

Deconstructing Bipolar Disorder: A Critical Review of its Diagnostic Validity and a Proposal for *DSM-V* and *ICD-11*

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The development of *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*, and *International Classification of Diseases, Eleventh Edition*, deserves a significant conceptual step forward. There is a clear need to improve and refine the current diagnostic criteria, but also to introduce dimensions, perhaps not as an alternative but rather as a useful complement to categorical diagnosis. Laboratory, family, and treatment response data should also be systematically included in the diagnostic assessment when available. We have critically reviewed the content, concurrent, discriminant, and predictive validity of bipolar disorder, and to overcome the validity problems of the current classifications of mental disorders, we propose a modular system which may integrate categorical and dimensional issues, laboratory data, associated nonpsychiatric medical conditions, psychological assessment, and social issues in a comprehensive and nevertheless practical approach.

Key words: bipolar disorder/classification/diagnosis/*DSM-V/ICD-11*

Introduction

Challenging the Kraepelinian Dichotomy: Categorical Versus Dimensional Approaches

Modern classifications of mental disorders assume a categorical model which may be helpful in terms of reliability and communication among clinicians and researchers but which raise serious concerns about diagnostic validity and boundaries between entities. The concept of psycho-

sis and the entities that may be grouped under that umbrella may themselves be questionable. Moreover, the classification of psychoses has been a topic of vigorous debate ever since its conception with the formulation of the disease concepts of dementia praecox and manic-depressive insanity by Emil Kraepelin in 1896 and their subsequent codification into the nosologic entities of schizophrenia and bipolar illness.^{1,2} There has been an intensive debate on whether these 2 conditions are distinct or related and potentially overlapping illnesses. Categorical approaches, as those from *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)*, and *International Classification of Diseases, Tenth Edition (ICD-10)*, may be useful in clinical practice but leave many patients out of the diagnostic system (the disappointing subcategory of “not-otherwise-specified”) and provide a very poor solution to the problem of symptomatic overlap, either by causing huge comorbidity or by creating intermediate categories such as “schizoaffective disorder.” From the research point-of-view, dimensional approaches seem much more useful, but are clearly less practical under routine clinical conditions.

The Validity of Psychiatric Diagnosis

In the absence of an etiologically based classification, attempts have been made to build a diagnostic system of mental conditions that could be used across different cultures. As formulated by Robins and Guze,³ introducing a biomedical approach to psychiatric nosology that has been extremely successful in the last 3 decades, the validity of psychiatric diagnosis may rely on several domains: (1) content validity, involving basically symptoms and clinical diagnostic criteria; (2) concurrent validity, defined by neurobiological correlates such as laboratory findings, neuroimaging and neuropsychology, genetics, family studies, and perhaps also treatment response; (3) predictive validity, which has mainly to do with diagnostic stability over time; and (4) discriminant validity, which involves delimitation from other disorders. This formulation, directly inherited from Sydenham’s approach to general medicine, had the virtue of approaching psychiatry to other medical specialities, to counteract

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the predominant Freudian theories that were leaving psychiatry orphan of any operational taxonomy, and to become the foundation of the first modern classification of psychiatric disorders based on operationalized criteria,⁴ and the grounds for the most successful one, the *DSM-III*.⁵ Further developments were the *DSM-III-R*, the *DSM-IV*, and *DSM-IV-TR*. In 1992, The World Health Organization applied the same approach to their latter version of the *International Classification of Diseases*, the *ICD-10*.⁶

The Validity of Bipolar Disorder as a Diagnostic Category

Content Validity Problems of Current Definitions of Bipolar Disorder

The concept of bipolar disorder involves the current or past occurrence of at least one episode of mania or hypomania or a mixed episode, which is usually, but not necessarily, preceded or followed by a depressive episode, cyclic changes between mood states, and eventually psychotic symptoms, which are assumed to be a marker of the severity of the episode. By excluding psychotic symptoms from the definition, leaving them as mere correlate of impairment or severity (criterion D), the *DSMs* have indirectly reinforced the (wrong) idea that psychotic symptoms are a core feature of schizophrenia but not bipolar disorder. Furthermore, they have taken little advantage of the potential value of characterizing psychotic features (ie, mood congruent vs mood incongruent) for discriminant validity vs schizophrenia.

