Broadening the diagnosis of bipolar disorder: benefits vs. risks

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There is considerable debate over whether bipolar and related disorders that share common signs and symptoms, but are currently defined as distinct clinical entities in DSM-IV and ICD-10, may be better characterized as falling within a more broadly defined “bipolar spectrum”. With a spectrum view in mind, the possibility of broadening the diagnosis of bipolar disorder has been proposed. This paper discusses some of the rationale for an expanded diagnostic scheme from both clinical and research perspectives in light of potential drawbacks. The ultimate goal of broadening the diagnosis of bipolar disorder is to help identify a common etiopathogenesis for these conditions to better guide treatment. To help achieve this goal, bipolar researchers have increasingly expanded their patient populations to identify objective biological or endophenotypic markers that transcend phenomenological observation. Although this approach has and will likely continue to produce beneficial results, the upcoming DSM-IV and ICD-10 revisions will place increasing scrutiny on psychiatry’s diagnostic classification systems and pressure to re-evaluate our conceptions of bipolar disorder. However, until research findings can provide consistent and converging evidence as to the validity of a broader diagnostic conception, clinical expansion to a dimensional bipolar spectrum should be considered with caution.

Key words: Bipolar I disorder, bipolar II disorder, bipolar spectrum, depression, diagnosis, hypomania, mania

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Bipolar disorder is a dynamic illness characterized by dramatic changes in mood, energy, cognition, and behavior that fluctuate over time. There are no objective markers for bipolar disorder, so that identification relies on clinical assessment of these changing symptoms in order to place them within a diagnostic framework (e.g., DSM-IV or ICD-10) (1). However, many of the symptoms used to define bipolar disorder overlap with other psychiatric conditions. Consequently, identifying the edges of the bipolar diagnosis can be difficult. This difficulty is highlighted by variable prevalence rates observed in epidemiological studies. For example, the Epidemiological Catchment Area study reported one-year prevalence rates of bipolar I disorder of 0.9% and bipolar II disorder of 0.4%; however, when clinical significance criteria were applied, these rates dropped to 0.5% and 0.2%, respectively (2). Moreover, in this same study, the lifetime rate of subthreshold mania/hypomania exceeded 5% (3). Hirschfeld et al (4) reported that the population prevalence of bipolar I and II disorder combined exceeds 3% when appropriately sensitive instruments are used, but Zimmerman et al (5) suggested that

such instruments overdiagnose bipolar disorder by misattributing symptoms of other conditions.

The variability in rates of bipolar disorders in these studies occurs in part from difficulty distinguishing bipolar disorder from related illnesses. At the boundaries between diagnoses there are overlapping symptoms, such that subtle differences in only one or two DSM-IV or ICD-10 criteria determine whether a patient is diagnosed with bipolar disorder or with something else (e.g., unipolar depression). As reviewed by Phelps et al (1), there are no obvious “points of rarity” in the continuum of affective symptoms between bipolar and unipolar disorders, or with healthy subjects and other diagnoses. Because transitions between diagnostic conditions are stepwise rather than abrupt, some investigators advocate for a broader or “spectrum” approach to bipolar disorder (6,7). To some extent, this approach moves away from the categorical definitions of DSM-IV or ICD-10 toward identifying individual symptoms that suggest “bipolarity”. For example, in the pediatric realm, clinicians struggle with the potential “bipolarity” of attention-deficit/hyperactivity disorder (ADHD)

symptoms, temper tantrums, and severe mood dysregulation (8). In adults with depression, Akiskal (7) suggested a wide range of signs of bipolarity, including “ornamentation” with red clothes and creative achievement.

