Is Bipolar II a Unique Disorder?

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The authors investigated differences between 27 outpatients who met RCD "definite" criteria for bipolar II disorder and 188 unipolar patients on several dimensions: clinical characteristics, response to acute treatment, personality profiles after recovery, and family history. The bipolar II group was found to have a higher morbid risk for depression among fathers, a greater incidence of past suicidal attempts, and a greater frequency of psychomotor retardation. A high degree of selectivity for protocol inclusion may account for the similarity seen between the bipolar II group and the unipolars on the other variables examined. The present findings suggest these two groups can be successfully combined in the treatment of recurrent depressive episodes.

BIPOLAR II ILLNESS has become a "step-child" in the affective disorder nosology. In DSM-III-R it is included among the hodge-podge of not-quite-manic-depressive presentations labelled, "Bipolar Disorder Not Otherwise Specified," reflecting the confusion among clinicians regarding those patients who present with a history of major depression and hypomania.[1]

Nosologic controversy also exists among researchers in affective disorders regarding the nature of bipolar II illness: is it more similar to unipolar depression or to bipolar I? Or, does it represent a unique disorder? While the specific criteria for the diagnostic classification of bipolar II disorder (or its equivalent by another name) may vary from one investigator to the next, this category is generally understood to include those patients whose major depression alternates with hypomanic rather than manic episodes. In an effort to determine whether such a group should be separated out from populations of unipolar and bipolar I subjects for purposes of analysis, researchers have compared the three groups in a variety of areas: family history (morbid risk), biological markers, treatment outcome, and historical and symptom characteristics. The published data from a variety of investigators suggest that bipolar II disorder is closer to bipolar I than to unipolar depressive disorder[2-6]; however, enough distinguishing features of the bipolar II group have been found to warrant recommendations from these same investigators that the separate bipolar II subclassification be maintained. Continued concern that the inclusion of bipolar II subjects would increase sample heterogeneity stems from those findings which significantly differentiate bipolar II as a unique subtype.

The present study was designed to investigate the degree to which a population of 27 outpatients who met Research Diagnostic Criteria (RDC) "definite" criteria for bipolar II disorder differed from a group of 188 unipolar outpatients on several dimensions: clinical characteristics, personality profiles after recovery, response to acute treatment, and family history. We were particularly interested in the

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differences between these two groups with regard to the implications they might have for differential treatment of their recurrent depressive episodes.

METHODS

Subjects

The subjects for this investigation were participants in the Maintenance Therapies in Recurrent Depression protocol, which required that all patients (ages 21 to 65) present in their third or greater episode of definite major depressive disorder (according to RDC[7]), with the immediately preceding episode occurring no more than 2½ years prior to the onset of the index episode. All previous depressive episodes must have required psychiatric treatment or resulted in significant functional impairment, with a minimum of 20 weeks remission between the previous episode and the index episode. Patients with a recent history of a major nonaffective psychiatric disorder were excluded, as were those individuals who had significant medical histories or a history of drug or alcohol abuse. Patients meeting criteria for personality disorders were also excluded from the study. The 27 bipolar II patients were isolated using the RDC completed by independent raters at initial screening and, if possible, again when the patients were recovered from their index episode. For those patients who achieved a stable remission, all previous affective episodes were documented through the use of the Lifetime History of Affective Disorders (LHAD) interview, developed specifically for this study. Patients were selected for the bipolar II group if they received a definite RDC lifetime diagnosis of bipolar II disorder at the second assessment, and their detailed LHAD accounts of past affective illness confirmed such a diagnosis (N = 21). There were also six patients included in the bipolar II group based on a definite RDC lifetime diagnosis of bipolar II disorder at baseline (no data from the second assessment were available). Since none of the patients was actually presenting with hypomania when admitted to our study, rigorous standards were employed in determining that the bipolar II diagnosis was confirmed with a high degree of certainty. Patients who were categorized as "probable" for past bipolar II disorder at either or both assessment times, or whose LHAD information did not unequivocally support a bipolar II diagnosis, were put into a third group which was excluded from the present analyses. The group of 188 unipolar patients, therefore, is free of any possible contamination by patients with hypomania.