Moreover, the definition of major depression in bipolar disorder in the *DSMs* does not make any difference with unipolar depression. Nevertheless, the *DSM* acknowledges the bipolar/unipolar dichotomy as opposed to the Kraepelinian concept of manic-depressive illness, which is still advocated by some authors.⁷ This carries the problem that the diagnosis of bipolar depression can only be made after a manic, hypomanic, or mixed episode has occurred. The system is, thus, assuming some loss of predictive validity in unipolar depression and increasing the heterogeneity of the concept of major depression, which may be too broad. Conversely, the concept of mixed episodes is very narrowly defined as the concurrence of a full manic and depressive episode, leaving behind many potentially useful concepts such as mixed hypomania^{8,9} and excluding the possibility that bipolar II patients may have mixed episodes. The definition of mixed states underlines once again the difficulties of converting dimensional concepts into diagnostic categories.

ICD-10 was to *ICD-9* what *DSM-III* was to *DSM-II*: a major switch from a pure classification code towards a novel classification with operational diagnostic criteria; in some way, it was born as a “global” alternative to *DSM-III*. As far as bipolar disorder is concerned, the most relevant difference between the 2 systems is that

in *ICD-10* episodes are also diagnosis and that hypomania is seen as mild form of mania in the latter (1 week duration, social impairment needed); to differentiate the concept between affective and nonaffective psychoses, the “prominence” of psychotic vs affective symptoms is claimed, without any clear definition of what prominence means.

Concurrent Validity: The Need of Embedding Biological Markers Into the Diagnostic System

To a great extent, the social success of Medicine over the last 100 years has depended on laboratory findings and the support of technology to clinician’s skills. In psychiatry, practically no tools other than psychopathological assessment are still available as routine diagnostic tests, and in fact, this is one of the main reasons why a reliable, clinically based diagnostic system is still necessary, but there has been substantial progress in using biological findings as diagnostic validators. Hence, the list of findings in bipolar disorder with significantly better sensitivity and specificity than chance is quite long, but none of them has a clear use in clinical practice. However, the coming diagnostic systems cannot ignore anymore this long list of validators, including laboratory, neuroimaging, neuropsychology, genetic, and therapeutic data. Therefore, it may be the time to design a “psychiatric toolbox,” including genotyping, neurophysiologic, neuroimaging, and neuropsychological tests, which may help to identify biomarkers that are persistent, rather than trait dependent, to improve the validity of the psychiatric classification and its pathophysiological grounds. Clearly, more research is urgently needed in order to be able, as soon as possible, to add laboratory measures to the classification system.

Although concurrent validity can be narrowly defined to include only “hard” laboratory data, we think that family studies, which were defined separately by Robins and Guze,³ and neuropsychological findings can be included in this concept too. There is no question that the exclusion of family data from the diagnostic systems was not decided merely on sensitivity/specificity ratio; in fact, family history may be much more useful for certain conditions, including bipolar disorder, than some of the official criteria in the *DSM-IV* list. It was rather a “philosophical” decision, which should be revised promptly. Assuming that there is no single symptom which is exclusive of bipolar disorder or schizophrenia, including the Schneiderian first-rank symptoms,¹⁰ the utility of family history is probably higher than that of many of the current criteria.

With regards to genetics, current knowledge supports that there is indeed some overlap in the genes that predispose to bipolar disorder and schizophrenia. One gene, (G72), has been repeatedly implicated as an overlap gene,¹¹ whereas DISC1, COMT, BDNF, and others may constitute additional shared susceptibility genes.¹²

However, potential nonoverlap syndromes—such as nonpsychotic bipolar disorder or cyclothymia, on the one hand, and negative symptoms or the deficit syndrome, on the other—could turn out to have their own unique genetic determinants.¹³ If genotypes are to be the anchor points of a clinically useful system of classification, they must ultimately be shown to inform prognosis, treatment, and prevention. No gene variants have yet met these tests in bipolar disorder or schizophrenia but may hopefully be used as diagnostic validators concurrently with clinical criteria in the near future.