Before discussing the potential value of broadening the bipolar disorder diagnosis, it is useful to remind ourselves why we make diagnoses. People with bipolar disorder are identified from the general population in order to assign therapies that will alleviate their suffering (i.e., symptoms), ideally through evidence-based treatment guidelines developed from past studies of similar individuals (9,10). Diagnoses also identify individual cases to populate research efforts toward improving our understanding of the condition, ideally in order to identify an etiopathogenesis that will lead to better treatments. In the absence of treatment and research considerations, diagnostic debates can quickly degenerate into circular academic blustering of little value. With these thoughts in mind, we discuss the potential risks and benefits associated with broadening the diagnosis of bipolar disorder.

RISKS AND BENEFITS: TREATMENT

One reason to broaden the diagnosis of bipolar disorder is that patients who exhibit bipolar-like symptoms, but do not meet DSM-IV or ICD-10 criteria for bipolar I or II disorder, might benefit from treatment approaches used for managing bipolar illness. By expanding the diagnosis of bipolar disorder, applying bipolar treatment algorithms might improve the likelihood that these “spectrum” individuals will find an effective therapeutic regimen. Indirect support for this notion has come when “mood stabilizers”, that are thought to be relatively specific for bipolar disorder, have been found to be effective for other conditions. For example, lithium augmentation has been effective in major depressive disorder following partial antidepressant response (11), and carbamazepine improved outcomes in borderline personality disorder (12). One interpretation of these types of studies is that improvement occurred from a failure to recognize the underlying “bipolarity” of the depressed or borderline patients.

Indeed, a major impetus for broadening the bipolar diagnosis is recent research suggesting that hypomania is commonly missed in depressed patients, leading to misdiagnoses of major depressive disorder when bipolar II disorder would be more appropriate (e.g., 7). Many other depressed patients exhibit subthreshold mania or hypomania, i.e., symptoms of mania or hypomania that are too few to reach DSM-IV or ICD-10 criteria (1,3,6,7,13-19). These observations suggest that there may be a subgroup of people with major depressive disorder who exhibit “bipolarity”, e.g. symptoms and signs of mania, multiple recurrent affective episodes, or a family history of bipolar disorder, that suggest that the patients would be better considered “bipolar spectrum”. These subgroups of “major depressive” patients may be over-represented in treatment unresponsive samples (20-22), so that a broader bipolar framework might lead to improved treatment response.

In particular, one concern related to missing “bipolarity” in a depressed sub-

ject is the putative risk of antidepressants worsening the course of illness by increasing affective cycling or precipitating mania (23). However, considerable controversy rages about the level of this risk, with recent data from the large STEP-BD study suggesting that newer antidepressants do not impart these risks in bipolar I or II depression (24). Nonetheless, in STEP-BD, antidepressants appeared to be largely ineffective, supporting the notion that “bipolarity” in a depressed subject may decrease the likelihood of a standard antidepressant treatment response.

To directly determine whether “bipolarity” was associated with treatment resistance, Perlis et al (25) identified a bipolar spectrum (excluding bipolar I and II disorder) in 4041 major depressed patients that were part of the large STAR*D depression study. In STAR*D, all subjects received the same treatment algorithm designed for unipolar depression, and bipolar spectrum patients comprised 28% of the sample. However, the presence of a bipolar spectrum was not associated with any differences in outcome or treatment response in these depressed subjects, suggesting “bipolarity” in these depressed subjects did not impact treatment response. Further complicating this discussion are recent studies suggesting that patients with bipolar II disorder respond well to antidepressant monotherapy (26-28). To our knowledge, there are no studies demonstrating that depressed bipolar spectrum patients exhibit a better course and outcome when following bipolar rather than unipolar depression treatment guidelines.

