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Bipolar Pathophysiology and Development of Improved Treatments

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Abstract

The purpose of this review is to provide strategies and their rationale which can facilitate scientifically productive investigations into genetic, neuronal, brain functional and clinical aspects of bipolar disorder. The presentation addresses both factors that have impeded and those that have facilitated landmark advances on the pathophysiology and treatment of bipolar disorders. Application of the strategies can provide a scientific platform that may be useful to basic and clinical scientists for the purposes of achieving seminal advances in understanding pathophysiology, including inherited and experience based contributors to disease expression. Current diagnostic criteria omit certain key symptoms, do not include illness course or family history and lack specification of the importance of fundamental symptomatology. Consideration of such factors in inclusion and exclusion criteria, and in assessment instruments in basic and clinical studies, serves to strengthen the capability of a research plan to test key hypotheses regarding moderating and mediating factors of this complex illness. For example, most studies of brain structure and function and of new interventions have selected subjects on the basis of traditional full syndromal criteria. Evidence indicates that additional consideration of principal behavioral domains of bipolar symptomatology, e.g., anxiety, psychosis, impulsivity, elevated psychomotor and cognitive processing speed, rather than strictly depressive or manic syndromes can provide more homogeneous samples for study, and increase the focus of experimental hypotheses.

Keywords

bipolar; mood disorders; drug treatment; genetics; endophenotypes; diagnosis

Introduction

Bipolar disorder, recognized by Hippocrates and Areteus, has received renewed scientific interest consequent to development of effective, novel treatments over the past 50 years. Certain features of bipolar disorder and its scientific study have facilitated these landmark developments, while others have impeded advances. This review focuses on both the facets of bipolar disorder which have aided advances and several methodological approaches which have impeded or slowed advances. A principal aim of the review is to suggest those research strategies which hold the best promise for providing a scientific platform that will aid basic and clinical scientists in achieving seminal advances in understanding

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pathophysiology, including inherited and experience based contributors to disease expression in bipolar disorders. Experience based factors contributory to bipolar disorders are better understood than genetic factors. These include hypothalamic pituitary axis dysregulation, early life psychological and physiological insults, e.g., CNS infections, use of abusable drugs, and vascular or traumatic brain injury. The limited advances to date from genetic studies are in part consequent to the flawed syndromal phenotype currently in vogue. DSM criteria largely resolve problems of criterion variance, but both include false positive cases and exclude true positive ones.

Diagnostic criteria

Current diagnostic criteria for bipolar disorders, whether in the Diagnostic and Statistical Manual-IV-TR, (DSM-IV-TR) or the International Classification of Diseases-10, have both strengths and limitations. (American Psychiatric Association, 2000) The strengths come from an aim of the Research Diagnostic Criteria, which provided the conceptual basis for all subsequent versions of the DSM, to reduce criterion variance across clinicians assessing the same clinical information. Thus, a mental health professional seeing a patient in any country with the same set of symptoms will arrive at the same or nearly same diagnosis, including secondary identification of severity. The criteria for mania are quite specific and selective. Therefore, enrollment of subjects while acutely manic into studies is likely to yield a highly representative sample, with little likelihood of enrollment of false positive cases.

The limitations deal with temporal requirements, lack of specification of core symptoms, failure to incorporate several behavioral characteristics which are highly characteristic of bipolar disorders, and no utilization of family history or illness course data. Two temporal problems exist. The duration of symptoms required for an episode is a minimum of 7 days for mania, 4 for hypomania, or hospitalization for the acute illness state. Hospitalization is less frequently employed as a management technique in the 21st century than it was a quarter century ago, both because of the quicker effectiveness of the array of antimanic agents currently available than was the case with lithium when it was the only recognized antimanic agent and more emphasis on ambulatory than hospitalized based care. However, particularly for early onset bipolar in adolescence and prepubertal youth, hypomanic symptoms are often present for 1 or 2 days and in some instances even shorter periods. (Angst, 1998, Geller, Zimmerman et al., 2001, Angst J, Gamma A et al., 2003) [cindy, does the journal require parentheses around each reference? Also, throughout, I do not think there should be a semicolon following the last reference. I have never seen such style] Further complicating this is the evidence that mixed states, rather than strictly depressed or manic/hypomanic syndromes, constitute the majority of syndromal level cases in adolescents. (Craney 2003)(Dilsaver 2005)