Measures

Patients were evaluated at screening with a number of instruments, including the Schedule for Affective Disorders and Schizophrenia (SADS).[8] The RDC assessments were also conducted at this time. All patients were then given physical and neurological examinations and kept drug-free for 2 weeks before the initial psychiatric, EEG sleep, and neuroendocrine evaluations which preceded entry into the study. Patients subsequently underwent a comprehensive independent assessment to ascertain whether they met severity criteria for the investigation, including a Hamilton Rating Scale for Depression (HRSD)[9] score of 15 or greater (single rater on the 17-item version), and a score of seven or greater on the Raskin Severity of Depression Scale.[10]

Following the initial evaluation, all patients received the same acute treatment regimen which consisted of pharmacotherapy (imipramine, 150 to 300 mg) and Interpersonal Psychotherapy (IPT).[11] Patients were seen weekly for the first 12 weeks, and then biweekly for the next 8 weeks, and then monthly until they had completed a continuation treatment period of 20 weeks during which their drug dose did not change and their rating scale scores remained stable and consistent with a clinical remission (HRSD $\leq$7, Raskin $\leq$5). Those patients who completed this 20-week period were then entered into the experimental phase of the study in which five maintenance treatments are being examined: psychotherapy alone, psychotherapy with active medication, psychotherapy with placebo, clinic visit with active medication, or clinic visit with placebo.

At the end of the first 16 weeks of acute treatment, patients were classified as "normal responders," "slow responders," "partial responders," or "treatment terminators." Response type was determined using a computer algorithm which took into account the patient's Hamilton score at 8, 12, and 16 weeks of treatment. "Normal responders" were characterized by a rapid and sustained recovery completed by 8 weeks, while "slow responders" either took longer to become asymptomatic or showed a more variable course of recovery. "Partial responders" completed the 16 weeks, but failed to meet the relatively stringent criteria for recovery. "Treatment terminators" were individuals who were terminated from the

study prior to 16 weeks, generally because of intolerable side effects or failure to show any response to the combined pharmacotherapy/psychotherapy treatment regimen.

Personality was assessed at the end of continuation treatment, at which time both Hamilton and Raskin scores and imipramine dose were required to have been stable for 20 weeks. Thus, the personality data were collected only on the subsample who completed the 20-week remission period and were assigned to maintenance treatment. The Hirschfeld-Klerman Personality Battery[12] is a 436-item self-report inventory which is comprised of 17 scales drawn from five preexisting personality inventories. The Personality Assessment Form (PAF),[13] is a structured interview designed to assess personality on the basis of the DSM-III personality disorder categories. The interview was constructed for use in the National Institute of Mental Health (NIMH) Treatment of Depression Collaborative Research Program and was further refined for use in the present protocol. The PAF was administered, also at the end of continuation treatment, by the subject's primary clinician who asked a series of 15 to 25 standardized probe questions for each DSM-III category and then, using those responses and their own experience with the patient, rated the extent to which the subject conformed to the description of each DSM-III personality disorder.

When their index episode had remitted, patients served as informants for the collection of family history data. The family history (FH) method[14] was used with a slight modification to the scoring procedure (our clinicians assigned "absent," "probable," or "definite" status for each diagnostic category instead of numbering them in order of occurrence). A "probable" or "definite" diagnosis of Major Depression or Recurrent Unipolar was considered a positive history of non-bipolar depression. Likewise, probable and definite diagnoses were considered together when the rates of alcoholism and bipolar disorder were determined. One or more discrete suicidal attempts constituted a history of suicidal behavior in relatives.

Patients were questioned about their own past suicidal behavior as part of the SADS administered at screening and then again when well. Discrete suicidal gestures made during the index episode or during previous episodes (as reported during a SADS assessment) constituted a positive history of suicidal behavior in patients.

Data Analysis

Variables describing clinical/historical characteristics were analyzed with t-tests or χ^2 tests. While only patients who received "definite" diagnoses of bipolar II disorder were so classified, "probable" diagnoses were collapsed with "definite" diagnoses in the analysis of other RDC subtypes. Personality data was analyzed in the following way: the PAF diagnostic categories were individually examined with χ^2 tests, where a score of 1 through 3 was considered "absent" and 4 through 6 as "present"; differences between the two groups' mean scores on the 17 scales of the Hirschfeld-Klerman inventory were tested with individual t-tests.

Chi-square analyses were run on the outcome data (response to acute treatment), once with the treatment terminators included and a second time with only those patients who completed 16 weeks of treatment. Strömgren age correction procedures[15] were applied to the family history data with the age of risk function provided by a distribution of ages at onset in our depressed probands. The same age at onset distribution was used to assign "weights" to the data on bipolar disorder, alcoholism, and suicidal behavior. Chi-square tests were run with records excluded if their completeness of information was judged to be "poor" or "essentially none" (variable 250 on the FH-RDC data sheet equal to 4 or 5).