Imaging data examining volume loss in brain structures are also consistent with some overlap between diagnostic categories within the spectrum of psychoses. Genetic risk for schizophrenia may be associated with volume loss in gray matter in left frontal-striatum-thalamic and temporal areas, whereas the genetic risk for bipolar disorder may be associated with volume loss in gray matter in the right anterior cingulate cortex and in the ventral striatum. However, genetic risk for both conditions is also associated with brain changes as volume loss in white matter in frontal and temporoparietal areas.¹⁴ The most prominent brain abnormality in bipolar disorder is enlargement of the amygdala.¹⁵ In addition, there might be structural changes in other limbic structures and hippocampus, the frontal lobe, cerebellum, and pituitary.¹⁶ Again, none of these findings is specific enough to be used as a diagnostic test in clinical practice, but the consistency of the findings suggests that they do have some diagnostic validity. As an example of the progress made by neuroimaging studies in particular in providing data to support the diagnostic validity of bipolar disorder, we discuss in the companion article to this article recent promising findings from structural and functional neuroimaging studies that suggest persistent regional neural abnormalities in bipolar disorder.

Neuropsychological tests have shown consistently that both schizophrenia and bipolar disorder are associated to significant cognitive problems, which may be more intense in the former.^{17,18} Differences may involve attention, verbal memory, and executive function,¹⁹ and particularly premorbid intelligence.^{20–22} None of these issues is currently included in the classificatory system. Some of the reasons that are often given to exclude this kind of information from the diagnostic criteria are that their specificity is not very high and they are not available to the majority of clinicians. However, this could be easily solved by devoting a supplementary axis to biological and neuropsychological markers, which could, initially, work just as a source of complementary or supportive information which might also help to stimulate further research.

Indeed, there is a long-lasting tradition in psychiatry to try to use laboratory test to verify clinical impressions. The initial expectations related to rapid eye movement (REM) latency tests and dexamethasone suppression

tests were not accomplished because they would not be able to replace clinical judgment, and actually their sensitivity/specificity ratio was poorer than that of most clinical criteria used in the classificatory system. Subsequently, many other neurophysiological and biochemical tests have been developed, showing consistently that bipolar disorder has significant neurobiological correlates that may enhance concurrent validity, as suggested in our proposal for a modular classification below.

Biomarkers may not only increase concurrent validity but also discriminant validity. The same applies to treatment response. In the case of bipolar disorder, treatment response may be particularly helpful as far as lithium and perhaps other so-called mood stabilizers are concerned: Lithium has been reported to be effective in mania but not in schizophrenia²³ and is likely to be more effective in bipolar depression than unipolar depression.²⁴ Lamotrigine may also be more helpful for bipolar depression than unipolar depression.²⁵ There may be a familial disposition to lithium response.²⁶ Bipolar patients are also more likely to switch to mania when treated with antidepressants than unipolar patients.²⁷

Discriminant Validity of Bipolar Disorder: Delimitation From Other Disorders

In the absence of an etiological classification, discriminant validity is far from ideal in any classification. Symptom overlap is huge in psychiatry, and differences between conditions are more quantitative than qualitative. This is one of the reasons why dimensional approaches may be much more valid, albeit less practical, than categorical. The problems of a categorical classification in a dimensional world are as follows: (1) many patients do not fit in any category (due to artificial boundaries and “holes” between them); (2) many patients do not achieve enough severity or duration of symptoms to qualify for the full picture, despite suffering from similar consequences as those with the whole syndrome (spectrum); and (3) many patients fulfill criteria for several conditions because of symptom overlap (comorbidity). The only way that *DSM-IV*, *ICD-10*, and similar systems have found to cope with problems related to discriminant validity as those mentioned above has been to allow for switching within categories (ie, unipolar to bipolar after a manic episode) to include broad categories as “not otherwise specified,” the inclusion of milder categories within a spectrum (ie, bipolar II), and to allow for coexistence of several diagnosis within the same patient (comorbidity). However, and challenging the statement that these classifications are atheoretical, some particular comorbidities are not allowed: for instance, the apparent dilemma of allowing the co-occurrence of the 2 major psychoses, schizophrenia and manic-depressive illness in the same patient, is solved with the introduction of another intermediate category, schizoaffective disorder,

which has poor content validity and reliability but helps to avoid the problem. Conversely, some patients may happen to fulfill criteria for over 10 different conditions, a phenomenon that does not happen in any other medical speciality.