The second temporal issue is that only cross sectional, current symptoms are specifically utilized in supporting a syndromal diagnosis. This does not allow consideration that the proportion of time symptomatic, both syndromally and subsyndromally, is much higher in bipolar than major depression (Goldberg and Harrow, 2004) and that persons with bipolar I disorders may have had a manic syndrome briefly many years ago, but experience only subsyndromal manic symptoms in the present, thus not be diagnosable as bipolar. (Akiskal, 1996, Judd, Akiskal et al., 2002, Kupka RW, Altshuler LL et al., 2007 order more than one reference with the first published listed, first, next published second, etc)

Non-psychiatric disorders often have core symptoms or signs that must be present to establish a diagnosis, but which do not require presence of secondary or less consistent illness features to make the diagnosis. In contrast, bipolar requires that at least one of three classical manic symptoms; elevated, expansive or irritable mood be present, despite

evidence that the first two symptoms are less prevalent than are, for example, core behavioral disturbances of increased activation motorically and cognitively. (Wicki W and Angst J, 1991; Bowden CL, Swan AC et al., 2006) Alternatively, irritability can substitute for these, but, in such instances, an additional symptom is required to confirm diagnosis. The second level symptoms listed in DSM-IV-TR have two problems. Most allow more than one symptom to suffice. For example, agitation or psychomotor slowing can qualify, despite their lack of equivalence. Additionally, several symptoms highly characteristic of bipolar clinical states are not recognized. These include reduced sexual drive in bipolar depression and, in manic states, increased sexuality, risky behavior, impulsivity, increased evening energy, and affective lability. This last group is particularly useful in recognizing illness features that are indicative of bipolarity even when individuals are not syndromally ill, and have been incorporated into screening scales for bipolar disorder. (Angst J, Adolfsson R et al., 2005) Bipolars have higher rates of positive family histories for bipolar but also for any mood disorder, bipolar or unipolar. (Geller, Zimmerman, Williams, Bolhofner, Craney, 2001, Hirschfeld, 2004) In addition, bipolar has its onset before age 20 in at least half of individuals, a considerably earlier onset than observed for major depression. (Kupfer, Frank et al., 2002), (Hirschfeld RM, Lewis L et al., 2003)

A consequence of these distorting criteria for diagnosis is that many studies will under recognize bipolarity, and thereby run a risk of including in control groups persons with bipolar features. (Hantouche, Akiskal et al., 1998) This in turn often leads to intervention for depression with use of antidepressants without attention both psychoeducationally and with mood stabilizers to the fundamental bipolarity, and, consequently, a poor course of illness. (Ghaemi, Boiman et al., 2000) Authorities have proposed both short term and long term strategies for overcoming and/or minimizing the undesirable consequences of present schema. Several of these can be implemented without changes in DSM-IV TR criteria. The task force working toward DSM-V recognizes these issues and may propose revisions to address the issues for DSM-V. (Kraemer HC, Shrout PE, Rubio-Stipec M 2007. Developing the Diagnostic and Statistical Manual V: What Will "Statistical" Mean in DSM-V?. *Social Psychiatry & Psychiatric Epidemiology*. 42(4):259–67)

Profiles of bipolar symptomatology

Characterization of patients in fundamental behavioral domains can be employed to establish profiles that are more sensitive and reliable than total scores from historical symptom constellations of mania and depression.

Domain profiling can aid in cross system studies of cognition, brain circuitry dealing with recognition of danger and the salience thereof and studies of the consequences of traumatic early life experiences. Of particular importance, domain profiling can clarify differences in spectra of benefits for specific drug or psychotherapeutic interventions. The full spectrum of BD symptomatology covered in the Bipolar Inventory of Symptoms Scale (BISS) addresses these limitations with reliable items, reliable and valid depression and mania scales, and five behavioral domains (depression, mania, irritability, psychosis and anxiety) established in factor analyses. (Bowden C, Singh V et al., 2007, Thompson PM, Gonzalez JM et al., 2007) Inclusion of behavioral domains in studies of psychopathology of BD may better characterize simpler or more homogeneous phenotypes within BD in relationship to genetic, imaging and other psychobiological investigations. For example, a major focus of imaging studies in bipolar disorders has been on increased CNS activation in prefrontal circuitry in response to fearful stimuli. If imaging study results of this system can be related to a domain of anxiety, rather than simply a diagnosis of bipolar disorder, it is plausible that relationships lost in the noise of heterogeneous diagnostic groupings can be identified. This strategy has proven effective in clarifying the distinct profile of mixed mania (Cassidy, Forest et al.,