Similar considerations arise along the borders of bipolar disorder with other conditions. For example, psychotic mania and an acute exacerbation of schizophrenia can be difficult to distinguish (29). The boundary with schizophrenia is further complicated by the presence of schizoaffective disorder, which itself is subcategorized into “depressive” and “bipolar” types. Schizoaffective disorder is a controversial classification that has been criticized as a “waste basket” for schizophrenic and psychotic mood disorder patients who do not fit neatly

into either of the major categories (30). Alternatively, other investigators suggest that schizoaffective patients have unique characteristics setting them apart from the other patient groups (30). Other than recent studies with paliperidone (31), there have been few specific controlled treatment trials for schizoaffective disorder. Treatment guidelines tend to combine interventions for mood and schizophrenic disorders (30,32), rather than develop specific approaches to schizoaffective disorder *per se*. A few studies have suggested that the newer, so-called atypical, antipsychotics may be more effective than conventional antipsychotics in schizoaffective disorder, consistent with “bipolarity” in this group (33,34). However, atypical antipsychotics in general appear to have similar efficacy in both bipolar and schizophrenic disorders (e.g., 35).

A number of other diagnoses have been suggested to potentially include bipolar spectrum patients, including borderline personality disorder (36,37), eating disorders (38,39), and ADHD (40). In these conditions, bipolar symptoms may occur, but whether these subjects with subthreshold bipolar disorder will respond more effectively to a bipolar treatment algorithm rather than the algorithm for their “primary” diagnosis is unknown. Complicating considerations in all of these instances, psychotropic medication effects are generally modest, and many of our interventions appear to be relatively nonspecific. For example, in treating large groups of people with well-defined bipolar I disorder mania, only about 50% respond to any given medication (41). Trial and error, sometimes for many years, is often required to find an effective intervention (41). Nonetheless, in a small study of “bipolar spectrum” youth who had bipolar parents, Duffy et al (42) found that lithium response was predicted by a history of lithium responsiveness in the family, suggesting that, even with the limitations of our current treatments, treatment response provides a useful metric to inform diagnostic discussions. However, lithium is unusual among psychotropic drugs for its relative specificity in the treatment of classic bipolar I

disorder. Most of the other psychotropic drugs are modestly but broadly effective across a wide range of conditions.

Indeed, the advent of lithium dramatically altered the psychiatric landscape. Lithium was specifically useful for patients with a traditional bipolar I course (i.e., mania alternating with depression), yet had little benefit in schizophrenia and unipolar depression (at least as monotherapy). The eventual approval of lithium in the US in 1970 led psychiatry to critically examine how bipolar disorder was distinguished from schizophrenia, leading to the US/UK cross-national studies and recognition that schizophrenia was over-diagnosed in the US at the expense of bipolar disorder (43). The presence of nonspecific treatments may contribute to diagnostic imprecision, as was the case for schizophrenia in the US prior to 1970. Faced with a number of new treatments (e.g., atypical antipsychotics) that appear to be relatively nonspecific across a wide range of psychiatric conditions, we need to be careful that treatment nonspecificity is not driving our diagnostic categories, as doing so may limit our ability to identify patients for more effective and specific treatments in the future (1,44).

A significant risk, then, of broadening the diagnosis of bipolar disorder is that the label will be overused, misclassifying patients who might benefit from alternative treatment approaches. For example, in a series of papers, Zimmerman et al (45-47) found that patients with borderline personality are frequently misdiagnosed with bipolar disorder, which might lead to excessive medication trials when specific therapies, for example dialectical behavioral therapy, would be more effective (48). The potential benefits of a broader treatment algorithm applied to "bipolar spectrum" patients must be balanced against the risks of exposing individuals to adverse medication effects from unnecessary drug trials. None of the compounds commonly used to treat major mental illness are without risks for adverse effects (41). From a treatment standpoint, then, the advantages of broadening the diagnosis of bipolar disorder should meaningfully advance how affected individuals are

therapeutically managed. More studies are needed like that of Perlis et al (25) to specifically test the treatment advantages of expanding diagnostic groups.