Laboratory data have been disappointing with regards to support boundaries between conditions; they seem to behave as symptoms, with important overlap and poor specificity. There are some emerging data from neuroimaging studies, though, pointing to bipolar-specific regional neural functional abnormalities (reviewed in the companion article to this article). Again, however, genetics, neuropathology, neurophysiology, neuroimaging, biochemical challenge tests, and neuropsychology, while providing some support to diagnostic boundaries, are unable to work at present as diagnostic tests in clinical practice. But even if we are not there yet, the preliminary inclusion of laboratory data to support to some extent the validity of either categories or dimensions may carry more benefits than problems. In the future, laboratory findings from research studies that appear to discriminate between groups in highly selected and artificially enriched research samples should be the focus of subsequent diagnostic research in an attempt to research whether such laboratory findings may have diagnostic value, in terms of a sufficiently elevated likelihood ratio, in routine clinical practice settings. It would be useful to compile a list of diagnostic likelihood ratios of these measures, taking into account the setting, the base prevalence of the disorder to be diagnosed in that particular setting, and use these to develop quantitative diagnostic algorithms and decision trees in a new module in the *DSM* and *ICD* systems. This approach is further discussed at the end of this article.

Temporal Stability of Bipolar Disorder: Assessing Predictive Validity

Temporal stability may be invoked as a criterion for assessing the validity of psychiatric diagnosis as far as the category in question is supposed to be stable over time. Diagnostic reliability may also influence predictive validity, as poor reliability might hamper the theoretical stability of a certain diagnostic category. Follow-up studies are crucial to assess predictive validity. Categories that include chronicity as part of their definition are more likely to be temporally stable (ie, schizophrenia), whereas others are unstable almost by definition (schizophreniform disorder). In bipolar disorder, bipolar I is more stable than bipolar II just because bipolar II may switch to bipolar I, but not vice versa. The stability of bipolar disorder has generally been reported to be high, ranging from 70% to 91%.²⁸⁻³¹

Certain situations that may be developed by patients over time, but which may not be part of the core syndrome but rather a particular longitudinal pattern, are included in current classifications as course specifiers.

Table 1. Predominant Polarity Correlates

Depressive Polarity	Manic Polarity
60% bipolar patients	40% bipolar patients
More bipolar II	More bipolar I
More depressive onset	More manic onset
More seasonal pattern	Younger and earlier onset
More suicide attempts	More substance misuse
Better long-term response to lamotrigine	Better long-term response to atypical antipsychotics
More antidepressant use	

For bipolar disorder, they include chronicity (with or without full interepisode recovery), seasonality, and rapid cycling. A further potential specifier for *DSM-V* may be “predominant polarity.” As many as 56% bipolar patients display a specific pattern of predominant polarity; 60% of those may be classified as predominantly depressed (with at least two-thirds of past episodes fulfilling criteria for major depression), whereas 40% may be classified as predominantly manic or hypomanic.³² Table 1 shows the characteristics of the 2 groups.

A Proposal for *DSM-V* and *ICD-11*

Overcoming the Categorical Versus Dimensional Approach Dilemma

The only way to overcome the problems associated to either the categorical or the dimensional approach is to adopt both. As discussed above, the dimensional approach may be closer to reality but may carry reliability problems and be difficult to implement in real life, including aspects with important financial and social implications such as reimbursement policies, insurance issues, and drug regulations; on the other hand, the categorical approach has proved to be unsatisfactory with regards to diagnostic validity and has carried problems such as inflated comorbidity rates and a growing number of diagnostic categories (psychiatry is probably the only medical speciality where the number of conditions is continuously increasing rather than decreasing); however, the categorical approach is practical, easy, and reliable. We believe that switching from a categorical to a dimensional classification would be unfeasible and extremely confusing, but we also think that the time has come to include some dimensional information into the system. With this regard, we propose the development of a dimensional module within the categorical classification that may end up to be extremely helpful for research, teaching, and clinical practice, by allowing to assess in a systematic way a limited number of issues, as listed in table 2. These dimensions have been thought to work for the majority of mental disorders, not just bipolar disorder. Patients would eventually be rated according

Table 2. A proposal for dimensional classification as a further axis or module for the classification of mental disorders

