

# Delusional Depression and Bipolar Spectrum: Evidence for a Possible Association from a Family Study of Children

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Recent pedigree studies demonstrating a possible linkage of bipolar disorder to markers on different chromosomes have included family members with major depression and cyclothymia as affected. There is general agreement that cyclothymia is related to bipolar disorder and that major depression is heterogenous. It is unclear which subtype of major depression is related to bipolar disorder. Data suggesting a relationship between delusional subtype of major depression and bipolar spectrum are presented. The data derive from a direct-interview study of 220 offspring (ages 6 to 23 years) of probands with either delusional or nondelusional major depression and normal controls. The

children of delusional as contrasted with nondelusional probands had nearly a threefold increase in cyclothymia, were more often described by health professionals as hyperactive, and had increased school and social impairments. These findings in children replicate earlier findings in adults on the possible relationship between delusional depression and bipolar disorder and its spectrum. The findings must be considered tentative, however, because of the small sample of children in the subgroups of interest. [*Neuropsychopharmacology* 1:257-264, 1988]

**KEY WORDS:** *Depression; Bipolar affective disorders; Psychotic psychogenetics; Cyclothymic disorders; Pedigree*

Recent pedigree studies demonstrating a possible linkage of bipolar disorder to markers on different chromosomes, although not conclusive or consistent, have received considerable attention. These studies focus attention on the specification of the phenotype.

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All of the studies have included as affected family members with cyclothymia or with major depression. Although there is evidence that cyclothymia is part of the bipolar spectrum, there is general agreement that major depression is heterogeneous. It is unclear which subtype, if any, of major depression may be related to bipolar disorder.

Delusional depression appears to be an important subtype of major depression. Whether it represents a distinct subtype (Leckman et al. 1984; Coryell et al. 1986; see Thase et al. 1986 for review) or a severity variant of major depression has not been resolved (Kocsis et al. 1986; Lykouras et al. 1986; Frangos et al. 1983).

There is evidence that delusional major depression may be related to bipolar disorder. This possible link has been suggested by previous family studies of adults (Coryell et al. 1985; Weissman et al. 1984; Kendler and Hays 1983; Strober, personal communication, 1986) and by clinical (Coryell et al. 1984b;

Guze et al. 1975; Andreasen et al. 1986; Garvey et al. 1982), follow-up (Coryell et al. 1984a; Strober and Carlson 1982; Akiskal et al. 1983), and treatment studies (Price et al. 1983; Pai et al. 1986; Weaver 1983; de Montigny et al. 1983; Heninger et al. 1983).

Data from our family study of the adult relatives of probands with various subtypes of major depression compared to the relatives of normal controls provided preliminary evidence for a link between delusional depression and bipolar disorder (Weissman et al. 1984). We found that the relatives of delusionally depressed probands were significantly more likely to have bipolar than were the relatives of either depressed probands without delusional features or normal controls. The previous study included only adult relatives. This article presents additional evidence for a possible relationship between delusional depression and spectrum of bipolar disorder, using data from a direct-interview study of the offspring (ages 6 to 23) of these affectively ill probands.

## METHOD

### Probands

The proband parents were drawn from the family study of major depression, which included 215 probands, 133 with a history of treated major depression and 82 normal (never psychiatrically ill) controls drawn from a community survey. (See Weissman et al. 1982 for complete methodology.) Probands were white and were group matched by age and sex. Diagnostic data on probands were obtained through direct SADS-L interviews, multiple relatives, and clinical records. The criteria for major depression were modified to be more stringent than the RDC so that 4 weeks of symptoms and evidence of impairment in major social role were required. The delusional subtype was based on the SADS-L interview in which symptoms associated with the most severe episode were recorded. A proband who met these criteria during any episode was characterized as delusionally depressed. Evidence for delusions of guilt, poverty, or punishment or for somatic delusions was required. The delusions were mood congruent. This definition is comparable to both the RDC and DSM-III criteria for psychotic depression. Probands who had any evidence of bipolar I or II or cyclothymia current or in the past, by direct interview, history from informant, or medical records were excluded from the study.