RISKS AND BENEFITS: RESEARCH

In addition to guiding therapeutic decisions, diagnostic considerations are critically important for defining patient subgroups for scientific inquiry into the etiopathogenesis of bipolar disorder. The primary benefit of expanding the diagnosis for research would be to improve our ability to identify objective markers that transcend phenomenological observation (49). Such markers would be specific to the broadly-defined bipolar diagnosis, but independent of mood symptoms and mood episodes, so could serve as treatment targets and to help predict clinical outcomes. Before these expectations can be met, however, there are still significant issues complicating inquiries into the etiopathogenesis of bipolar disorder at the level of basic science. For example, there are few animal models of mania, the defining mood state of bipolar disorder. It is difficult to produce manic-like symptoms in rodents, so only proxy behaviors can be examined (e.g., social behavior, motivation, and certain cognitive abilities). Additionally, there is no model of spontaneously alternating manic and depressive behaviors to date (50). Considering these knowledge gaps, the question remains: "Does expanding the diagnosis of bipolar disorder assist research efforts toward clarifying the etiopathogenesis of bipolar disorder to improve treatment assignment in the future?"

Genetic studies provide one foundation for addressing this question. There is compelling evidence that bipolar disorder is highly heritable. Concordance rates are estimated to be at least 67% in monozygotic twins (51), and family studies demonstrate a relative risk 8-10 times higher in first-degree relatives than in the general population (52). To date, however, twin and family studies have failed to identify consistent disease specific genetic underpinnings for bipolar disorder, and, instead, demonstrate

considerable genetic overlap with related conditions. For example, as reviewed in Barnett and Smoller (53), individuals at risk for bipolar disorder are also at increased risk for unipolar depression, schizophrenia, and schizoaffective disorder. Even in the context of a greater relative risk for developing bipolar disorder than these other conditions, much of the genetic risk for bipolar disorder is shared with spectrum conditions, which can be interpreted as research evidence for expanding the bipolar diagnosis.

Although genetic research, in large part, seems to support a bipolar spectrum view, due to the nonspecificity of findings to date for DSM-IV or ICD-10 categorizations, this may as likely be due to methodological inadequacies and "low signal" as to a true lack of disease specific findings. In comparing bipolar disorder and schizophrenia specifically, common linkage regions and candidate genes appear to support a spectrum view (54) but, as yet, results are not fully replicable and the make up of the spectrum itself is unsettled. Although the bipolar spectrum might be expected to involve mood dysregulation at its core, common genetic findings in bipolar disorder and schizophrenia may be primarily the result of commonalities in psychotic symptoms. It has been proposed, based on risk factor and clinical history considerations, that bipolar disorder may be better classified with schizophrenia in a psychotic cluster than with unipolar depression in an emotional cluster (55). Since the occurrence of mania is predominantly accompanied by psychotic symptoms (56), and in light of suggestions that psychosis provides a reliable phenotype for genetics research (57), psychotic symptoms might, then, provide as reasonable a basis for defining the bipolar spectrum as mood dysregulation. Until the make up of the bipolar spectrum receives support from converging lines of research, however, there is a risk of broadening the diagnosis prematurely. Moreover, there may also be a vicious cycle in which failure to isolate homogeneous subpopulations of bipolar disorder leads to "noisy" and nonspecific genetic finding; further broadening the diagnosis might worsen this situation.

Another reason for exercising caution in expanding the bipolar diagnosis is that clinical outcomes are difficult to predict, due to the interaction of various genetic and environmental factors. Although one model recently estimated that 22% of the genetic risk in bipolar disorder may be explained by six common gene variants (58), it is difficult to ascertain the disease specificity of such findings, and the relative importance of various genes is not easy to estimate. Different gene combinations and interactions can have an additive effect on behavior, resulting in variable phenotypic expression, which is particularly pronounced in complex behavioral disorders like bipolar disorder. Exactly how genes, experience, and their interaction influence etiopathogenesis, psychopathology, and outcome in bipolar disorder remains a complicated and speculative issue. Other overarching issues, such as why certain individuals are more or less “resilient” to genetic and psychosocial stressors that produce and propagate psychopathology, provide additional challenges for researchers (59).

