriate to consider a return to a broader view of the bipolar spectrum. Here we review the evolving concept of bipolar spectrum disorders with particular reference to dimensional aspects of symptoms and the interfaces between unipolar depression and bipolar disorder and between bipolar disorder and psychosis. (Archives of Neuropsychiatry 2011; 48: 167-70)

Key words: Diagnosis, major depression, bipolar spectrum disorders, genetics, bipolar disorder, psychosis, Kraepelinian dichotomy

ÖZET

Anahtar kelimeler: Tanı, majör depresyon, bipolar spektrum bozuklukları, genetik, bipolar bozukluk, psikoz, Kraepelinian dikotomi

Introduction

“There is a certain category of patient who continually exhibits a nearly regular succession of mania and melancholia. This seemed sufficiently important to us to serve as a basis for a specific mental disorder, which we call circular insanity because these patients repeatedly undergo the same circle of sickness, incessantly and unavoidably, interrupted only by rather brief respite of reason.” Jean Pierre Faret, 1854

“Virtually all of the patients presented with a depressive state. The state of excitement had escaped the attention of the patient’s doctor, his family and friends, and the patient. The patients only became aware of it when I described the characteristics of this state to them and, having up until that moment considered them as their ‘healthiest’ periods, were forced to recognize that they were ill during these periods also.” Ewald Hacker, 1882

“Manic-depressive insanity… includes on the one hand the whole domain of the so-called periodic and circular insanity, on the other hand simple mania, the greater part of the morbid states termed melancholia and also a not inconsiderable number of cases of amentia.” Emil Kraepelin, 1921

Bipolar affective disorder is a serious, recurrent disorder of mood characterized by episodes of major depression which alternate with episodes of mania or hypomania (hypomania is a less severe form of mania) (1). Although current psychiatric practice conceptualizes major depressive disorder and bipolar affective disorder as separate diagnostic entities, in recent years there has been renewed interest in the concept of a broadly-defined bipolar spectrum which might include a substantial proportion of depressed patients who can be considered to have ‘bipolar spectrum disorder’. This issue is not simply of academic interest: there are several important

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reasons why an under-recognition of bipolar spectrum disorders could impact substantially on patient care. Here we review the historical development of the concept of the bipolar spectrum and highlight implications for future research and practice.

**Early Evolution of the Bipolar Spectrum**

The relationship between mania and depression has been a matter for debate since antiquity. Hippocrates described melancholia as a condition associated with ‘aversion to food, despondency, sleeplessness, irritability and restlessness’ and felt that the cause of all mental disorders could be explained by humoral disturbances of ‘blood, yellow bile, black bile and phlegm’. According to this paradigm, an excess of black bile was the cause of melancholia, whereas excess yellow bile caused mania. In contrast to this view, Aristotle viewed the heart, rather than the brain, as the dysfunctional organ in melancholic illnesses. Another ancient Greek, Soranus of Ephesus, believed that mania and melancholia were two distinct diseases with similar prodromal symptoms and which required similar treatments (2). Aretaeus of Cappadocia, who lived in the second century AD, suggested that melancholia was usually both the beginning and an integral part of mania. Consistent with these observations, Avicenna (980-1037) conceptualized the nature of depression and mania as essentially the same. Overall, although most early authors described mania and depression as separate clinical syndromes, a close connection between them has almost always been recognized.

**The Kraepelinian Dichotomy and 20th Century Psychiatry**

Emil Kraepelin popularized the term ‘manic-depression’ when he distinguished manic-depressive insanity from dementia praecox at the turn of the 20th century (3). His idea that manic depression could be differentiated from dementia praecox (now called schizophrenia) strongly influenced Western psychiatry within a relatively short period. Kraepelin placed special emphasis on those features of manic-depressive illness which he felt most clearly differentiated it from schizophrenia: the periodic or episodic course; the more benign prognosis; and a pattern of positive family history for mania within manic-depressive illness.