Only probands with offspring ages 6 to 23 at the time of the current study were included in these analyses. Of 104 eligible probands, 91 (87%), with 220 offspring, agreed to participate. Three probands

in the normal group who had developed a major depression since their participation in the earlier study were excluded from the normal group and were included in the depressed proband group. The final sample included 32 normal probands who had 83 children, 37 probands with nondelusional major depression who had 91 children, and 22 probands with delusional major depression who had 46 children.

### Assessment

The diagnostic assessment of the children was made with the Schedule for Affective Disorders and Schizophrenia for School-Aged Children, Epidemiologic Version (K-SADS-E) (Puig-Antich et al. 1980; Orvaschel et al. 1982; Gammon et al. 1983). The K-SADS-E is the core of a comprehensive interview that was administered to a parent about the child and the child about himself or herself. Included were assessments of overall psychopathology with the Global Assessment Scale (GAS) (Shaffer et al. 1983) of medical, neuropsychiatric, and treatment history and of social functioning using the Social Adjustment Inventory of Children and Adolescents (SAICA) (John et al. 1987). Estimates of the child's IQ were derived from the Peabody Picture Vocabulary Test (PPVT), Form M (Dunn and Dunn 1981), and the WISC-R Vocabulary and Block Design Subscales (Wechsler 1974).

Direct interviews were obtained from 83% of the eligible children and from a parent for 97% of the children. In all but six cases the parent interviewed was the biologic mother. Interviewers were M.D., Ph.D., and masters-level mental health professionals with a minimum of 4 years' experience in child assessment and/or treatment. The interviewer of the child and of the mother about the child was blind to the diagnostic status of the child's parents. Details of the interviewer training and monitoring are described elsewhere (Weissman et al. 1987).

### Child Psychiatrist Best Estimate Diagnosis

As in the adult sample, a best-estimate diagnostic procedure was employed. A child psychiatrist (G.D.G.) and a psychologist, who had not been involved in the interviewing process, reviewed all sources of information and independently assigned a diagnosis. Discrepancies in diagnoses by the independent evaluators were resolved by arriving at a consensus. The initial level of agreement between the two best estimators on child diagnosis was 83%. Further testing of the reliability of the child's diagnosis by a second psychiatrist is described elsewhere (Weissman et al. 1987).

**RESULTS**

**Age and Sex of Children**

There were no significant age and sex differences in the children by proband group. There was an approximately equal number of boys and girls. The majority of children were aged 12 to 23, with a mean age of 17 years.

**Sociodemographic Characteristics Among the Probands**

The probands were derived from demographically comparable groups. There were no statistically significant differences in probands by mean age (46 years), sex (57% were females), marital status (77% currently married), number of marriages (81% had only one marriage), religion (72% were Catholic), or social class.

**Clinical Characteristics among Probands**

There were no statistically significant differences between proband groups on mean age at onset of major depression, inpatient treatment, or suicidal gestures or attempts (Table 1). The delusional depressives did

have significantly more continuous outpatient treatment ( $p < 0.10$ ) and more depressive episodes ( $p < 0.01$ ).

**Psychiatric Disorders in the Children**

Table 2 shows that children of delusionally depressed as compared to nondelusionally depressed parents were at significantly increased risk for cyclothymia; anxiety disorders, any psychiatric diagnosis, and number of psychiatric diagnoses. Children of delusional as compared to nondelusionally depressed parents had nearly a threefold risk for cyclothymia. The one case of bipolar disorder was an offspring of a delusionally depressed proband. Delusional depression, not shown here, was rare in this sample of children and there were only two possible cases.

Rates of cyclothymia were examined by number of parents with delusional depression. In three families (five children), both the proband and spouse had delusional depression. In these families two (40/100) of the children had cyclothymia, as contrasted with families where only one parent was ill with delusional depression, where five (11.4/100) of the children had cyclothymia. There were no significant differences between offspring of the dual-mated pairs for other disorders.