1998), different profiles of beneficial behavioral effects for lithium and divalproex in mania, (Wang PW, Ketter TA et al., 2003) and the association between the BDNF Val66Met genotype and differential gray matter content in brain structures relevant to working memory in subjects affected with BD, to select out three examples of this multi-system approach. (Matsuo K, Walss-Bass CM et al., 2008) Inclusion of indices of anxiety in research designs, rather than simply a DSM-IV bipolar diagnosis, or a total mania or depression scale score, could strengthen the testing of hypotheses linking biological substrates of BD to clinical phenomena.

The strong evidence of interlink age of anxiety with bipolar disorders comes largely from studies of current axis I diagnoses, (Perugi G, Akiskal HS et al., 2001 Mantere O, Melartin TK et al., 2006) since the most commonly used rating scales for depression and mania provide no more than 2 anxiety items for any combination of depression and mania scales. The factor analyses in bipolar that have identified an anxiety factor have either employed a separate, nurse rated, observed rating scale with anxiety items, or the BISS, which provides coverage for observed and reported anxiety, somatic anxiety and fearfulness, which is infrequently addressed in other rating scales. (Swann, Janicak, Calabrese, Bowden, Dilsaver, Morris, Petty, and Davis, 2001) The benefits of such an approach were supported by a study which showed a direct relationship between severity of anxiety and delay in recovery from acute episodes in bipolar depression. (Feske U, Frank E et al., 2005) The potential benefits of scalar, rather than diagnostic strategies should extend to subsyndromal anxiety manifestations, which could provide indications of magnitude of relationship, rather than simply dichotomous test relationships.

Genetic contributions to pathophysiology of bipolar disorder

Given the high heritability of bipolar disorders, it is noteworthy that only a small number of genes or polymorphisms thereof have been reported consistently across studies. Although the heterogeneity contributed to by the current diagnostic schema, summarized above, is a contributory factor, evidence indicates that no single gene is likely to contribute more than a small proportion of the variance between bipolar and non-bipolar individuals. Individual genes have yielded odds ratios between 1.07 and 1.18. Positional gene odds ratios have been somewhat higher, with reports up to 1.8. In contrast, several environmental contributors to gene influences appear to have greater influence than the individual genes. In a thoughtful review, Kendler concludes that genetic factors have important, modest effects in bipolar disorder and schizophrenia. These effects are not likely to be mediated at the syndromal level, but rather are likely to contribute to basic biological and behavioral processes which characterize the disorders, and which also impact other psychiatric disorders and humans without psychiatric disorders. He suggests that investigators who turn to componential studies of domains of bipolar disorder, temperaments, or other endophenotypical characteristics may more likely identify genetic contributors to such components of the full disorder. (Kendler KS, 2005) Other thorough reviews of genetic factors in bipolar disorders emphasize additional perspectives, e.g., insights from and implications for non-human studies. (Alesci S, Rodak M, Ilias I, Zhou R, Manji HK 2006. The Genomics of Mood Disorders. Progress in Brain Research. 158:129–39)

Endophenotypes

Endophenotypes will often provide simpler, more homogeneous groupings of bipolar individuals with resulting benefits for testing of hypotheses. Behavioral endophenotypes are synonymous with domains. As suggested by Kendler above, such characterization can reveal latent variables underlying a scale or historical, syndromal phenotype. Endophenotypes are inherently complementary to syndromal classifications, particularly in that endophenotypes

as well as syndromes require some setting of thresholds of severity or functional impairment.

Although behavioral phenotypes are useful and avoid confounding by some variables required by current DSM-IV-TR criteria, other levels of endophenotypic characterization, either alone or in combination, can facilitate conduct of studies on aspects of the pathophysiology of bipolar disorder. These additional levels of characterization include physiological, genetic, brain structure or function based and treatment outcome based measures as well as combinations thereof.