RESULTS

As Table 1 indicates, the two groups appear remarkably similar in both clinical and historical characteristics including age at screening, age at onset, duration of index episode, number of previous episodes, and total Hamilton score at screening. The bipolar II group contained a significantly higher percentage of individuals meeting the RDC probable or definite retarded subtype ($P < 0.001$), but the rest of the subtypes did not differentiate between bipolar II and unipolar patients. The bipolar II group was also characterized by a greater percentage of patients with a history of suicidal behavior ($P < 0.01$). The proportions falling into each of the four acute treatment response type categories did not differ statistically between the two

Table 1. Clinical Characteristics of the Bipolar II and Unipolar Groups

	Bipolar II (N = 27)	Unipolar (N = 188)
Sex		
Female	23 (85%)	146 (78%)
Male	4 (15%)	42 (22%)
Age at Screening		
Mean (SD)	38.9 (9.2)	39.1 (10.6)
Age at Onset First Major Depressive Episode		
Mean (SD)	25.0 (11.3)	26.8 (9.9)
Duration Index Depressive Episode		
Mean (SD)	23.3 (19.5)	23.1 (17.1)
Number Previous Episodes of Major Depression		
Mean (SD)	6.1 (4.1)	6.3 (6.4)
Hamilton at Screening (17-Item)		
Mean (SD)	23.2 (4.2)	21.8 (4.5)
History of Discrete Suicidal Gestures*	13 (48%)	45 (24%)
RDC Subtypes:		
Primary		
Absent	3 (12%)	14 (7%)
Probable	0 (0%)	1 (1%)
Definite	23 (88%)	173 (93%)
Psychotic		
Absent	25 (96%)	185 (99%)
Probable	0 (0%)	1 (1%)
Definite	1 (4%)	1 (1%)
Incapacitating		
Absent	22 (85%)	174 (94%)
Probable	4 (15%)	1 (0%)
Definite	0 (0%)	11 (6%)
Endogenous		
Absent	1 (4%)	19 (10%)
Probable	6 (23%)	63 (34%)
Definite	19 (73%)	104 (56%)
Agitated		
Absent	22 (85%)	163 (87%)
Probable	1 (4%)	10 (5%)
Definite	3 (12%)	14 (7%)
Retarded†		
Absent	15 (58%)	159 (85%)
Probable	4 (15%)	13 (7%)
Definite	7 (27%)	14 (8%)
Response to Acute Treatment (Imipramine and Interpersonal Psychotherapy)		
Normal	11 (41%)	56 (30%)
Slow	7 (26%)	50 (27%)
Partial	6 (22%)	51 (27%)
Terminated	3 (11%)	27 (14%)

*$\chi^2 = 7.0$, $P < .01$, $df = 1$.
†Absent *v* Probable + Definite, $\chi^2 = 12.0$, $P < .001$, $df = 1$.

groups, nor were any differences observed when only the three groups of completers were analyzed.

The recovered patients with a bipolar II disorder appeared to have personality profiles very similar to those of the recovered unipolar patients as reflected by an absence of statistically significant differences between them on any of the 17 scales of the Hirschfeld-Klerman instrument or on the 12 personality pathology categories of the PAF (Table 2).

Table 2. Personality Profiles of Recovered Bipolar II Versus Unipolar Patients

	Bipolar II (N = 16)	Unipolar (N = 101)
	Mean (SD)	
Hirschfeld-Klerman Personality Scales	(N = 16)	(N = 101)
General Activity	15.4 (7.0)	14.6 (5.7)
Restraint	19.1 (4.5)	19.7 (4.2)
Ascendance	14.3 (6.4)	14.0 (6.3)
Sociability	17.7 (9.4)	16.7 (7.5)
Objectivity	18.3 (6.9)	18.4 (4.9)
Thoughtfulness	17.8 (4.9)	18.3 (4.8)
Emotional Reliance	42.9 (13.9)	41.3 (10.3)
Lack of Self Confidence	31.9 (10.4)	31.9 (8.8)
Assertion of Autonomy	24.5 (6.6)	27.1 (6.8)
Obsessionality	11.6 (3.2)	11.5 (3.8)
Hysterical Pattern	7.9 (3.3)	8.1 (3.5)
Orality	5.4 (4.4)	5.6 (4.1)
Neuroticism	22.8 (14.1)	21.6 (12.4)
Extraversion	24.2 (11.5)	22.9 (10.5)
Ego Control	16.3 (4.6)	18.1 (4.5)
Ego Resiliency	20.6 (7.5)	22.9 (5.7)
	% meeting definite criteria	
Personality Assessment Form (PAF)	(N = 14)	(N = 86)
Paranoid	7.1%	3.5%
Schizoid	0.0%	5.8%
Schizotypal	7.1%	3.5%
Histrionic	7.1%	7.0%
Narcissistic	0.0%	3.5%
Antisocial	7.1%	2.3%
Borderline	7.1%	2.3%
Avoidant	35.7%	27.9%
Dependent	28.6%	14.0%
Compulsive	14.3%	18.6%
Passive Aggressive	7.1%	9.3%
Dysthymia	7.1%	12.8%