Dimension/Severity	None (absent)	Mild	Moderate	Severe
Psychotic (positive) symptoms	0	1	2	3
Negative symptoms	0	1	2	3
Manic symptoms	0	1	2	3
Depressive symptoms	0	1	2	3
Cognitive impairment	0	1	2	3
Anxiety	0	1	2	3
Obsessive-compulsive symptoms	0	1	2	3
Substance misuse	0	1	2	3
Impulsivity	0	1	2	3
Suicidality	0	1	2	3
Eating problems	0	1	2	3
Sleeping problems	0	1	2	3
Sexual problems	0	1	2	3

to whether the specific dimension is present with mild, moderate, or severe intensity or whether is absent at all. Of course, every dimension should be very well defined a priori, and high scores in any dimension would deserve further specifications in every case, but this would be a simple way to start to develop a complementary dimensional view over our rigid and poorly valid taxonomy.

Refining Current Diagnostic Criteria

As mentioned, we do not want the categorical classification to disappear. In fact, the dimensional module would be a poor contribution if we were not able to refine, at the same time, the current nosology. Refinements should be data-driven. Further research is needed to assess the sensitivity and specificity of diagnostic criteria and categories. Some of the specific problems related to the diagnosis of bipolar disorder and issues that require urgent revision are listed in table 3.

The Modular Approach

The modular approach aims to be a step forward the axial approach, which proved successful in *DSM-III* but has become partially obsolete. The modular approach includes a first module which basically corresponds to a refined axis I in current classification but also includes some of the categories included in axis II, as certain conditions controversially classified as personality disorders (ie, borderline disorder); module I is the clinical diagnostic classification, in which some hierarchical issues (primary vs secondary, etc) may or may not be included. Module II involves the dimensional approach and

Table 3. Limitations of Current Diagnostic Criteria for Bipolar Disorder

- Psychotic symptoms are common in mania and may also happen in depression, but they are not part of the diagnostic criteria, reinforcing the idea that psychosis is a core feature of schizophrenia but not bipolar disorder
- Mood-congruent vs mood-incongruent psychotic symptoms are not well defined
- Bipolar depression is undistinguishable from unipolar major depression
- Recurring depressions are not recognized as a potential precursor to bipolar disorder—may be diagnosed as a depressive disorder
- Mixed symptoms are not sufficiently characterized, and mixed episodes are too narrowly defined
- Cognitive symptoms are not included
- Drug-induced mania and hypomania are excluded: problems in judging what “direct physiological consequence of a drug, medication, or somatic treatment” means
- No account is taken of family history and biological markers
- Four-day duration required for diagnosis of hypomania and 1 week for mania may be too long
- Bipolar disorder not-otherwise-specified may include the majority of cases, particularly in children and adolescents

includes a limited number of potential symptomatic dimensions (see table 2, for a preliminary proposal), which can be dimensionally rated regardless of the diagnostic category according to module I. Module III is the laboratory module and should include all the items in the psychiatric toolbox (genotyping, structural and functional neuroimaging, REM latency, hormonal tests, cognitive data) that would enhance diagnostic validity. In the companion article to this article, we therefore discuss further the extent to which findings from recent structural and functional neuroimaging studies in particular might have increased our ability to identify potential biomarkers of bipolar disorder to indeed enhance the diagnostic validity of the disorder. The modular approach allows for a simple clinical diagnosis when such tools are not available or not cost effective but permits to integrate the biological data as well when appropriate and is the first step toward a future classification based on pathophysiological grounds. Module IV corresponds to axis III in *DSMs* and probably requires further attention, especially for some nonpsychiatric conditions that are overrepresented in the mentally ill and are likely to influence and to be influenced by the psychiatric disorder (ie, diabetes, obesity, cancer, cardiovascular disease, etc). The medical morbidity in bipolar disorder is extremely high and rapidly increasing.³³ Module V should be the psychological module and should include all the information about personality and usual behavior of the subject that may be relevant for psychiatric assessment. Some, but not all, of the items and categories currently included

Table 4. Proposal for a Modular Approach to the Classification and Diagnosis of People With Mental Disorders

Module I	Categorical classification
Module II	Dimensional assessment
Module III	Laboratory data
Module IV	Medical nonpsychiatric conditions
Module V	Psychological assessment
Module VI	Social issues (environmental factors and social function)

in *DSMs*' axis II should go here. This module should necessarily have a dimensional format, avoiding all the problems related to poor validity and reliability of personality disorders as described in *DSM-IV* and *ICD-10*. Finally, the social issues should be assessed in module VI, including what is currently included in axis IV and V of *DSM-IV*, namely psychosocial and environmental problems and social functioning. A summary of the modular approach is shown in table 4.