Work from our group supports this strategy within brain substructure measures. Abnormalities have been reported for hippocampus, amygdala, and cingulate and prefrontal cortices in bipolar compared with healthy control subjects. Rather than simply examine bipolar-control differences in brain structures, we examined aspects of brain structure and function in patients with differing allelic structure of left and right anterior cingulate (ACC) gray matter. Volumes of the ACC of the BP patients were smaller in the Val/Met compared to the Val/Val subjects ($P=0.01$). Val/Met carriers had smaller anterior cingulate cortex grey matter volumes compared to the Val/Val carriers, with the difference greater in the bipolar patients than in healthy subjects. Furthermore, within both the bipolar and healthy groups, the Val/Met carriers had smaller dorso-lateral prefrontal cortex and smaller anterior cingulate cortex grey matter volumes compared to the Val/Val carriers. These results suggest that variation expression of the BDNF genotype may play a role in determining structural differences in these brain regions which are relevant to memory, mood regulation and cognitive function in bipolar disorders. (Matsuo K, Walss-Bass CM, Nery FG, Nicoletti M, Hatch JP, Frey BN, Monkul S, Zunta GB, Bowden C.L., and Escamilla MA, 2008) The results obtained with Val/Met BDNF polymorphism in relation to AC structure in bipolar patients confirm the results of neuropsychological studies associated with this polymorphism in bipolar patients, where Val/Met carriers had significantly worse results of working memory (Wisconsin Card Sorting) Test than Val/ Val carriers (The results obtained with Val/Met BDNF polymorphism in relation to AC structure in bipolar patients have confirmed the results of neuropsychological studies associated with this polymorphism in bipolar patients where Val/Met carriers had significantly worse results of working memory (Wisconsin Card Sorting) Test than Val/ Val carriers (Rybakowski et al., Bipolar Disorders, 2003; Molecular Psychiatry 2006). The results obtained with Val/Met BDNF polymorphism in relation to AC structure in bipolar patients have confirmed the results of neuropsychological studies associated with this polymorphism in bipolar patients where Val/Met carriers had significantly worse results of working memory (Wisconsin Card Sorting) Test than Val/ Val carriers (Rybakowski JK, Borkowska A, Czerski PM, Skibinska M., Hauser J, 2006. Polymorphism of the Brain-Derived Neurotrophic Factor Gene and Performance on a Cognitive Prefrontal Test in Bipolar Patients. Journal Article. Research Support, Non-U.S. Gov't; Bipolar Disorders 2003 5(6):468–72, Rybakowski JK, Borkowska A, Skibinska M, Hauser J, Illness-Specific Association of Val66met BDNF Polymorphism with Performance on Wisconsin Card Sorting Test in Bipolar Mood Disorder Controlled Clinical Trial. Letter, Molecular Psychiatry 2006, 11(2):122–4 Neurocognitive deficits in bipolar disorder include impaired sustained concentration, executive functioning, episodic memory, and visuospatial skills. (Glahn DC, Bearden CE, Cakir S, et al (2006b): Differential Working Memory Impairment in Bipolar Disorder and Schizophrenia: Effects of Lifetime History of Psychosis. Bipolar Disorder 8:117–23. Bipolar patients have deficits in verbal memory and frontal executive function in comparisons to health subjects that are independent of clinical status (manic, hypomanic, depressed or euthymic for at least 6 months).(Martinez-Aran A, Vieta E, Reinares M, Colom F, Torrent C, Sanchez-Moreno J, Benabarre A, Goikolea JM, Comes, M, Salamero M. Cognitive Function Across Manic or Hypomanic, Depressed, and Euthymic States in Bipolar Disorder Am J Psychiat.

2004;161:262–270) Such deficits may explain in part the impairments observed in bipolar individuals in routine function, even during symptomatic remission.