Table 3 shows the morbid risk of non-bipolar depression, bipolar disorder, alcoholism, and suicidal behavior in the first-degree relatives (excluding offspring) of 22 bipolar II *v* 142 unipolar probands. The bipolar II probands had significantly more fathers with a diagnosis of non-bipolar depression than did the unipolar group ($P < .02$). However, when all first-degree relatives were combined, the morbid risk for depression was not different between the two groups. The morbid risk percentages for bipolar disorder, alcoholism, and suicidal behavior were similar for the two groups across all categories of relatives.

DISCUSSION

The present study set out to investigate possible differences between highly selected groups of bipolar II subjects and unipolar depressed subjects who were admitted to our protocol for maintenance treatments in recurrent depression. A variety of dimensions were explored including clinical and historical characteristics, response to 16 weeks of combined (imipramine and Interpersonal Psychotherapy) acute treatment, personality profiles when recovered, and family history.

Our results were similar to previous findings[16] inasmuch as a higher proportion of the bipolar II patients reported a past history of discrete suicide attempts. In

Table 3. Morbid Risk of Various Disorders in First-Degree Relatives of Bipolar II Versus Unipolar Probands

Relative	Bipolar II	Unipolar
Mothers		
Number of Records	21	134
Number at Risk	20.905	132.382
Depression (Morbid Risk)	6 (28.7%)	42 (31.7%)
Bipolar (Morbid Risk)	0 (0.0%)	0 (0.0%)
Alcoholism (Morbid Risk)	2 (9.6%)	3 (2.3%)
Suicidal (Morbid Risk)	0 (0.0%)	1 (0.8%)
Fathers		
Number of Records	20	131
Number at Risk	19.591	129.832
Depression (Morbid Risk)*	7 (35.7%)	18 (13.9%)
Bipolar (Morbid Risk)	1 (5.1%)	1 (0.8%)
Alcoholism (Morbid Risk)	6 (30.6%)	43 (33.1%)
Suicidal (Morbid Risk)	0 (0.0%)	1 (0.8%)
Brothers		
Number of Records	31	191
Number at Risk	26.015	145.373
Depression (Morbid Risk)	2 (7.7%)	19 (13.1%)
Bipolar (Morbid Risk)	0 (0.0%)	1 (0.7%)
Alcoholism (Morbid Risk)	6 (23.1%)	29 (19.9%)
Suicidal (Morbid Risk)	0 (0.0%)	2 (1.4%)
Sisters		
Number of Records	27	207
Number at Risk	23.595	165.703
Depression (Morbid Risk)	4 (17.0%)	41 (24.7%)
Bipolar (Morbid Risk)	0 (0.0%)	3 (1.8%)
Alcoholism (Morbid Risk)	0 (0.0%)	15 (9.1%)
Suicidal (Morbid Risk)	2 (8.5%)	11 (6.6%)
Parents and Siblings Combined		
Number of Records	99	663
Number at Risk	90.106	573.290
Depression (Morbid Risk)	19 (21.1%)	120 (20.9%)
Bipolar (Morbid Risk)	1 (1.1%)	5 (0.9%)
Alcoholism (Morbid Risk)	14 (15.5%)	90 (15.7%)
Suicidal (Morbid Risk)	2 (2.2%)	15 (2.6%)

*$\chi^2 = 5.6$, $df = 1$, $P = .018$.

reviewing the literature, Dunner[4] noted that a high rate of suicide attempts was the "main clinical feature" distinguishing bipolar II from other affective disorders.