In conclusion, the validity of psychiatric diagnosis in general and bipolar disorder in particular deserves further research and alternative approaches. There is a clear need to improve and refine the current diagnostic criteria and to introduce dimensions not as an alternative but rather as a useful complement to categorical diagnosis. Laboratory, family, and treatment response data should also be systematically included in the diagnostic assessment when available. There is little chance that *DSM-V* or *ICD-11* may represent a true step forward if these kinds of data are not included. We propose a modular system that may integrate categorical and dimensional issues, laboratory data, associated nonpsychiatric medical conditions, psychological assessment, and social issues in a comprehensive and nevertheless practical approach.

Acknowledgments

Supported in part by the National Institutes of Health grant for the conference titled "Deconstructing Psychosis" convened under the auspices of the American Psychiatric Association, the World Health Organization, and the NIH in Washington, DC, February 15–17, 2006. Eduard Vieta, has acted as a consultant, received grants, or been hired as a speaker by the following companies: Almirall, AstraZeneca, Bial, Bristol-Meyers-Squibb, Eli Lilly, GlaxoSmithKline, Janssen-Cilag, Lundbeck, Merck Sharp and Dohme, Novartis, Organon, Otsuka, Pfizer, Sanofi Aventis, Servier, UCB. He has acted as a consultant and has received grants from the Spanish Ministry of Health, Instituto de Salud Carlos III, RETICS RD06/0011 (REM-TAP) and from the Stanley Medical Research Institute. Mary L. Phillips has no conflicts of interest.

References

- Jablensky A. The conflict of the nosologists: views on schizophrenia and manic-depressive illness in the early part of the 20th century. *Schizophr Res*. 1999;39:95–100.
- Boteva K, Lieberman J. Reconsidering the classification of schizophrenia and manic depressive illness—a critical analysis and new conceptual model. *World J Biol Psychiatry*. 2003;4:81–92.
- Robins E, Guze SB. Establishment of diagnostic validity in psychiatric illness: its application to schizophrenia. *Am J Psychiatry*. 1970;126:983–987.
- Feighner JP, Robins E, Guze SB, Woodruff RA Jr, Winokur G, Munoz R. Diagnostic criteria for use in psychiatric research. *Arch Gen Psychiatry*. 1972;26:57–63.
- American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders: DSM-III*. Washington, DC: American Psychiatric Press; 1980.
- World Health Organization. *ICD 10: International Statistical Classification of Diseases and Related Health Problems*. Geneva: Ill World Health Organization; 1992.
- Goodwin FK, Jamison KR. *Manic-Depressive Illness*. New York, NY: Oxford University Press; 1990.
- Akiskal HS, Bourgeois ML, Angst J, Post R, Moller H, Hirschfeld R. Re-evaluating the prevalence of and diagnostic composition within the broad clinical spectrum of bipolar disorders. *J Affect Disord*. 2000;59:suppl 1: S5–S30.
- Suppes T, Mintz J, McElroy SL, et al. Mixed hypomania in 908 patients with bipolar disorder evaluated prospectively in the Stanley Foundation Bipolar Treatment Network: a sex-specific phenomenon. *Arch Gen Psychiatry*. 2005;62:1089–1096.
- Taylor MA, Abrams R, Gaztanaga P. Manic-depressive illness and schizophrenia: a partial validation of research diagnostic criteria utilizing neuropsychological testing. *Compr Psychiatry*. 1975;16:91–96.
- Schumacher J, Jamra RA, Freudenberg J, et al. Examination of G72 and D-amino-acid oxidase as genetic risk factors for schizophrenia and bipolar affective disorder. *Mol Psychiatry*. 2004;9:203–207.
- Berrettini W. Evidence for shared susceptibility in bipolar disorder and schizophrenia. *Am J Med Genet C Semin Med Genet*. 2003;123:59–64.
- Potash JB. Carving chaos: genetics and the classification of mood and psychotic syndromes. *Harv Rev Psychiatry*. 2006;14:47–63.
- McDonald C, Bullmore ET, Sham PC, et al. Association of genetic risks for schizophrenia and bipolar disorder with specific and generic brain structural endophenotypes. *Arch Gen Psychiatry*. 2004;61:974–984.
- Blumberg HP, Fredericks C, Wang F, et al. Preliminary evidence for persistent abnormalities in amygdala volumes in adolescents and young adults with bipolar disorder. *Bipolar Disord*. 2005;7:570–576.
- Benabarre A, Vieta E, Martínez-Arán A, et al. The somatics of psyche: structural neuromorphometry of bipolar disorders. *Psychother Psychosom*. 2002;71:180–189.
- Martinez-Aran A, Penades R, Vieta E, et al. Executive function in patients with remitted bipolar disorder and schizophrenia and its relationship with functional outcome. *Psychother Psychosom*. 2002;71:39–46.
- Altshuler LL, Ventura J, van Gorp WG, Green MF, Theberge DC, Mintz J. Neurocognitive function in clinically