Neurocognitive status, particularly memory, predicts employment and psychosocial functioning. (Osugi JJ, Dickerson FB, Boronow JJ, Stallings CR, et al.) Association Between Cognitive Functioning and Employment Status of Persons with Bipolar Disorder. *Psychiatr Serv.* 2004;55:54–58; (Atre-Vaidya N, Taylor MA, Seidenberg M, et al.) Cognitive Deficits, Psychopathology, and Psychosocial Functioning in Bipolar Mood Disorder. *Neuropsychiatry Neuropsychol Behav Neurol.* 1998;11:120–126) The persistence of such neurocognitive suggests that they may constitute an endophenotype for certain diagnostic and therapeutic purposes.

These studies provide examples of endophenotypic characterization, e.g., the risk haplotype of ValMet in the BDNF gene and working memory rather than solely a diagnostic group comparison to more powerfully discriminate both regionally specific differences in brain structure and to predict functional status from working memory in persons with bipolar disorders.

An example of a behavioral endophenotype of bipolar disorder is impulsivity, for which there is evidence of elevated trait scores compared to healthy controls both in patients with syndromal episodes and in recovered status. (Janowsky, Morte et al., 1999) Suicidal ideation and fatal attempts are significantly higher in bipolar both in depression and other syndromal states than in the general population (Rihmer A and Kiss K, 2002) Both suicidal ideation and suicidal behavior were significantly positively correlated with impulsivity (Swann, Secunda et al., 1991)

In one of the largest factor analytic studies of behavioral domains characterizing bipolar patients during manic episodes, Swann et al found impulsivity to be only consistently present set of behavior in 4 manic subtypes, pure, depressive, irritable and psychotic. (Swann, Janicak, Calabrese, Bowden, Dilsaver, Morris, Petty, and Davis, 2001) Both divalproex and lithium are robustly efficacious in reducing impulsivity in mania. (Swann AC, Bowden CL et al., 2002) Additionally, divalproex was significantly more effective in alleviating symptoms in patients with borderline personality disorders who had high scores at baseline on impulsivity (Simeon D, Baker B et al., 2007).

We have recently shown that trait impulsivity in bipolars is present in manic, euthymic and depressed states. (Peluso M, Hatch JP et al., 2007) Additionally, the impulsivity scores were significantly higher than in age and sex matched healthy controls and unipolar depressed subjects. This observation is important in establishing that impulsivity is largely independent of mood state in bipolar individual, consistent with the earlier work of. (Janowsky, Morte, Hong, and Howe, 1999); Impulsivity therefore could represent a predisposing risk factor contributory to development of bipolar disorder and/or a behavioral manifestation of a biological abnormality which predisposes toward bipolarity.

Studies of relatively small samples provide some evidence that genetic variations in COMT, which is involved in the metabolism of dopamine and norepinephrine, could account in part for neurocognitive and/or impulsive abnormalities observed in bipolar disorders. (Burdick KE, Funke B, Goldberg JF, Bates JA, Jaeger J, Kucherlapati R, Malhotra AK)

COMT genotype increases risk for bipolar I disorder and influences neurocognitive performance. (Bipolar Disorders 2007;9:370–376) Similarly, genome wide scans also suggest that a subunit of the N-methyl-D-aspartate (NMDA) receptor is over transmitted to affected subjects with a bipolar II phenotype. (Nwulia EA, Miao K, Zandi PP, MacKinnon DF, DePaulo JR, McGinnis MG. Genome-wide Scan of Bipolar II Disorder. *Bipolar Disord*

2007;9:580–588, (Mundo E, Tharmalingham S, Neves-Pereira M et al.) Evidence that the N-methyl-D-aspartate subunit 1 receptor gene (GRIN1) confers susceptibility to bipolar disorder. (Mol Psychiatry 2003;8:241–245) Lithium, valproate and lamotrigine each affect NMDA receptors and/or glutamatergic activity. A caveat in assembling evidence from the disparate studies that provide evidence toward genetic- brain system - behavioral and drug effect mechanisms is that no single study has had sufficient power, nor combines all elements of interest to achieve an integrated conclusion. Therefore the possibility of inaccurate inferences is high.