Although Kraepelin’s fundamental dichotomy has persisted for many years, vigorous debates about nosology have often occurred (4). Eugen Bleuler disagreed with Kraepelin, conceptualizing the relationship between affective illness and schizophrenia as a continuum without a sharp line of demarcation. According to Bleuler’s view, a patient was either predominantly schizophrenic or predominantly manic-depressive, with most patients situated somewhere along this spectrum. Overall, the prevailing view in recent decades has been that bipolar disorder and schizophrenia are essentially different diagnostic entities and this is reflected within the current classifications (5) of the American Psychiatric Association’s Diagnostic and Statistical Manual, DSM-IV (1994) and the World Health Organization’s International Classification of Diseases, ICD-10 (1990). This is despite the reality that many individuals with severe psychiatric illness have both prominent mood and psychotic symptoms – raising the possibility, and indeed the likelihood, that there is no simple, clear-cut biological (and diagnostic) distinction between schizophrenia and bipolar affective disorder.

**The Unipolar-Bipolar Dichotomy**

In the 1950s, Leonhard reported that depressed patients with a history of mania (described as ‘bipolar’) had a higher incidence of mania in their families than those patients who only experienced depression (described as monopolar). Angst and Perris subsequently supported this finding with systematic family history data (6,7). All of these clinicians (Leonhard, Angst and Perris) used both bipolar and unipolar definitions to describe patients with an episodic course of recurrent episodes, characterized by endogenous features and clear functional impairments. Although this bipolar-unipolar distinction was not formally incorporated into ICD-9, it was subsequently described within DSM-III (1980), DSM-IV (1994) and ICD-10 (1990).

The diagnostic categories of major (unipolar) depression and bipolar disorder have been helpful in terms of stimulating research and facilitating communication between clinicians, but recent evidence confirms that the boundaries between these diagnoses are not clear-cut. According to DSM-IV criteria, BP-II disorder (that is, depression alternating with episodes of hypomania) affects approximately 1-2% of the population. However, this DSM-IV definition of BP-II disorder may be overly restrictive in terms of the duration and required symptoms. For example, there is evidence that for the diagnosis of hypomania, the symptom of ‘overactivity’ should be given as much weight as the stem criteria of ‘euphoria’ and ‘irritability’ and, further, the 4-day duration threshold for hypomanic symptoms is probably too long (most hypomanic episodes last around 2 days).

These problems with the DSM-IV definition of hypomania exclude a large number of depressed patients who experience brief but clinically significant periods of hypomania and it has been convincingly argued that a more realistic definition of hypomania within BP-II disorder should: a) include overactivity as an additional stem criterion; b) specify a threshold duration for hypomanic symptoms of at least 1 day rather than 4 days; and c) stipulate the experience of negative consequences of the episode as necessary for the diagnosis (Table 1) (8).

Jules Angst and colleagues, in their long-term prospective studies of several thousand individuals, have demonstrated that this definition of BP-II is valid in terms of bipolar family history, treatment response, illness course and clinical characteristics (9). When this broader definition of hypomania is applied to datasets of patients with recurrent depression, between 25% and 50% of these patients meet criteria for BP-II and overall population prevalence estimates for BP-II rise from 1-2% to at least 5% (8,10).
Why is Improved Recognition of a Broad Bipolar Spectrum Important?

The misdiagnosis of a bipolar spectrum disorder as unipolar depression may be important for a number of reasons. There is currently considerable uncertainty about the long-term usefulness of antidepressants for bipolar-type depressions, as highlighted by the finding of a lack of benefit of antidepressants added to mood stabilizers within the STEP-BD trial (11). Antidepressants prescribed for patients with bipolar-type depressions (especially in the absence of concurrent prescription of a mood stabilizer) may cause some patients to experience more frequent mood episodes (12), treatment resistance (13), destabilisation of mood (14) and possibly even an increase in suicidal behaviours (15,16). These studies suggest that antidepressants are at best ineffective and at worst harmful for many patients with bipolar depression.