- stable men with bipolar I disorder or schizophrenia and normal control subjects. *Biol Psychiatry*. 2004;56:560–569.
19. Daban C, Martinez-Aran A, Torrent C, et al. Specificity of cognitive deficits in bipolar disorder versus schizophrenia. A systematic review. *Psychother Psychosom*. 2006;75:72–84.
 20. Cannon M, Caspi A, Moffitt TE, et al. Evidence for early-childhood, pan-developmental impairment specific to schizophreniform disorder: results from a longitudinal birth cohort. *Arch Gen Psychiatry*. 2002;59:449–456.
 21. Reichenberg A, Weiser M, Rabinowitz J, et al. A population-based cohort study of premorbid intellectual, language, and behavioral functioning in patients with schizophrenia, schizoaffective disorder, and nonpsychotic bipolar disorder. *Am J Psychiatry*. 2002;159:2027–2035.
 22. Zammit S, Allebeck P, David AS, et al. A longitudinal study of premorbid IQ score and risk of developing schizophrenia, bipolar disorder, severe depression, and other nonaffective psychoses. *Arch Gen Psychiatry*. 2004;61:354–360.
 23. Leucht S, Kissling W, McGrath J. Lithium for schizophrenia revisited: a systematic review and meta-analysis of randomized controlled trials. *J Clin Psychiatry*. 2004;65:177–186.
 24. Goodwin FK, Murphy DL, Dunner DL, Bunney WE Jr. Lithium response in unipolar versus bipolar depression. *Am J Psychiatry*. 1972;129:44–47.
 25. Vieta E. The role of third-generation anticonvulsants in the treatment of bipolar disorder. *Clin Neuropsychiatry*. 2004;1:159–164.
 26. Grof P, Duffy A, Cavazzoni P, et al. Is response to prophylactic lithium a familial trait? *J Clin Psychiatry*. 2002;63:942–947.
 27. Peet M. Induction of mania with selective serotonin re-uptake inhibitors and tricyclic antidepressants. *Br J Psychiatry*. 1994;164:549–550.
 28. Amin S, Singh SP, Brewin J, Jones PB, Medley I, Harrison G. Diagnostic stability of first-episode psychosis. Comparison of ICD-10 and DSM-III-R systems. *Br J Psychiatry*. 1999;175:537–543.
 29. Schwartz JE, Fennig S, Tanenberg-Karant M, et al. Congruence of diagnoses 2 years after a first-admission diagnosis of psychosis. *Arch Gen Psychiatry*. 2000;57:593–600.
 30. Schimmelmann BG, Conus P, Edwards J, McGorry PD, Lambert M. Diagnostic stability 18 months after treatment initiation for first-episode psychosis. *J Clin Psychiatry*. 2005;66:1239–1246.
 31. Kessing LV. Diagnostic stability in bipolar disorder in clinical practise as according to ICD-10. *J Affect Disord*. 2005;85:293–299.
 32. Colom F, Vieta E, Daban C, Pacchiarotti I, Sanchez-Moreno J. Clinical and therapeutic implications of predominant polarity in bipolar disorder. *J Affect Disord*. 2006;93:13–17.
 33. Kupfer DJ. The increasing medical burden in bipolar disorder. *JAMA*. 2005;293:2528–2530.