Despite these challenges, the identification of cognitive markers has already begun to address the question of whether to broaden the bipolar diagnosis. A few investigators have recently compared, or reviewed, neurocognitive performance between bipolar I and related disorders (60-62). These studies provide direct tests of the bipolar spectrum hypothesis. The research to date has fairly consistently identified differences in the neurocognitive profiles of bipolar I and II individuals (61). Bipolar I patient groups appear to have widespread dysfunction of verbal learning and memory, attention and executive function, and a greater likelihood of clinically significant impairment relative to bipolar II groups, who have less functional impairment, primarily restricted to working memory and executive function (60). A similar study, this time comparing bipolar II depressed and unipolar depressed patients matched on depression severity, also showed distinct cognitive profiles, with the bipolar and unipolar groups showing relatively intact cognition and impaired executive function, respec-

tively (62). Each of these studies, then, supports the view that there may be biologically-based cognitive differences between bipolar II and related mood disorders, inconsistent with a bipolar spectrum hypothesis.

Similar to cognitive research, much of neuroimaging research also provides little support for the spectrum hypothesis. For example, in a positron emission tomography study, it was demonstrated that midbrain serotonin transporter binding was lower in medicated bipolar I relative to bipolar II participants, supporting the current DSM-IV dichotomy (63). In a voxel-based morphometry study, Ha et al (64) demonstrated that bipolar I and II participants both show gray matter deficits at the intersection of the ventral prefrontal and anterior limbic circuits relative to healthy comparison participants. However, the bipolar I group also had greater gray matter deficits than the bipolar II group in four other widely distributed brain regions, suggesting some degree of neuro-structural distinction between these two subgroups as well.

Taken together, then, genetic, cognitive and imaging research to date provides no real consensus regarding the appropriateness of broadening the bipolar diagnosis. Although the research findings from a given perspective may lean toward or away from the spectrum view on the whole, there are instances of support for the contrary view, and the current state of the art in instrumentation and methodology can shift the equilibrium substantially. Of course, if null effects between spectrum conditions are not as widely reported in the research literature, as is often the case, the range and validity of the bipolar spectrum could be underestimated. This possibility further highlights the need for well-designed studies testing the assumptions of the spectrum itself, rather than simple disorder specific comparison studies.

CONCLUSIONS

Broadening the diagnosis of bipolar disorder offers the potential to identify

patients who might respond to bipolar treatment algorithms, and who might not otherwise be successfully treated. Similarly, less categorical and more dimensional conceptions of bipolar illness might help identify genetic risks or new endophenotypes. However, with frequent diagnostic changes, it becomes difficult to complete studies to validate the new diagnostic systems. Broadening the bipolar diagnosis risks diluting samples to the point of such heterogeneity that neither basic nor clinical research can progress, limiting discovery and potentially exposing patients to unnecessary adverse medication effects. In fact, bipolar disorder as defined by DSM-IV and ICD-10 is likely comprised by a heterogeneous collection of underlying etiologies that are too complex to distinguish by clinical presentation alone. However, to date the empirical evidence is still too scant to say with conviction whether or not broadening the diagnosis of bipolar disorder will assist with etiologic discovery or improvements in treatment development.

Until research findings can provide better insight into the validity of a broader diagnostic conception of bipolar disorder, clinical expansion to a “spectrum” concept should be considered with caution (49,73). Prematurely broadening a diagnostic category, prior to substantial evidence that doing so enhances either treatment development or etiological research, runs the risk of eliminating any value of the diagnosis (44). Before advancing a new bipolar diagnostic schema, it would seem prudent first to develop an agreed upon operational approach (1) and then develop specific studies to compare the advantages of the new approach for treatment and discovery. Changing diagnoses simply to meet new theoretical constructs prevents adequate systematic testing of the new approach and risks losing many of the evidence-based advances we have seen in psychiatry in the past 50 years.

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