A new finding in the present study was the greater likelihood for bipolar II patients to receive an RDC retarded subtype diagnosis. Psychomotor retardation, a well-established characteristic of depressed bipolar I patients, seems an unlikely variable to distinguish our bipolar II patients considering the remarkable absence of differences between the two groups in almost every area we studied. While this finding suggests that our bipolar II group more closely resembles a typical bipolar I group rather than a group of unipolar depressives with regard to psychomotor changes, such a conclusion may be misleading. Perhaps our highly selective process of removing all patients with any hint of past hypomanic symptoms from the unipolar group resulted in an extremely pure sample of endogenously depressed unipolars. In other words, it is likely that the difference we observe reflects an unusually low rate of retardation among our unipolars, rather than an unusually high rate of retardation among our bipolar II patients.

One important aspect of the present investigation is its failure to replicate differences between unipolar and bipolar II illness which others have reported. A population of bipolar II patients studied by Endicott et al.[5] were distinguished from unipolars by lower average age at onset of affective symptoms and earlier first outpatient treatment. Angst[6] compared the two subtypes and found bipolar II patients had an earlier age at onset, longer length of illness and shorter cycles, greater number of episodes, lower rate of recovery, and more frequent chronic outcome. Yet, the present study did not find any of these differences when the same or comparable variables describing clinical course were examined.

The apparent uniqueness of this population of bipolar II patients, relative to others which have been studied, calls for further explanation. One factor which may contribute to the apparent homogenity of our two groups is a high number of previous depressive episodes. With an average of greater than six previous major depressive episodes for the bipolar II group, it is unlikely that very many, if any, of these patients will switch eventually to bipolar I disorder. By requiring multiple past depressive episodes, our protocol inclusion criteria may have systematically eliminated those bipolar II subjects whose illness represented a mild form of bipolar I disorder which would eventually have become manifest as full-blown mania. Such cases not removed from other populations might be responsible for making bipolar II subjects appear more like bipolar I subjects, and more dissimilar from unipolars.

Stringent protocol criteria may also account for the absence of differences between our two groups in recovered personality data.[17] Coryell et al[18] found bipolar II subjects more likely to exhibit non-affective psychopathology, particularly schizotypal features. Liebowitz et al.[19] noted higher extraversion scores and lower neuroticism scores in bipolar IIs than in unipolars, and Russet et al also found bipolar II patients to demonstrate borderline behaviors not seen in unipolars.[20] By excluding subjects with a recent history of a major non-affective psychiatric disorder or borderline, as well as those with evidence of a history of primary drug or alcohol abuse, we were able to examine a unique subset of patients whose affective disorders were not confounded by non-affective psychopathology. Given these circumstances, we expected the present analysis to show an absence of borderline behaviors across both groups. This was indeed the case.

Family history analyses yielded overall morbid risks for depression and bipolar disorder comparable to those found by other researchers.[3,21] However, we are not aware that fathers of bipolar II probands have previously been noted as the category of first-degree relatives most at risk for depression. This rather curious finding should be replicated with larger samples before any conclusions can be drawn.

In keeping with the previously published results of Gershon et al[3] and Dunner et al,[22] proband diagnosis in our population (bipolar II or unipolar) did not differentiate the morbid risk for depression or bipolar disorder in all relatives combined. Early studies by Dunner et al.[23] showed an increased rate of alcoholism and suicide among relatives of bipolar II patients, but the present investigation found similar overall morbid risks for alcoholism and suicidal behavior across both groups of probands. This may be due to the exclusion of alcoholism in our probands by protocol entry criteria. However, Endicott et al.[5] found a significantly greater percentage of female bipolar II probands met criteria for alcoholism than did female recurrent unipolar probands, and there was no difference in the rate of alcoholism among female (or male) relatives in that study.

The main clinical implication which arises from this work is that bipolar II patients, if carefully chosen, can be successfully combined with unipolars in the treatment of recurrent depressive episodes. Coryell et al.[24] found that cycling during index episodes had no apparent prognostic significance for patients with bipolar II illness. Our data show equivalent responses to an acute treatment regimen for both groups. Furthermore, the bipolar II individuals were not more likely to develop hypomania while taking tricyclic antidepressant medication.[25] In sum, the few differences which do emerge (higher morbid risk for depression in fathers of bipolar II probands, greater incidence of past suicidal attempts, and greater frequency of psychomotor retardation) in this highly selected population do not appear to affect the treatment of depression in any differential manner.

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