The possibility of substantial unrecognized bipolarity in samples of recurrent unipolar patients may also call into question the validity of a large body of previous research on unipolar depression. Many clinical trials of antidepressants for unipolar depression conducted to date may have included a substantial proportion of patients with clinically significant bipolarity. Similarly, depression studies in the areas of molecular genetics, neuroendocrinology, biochemistry, and brain imaging are likely to have included an unknown and varying proportion of cases that actually suffer with unrecognized bipolar spectrum illness.

Contemporary Approaches to the Bipolar Spectrum

In the 1970s, Akiskal proposed a 'cyclothymic-bipolar spectrum' similar to the 'mania spectrum' proposed by Klerman (17,18). Klerman described a progression from normal spectrum to 'mania spectrum'. This arose from a longitudinal study which demonstrated that cyclothymia could progress to depressive and hypomanic episodes (17).

Angst has described (8) a two dimensional model of the bipolar spectrum, with one dimension referring to severity of mood problems (from normal to pathological) and the second referring to the proportion of depression and mania which predominates during the course of illness (Table 2).

The Future of the Bipolar Spectrum: A Three-Dimensional Descriptive Approach to Mood and Psychotic Disorders?

Emerging evidence from classical and molecular genetics suggests that the division between both unipolar depression and bipolar disorder and between bipolar disorder and schizophrenia is likely to be overlapping. Family studies, twin studies, genome-wide linkage studies and association studies fail to support the traditional diagnostic separation of bipolar disorder from schizophrenia (19). For example, the largest family study of schizophrenia and bipolar disorder ever undertaken, including over 2 million nuclear families identified from Swedish population and hospital discharge registers, showed increased risks of both schizophrenia and bipolar disorder to first-degree relatives of probands with either disorder. Moreover, there was evidence from half-sibs and adopted-away relatives that this is due substantially to genetic factors (20). Recent molecular data from genome-wide association has shown that variation at a polymorphism within the calcium channel gene, CACNA1C, is associated with risk of recurrent unipolar depression and schizophrenia (21) as well as with bipolar disorder (22).

Based on such findings, for the purposes of both research and treatment, it may be that unipolar depression, bipolar disorder and schizophrenia are best considered as an overlapping, multi-dimensional model according to which ratings are made on several domains (axes/dimensions) of psychopathology. For example, a simple three-dimensional model has been described used in research (23) (Figure 1), although more domains are almost certainly necessary to capture the complexity of mood and psychotic illness (24). This three-dimensional model is a simplified representation of major/minor mood or psychotic disorders according to hypomania, psychotic mania and delirious mania (18). Subsequently, Akiskal proposed a definition of "soft bipolar spectrum". This arose from a longitudinal study which demonstrated that cyclothymia could progress to depressive and hypomanic episodes (17).
dominant symptom profile of each disorders. All major or minor mood-psychotic disorders are replaced on this model considering the overlapping symptom clusters of each disorder. For example, lifetime mania axis mainly embraces bipolar disorders (type I and II), but it also includes schizoaffective (mostly bipolar type) and schizophrenic patients with lifetime mania. On the other hand, schizophrenia is a prototype of lifetime psychosis, however, there are some severe subtypes of bipolar disorders with psychotic features that can be replaced between the dimensions of lifetime psychosis and lifetime mania. This three-dimensional model allows clinicians to evaluate cases individually apart from their categorical diagnosis.

Conclusion

Taken together, the clinical and genetic studies reviewed above suggest that a spectrum or continuum concept provides a useful way to integrate a variety of observations concerning both mood and psychotic disorders. In the future, dimensional approaches may also allow clinicians to more fully characterize individual patients with a long-term view to developing more rational psychological and pharmacological interventions.

The challenge for psychiatric classification is to combine advances in bioinformatics and molecular genetic technologies with equally important developments in our understanding of the nosology of mood syndromes, with a long-term view to improving diagnosis and developing treatments for patients which are more closely targeted at biologically relevant clusters of symptoms, rather than heterogeneous diagnostic categories of uncertain biological validity.

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