We crafted items of several aspects of impulsivity for the BISS, including items for affective lability, distractibility, impulsivity and risky behavior. (Bowden C, Singh V, Thompson P, Gonzalez J, Katz M, Dahl M, Prihoda T, and Chang X, 2007) Each loaded on a primary mania factor, and most discriminated euphoric manic from mixed manic and depressed bipolar subjects. (Thompson PM, Gonzalez JM, Singh V, Schoolfield JV, and Bowden C.L., 2007) Janowsky has studied aspects of impulsivity in comparison study between bipolar and unipolar depressed patients. Impulsivity, novelty seeking, distractibility, disorderliness and extraversion were all significantly higher in bipolar than unipolar subjects. (Janowsky, Morte, Hong, and Howe, 1999)

Focusing on domains can have tangential benefits in treatment and treatment developments in bipolar disorders. Once bipolar patients have one domain, then two functioning well, they and their doctors can better maintain improved status. Treatment focus can then shift to any remaining unstable domains. Improvement in some behavioral domains can only unfold once foundation stability is attained, e.g. demoralization about job securing capability may be effectively addressed once behavioral disturbances, including impulsivity, are brought under control. Such a stepwise approach can reduce pressures on clinicians to make random changes in the treatment plan when patients overreact to small destabilizers and behavioral problems with requests for, or self initiated changes in a regimen. This concept allows the patient to address destabilizing elements with confidence that the entire system will not collapse.

Implications for new drug development and study designs for clinical testing

The scientific unveiling of lithium, valproate and lamotrigine as specifically efficacious treatments for domains of bipolar disorder is instructive in the effective application of inductive logic that has largely been absent in most other drug development efforts for bipolar disorder at the turn of the 21st century. For each of these fundamental mood stabilizers, astute observations by expert psychiatrists recognized fundamental illness features which appeared to be benefited by one of the drugs. Such observations led to hypotheses tied to a single drug tested first in open but meticulous observational studies, followed by refinements of the hypotheses for purposes of testing in randomized controlled trials. Additionally, the studies yielded critical information on the fundamental behavioral domains of bipolar disorder and the impact of the 3 drugs on these domains. Thereby, a close linkage between phenomenological, pharmacodynamic and efficacy based data was forged for each of these still first line treatments.

The overlapping effects of lithium and valproate on signal transducing systems, e.g, ERK, PKC and phosphatidyl inositol, despite differences in their first step actions (distinct from other drugs with utility in bipolar disorders) also serves to provide a road map forward for better understanding of pathophysiology and development of novel treatments for bipolar disorders. (PMID: 12917364) Lithium also has inhibitory effects on glycogen synthase kinase-3, suggesting GSK-3 as a potential novel target for molecules with mood stabilizing

properties. (Gould TD, Chen G, Manji HK. In Vivo Evidence in the Brain for Lithium Inhibition of Glycogen Synthase Kinase-3. *Neuropsychopharmacology*. 2003) Tamoxifen, a PKC inhibitor, exhibited antimanic properties in a small randomized clinical trial. (Zarate CA Jr. Singh JB. Carlson PJ. Quiroz J. Jolkovsky L. Luckenbaugh DA. Manji HK). Efficacy of a Protein Kinase C Inhibitor (Tamoxifen) in the Treatment of Acute Mania: A Pilot Study. *Journal Article. Randomized Controlled Trial. Research Support, N.I.H., Intramural, Bipolar Disorders* 2007 9(6):561–70, Zarate, C AM J Psychiat) The use dependent inhibition of sodium channels differentiates lamotrigine from other drugs with sodium channel effects, thus potentially suggesting another target and mechanism to base drug development efforts. These are illustrative of studies of the past decade that move beyond drugs with receptor blockade or reuptake effects on dopamine, serotonin and norepinephrine, and which have dominated drug development efforts in an unfortunately repetitive fashion for over four decades.

Conclusion

The inherent complexity of bipolar disorders at the levels of symptoms, treatment response and underlying biological processes which are disturbed in the disorder has impeded progress on some fundamental aspects of this important, severe mental disorder. Investigators who develop and test hypotheses around historical syndromes, and utilize global measures to assess the benefits of interventions, or similarly utilize crude measures of biological systems or, global measures of change in symptomatology will have difficulty in accomplishing major innovations in treatment, or revealing the pathophysiology of the disorder. In contrast, there is evidence that investigators who take a more componential approach for classification of subjects, and who formulate hypotheses and measurements which involve endophenotypes and evidence based behavioral domains are more likely to advance fundamental knowledge of underlying psychobiology and contribute to development of revolutionary treatments for this common, severe disorder.

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