**Table 1.** Clinical Characteristics Among Probands Stratified by Clinical Status

	Probands' clinical status for major depression			
	Delusional		Nondelusional	
Number of probands	22		37	
	Mean	SD	Mean	SD
Age of onset of major depressive disorder (yr)	27.4	(10.3)	31.5	(10.2)
Outpatient treatment	<i>n</i>	%	<i>n</i>	%
None	1	(4.6)	1	(2.7)
Brief (<6 mo)	2	(9.1)	8	(21.6)
Continuous (6-12 mo)	3	(13.6)	14	(37.8)
Continuous (>12 mo)	16	(72.7)	14	(37.8) <sup>a</sup>
Inpatient treatment				
None	17	(77.3)	26	(70.8)
Ever hospitalized	5	(22.7)	11	(29.7)
History of suicide gestures or attempts	5	(22.7)	8	(21.6)
Number of depressive episodes				
1	1	(4.6)	13	(35.1)
2	5	(22.7)	14	(37.8)
3	5	(22.7)	5	(13.5) <sup>b</sup>
≥4	11	(50.0)	5	(13.5)

<sup>a</sup>  $p < 0.10$ .

<sup>b</sup>  $p < 0.01$ .

**Neuropsychiatric, School, and Social Functioning**

The children of probands with and without delusional major depression and the children of normals were compared on a variety of developmental measures and neuropsychiatric, school, and social functioning (Table 3). Although previously we reported significant differences between children of depressed and normal parents (Weissman et al. 1986), for these analyses we compared the children of probands with and without delusional depression. The children of delusionally depressed parents were more often described by a health professional as being hyperactive ( $p < 0.10$ ). Although these other differences did not reach statistical significance in this small sample, it is interesting to note that the children of delusionally depressed parents more frequently had attention problems in school and were described as having learning disabilities. There were no significant differences between proband groups for children's IQ as assessed by PPVT or vocabulary test (data not given).

Children of delusionally depressed parents also had significantly poorer overall functioning, as assessed by the psychiatrist using the GAS, and independently by the child and the mother on the SAICA. The children of delusionally as compared to

**Table 2.** Lifetime Prevalence Rates per 100 and Relative Risk for Psychiatric Disorders in Children Based on Child Psychiatrist Best Estimate; Diagnosis Stratified by Probands' Clinical Status

Children ( <i>n</i> = 220)	Lifetime rates per 100 in children probands' clinical status for major depression			Relative risk <sup>a</sup>	Significance of differences <sup>a</sup>
	Delusional	Nondelusional	Normal		
Child psychiatrist best estimate diagnosis					
Major depression	21.7	34.1	21.7	1.3	NS
Bipolar disorder	2.2	0	0		
Cyclothymia	15.5	5.5	7.2	2.8	<i>p</i> < 0.06 <sup>b</sup>
Conduct disorder	28.3	19.8	15.7	1.4	NS
Substance abuse	15.9	15.4	4.8	0.99	NS
Any anxiety	52.2	35.2	20.52	1.5	<i>p</i> < 0.06 <sup>c</sup>
Any diagnoses	89.1	70.3	59.0	1.3	<i>p</i> < 0.02 <sup>c</sup>
Number of diagnoses mean (SD)	2.9 (0.34)	2.2 (0.24)	1.6 (0.25)	1.3	<i>p</i> < 0.1

<sup>a</sup> Between delusional and nondelusional.<sup>b</sup> Fisher's exact test.<sup>c</sup> Chi square.

nondelusional depressed parents did not differ on mean age of onset of major depression. However, as described elsewhere (Weissman et al. 1987), the children of normals had significantly later age of onset of major depression than did the children of depressed probands.

#### Age at Onset of Depression in Proband

As noted in Table 1, the mean age of onset of major depression was younger (although not statistically significantly so) in the delusional as compared to the nondelusional probands (27.4 vs. 31.5 years). Our

**Table 3.** Neuropsychiatric, School, and Social Functioning of Children

Description of children	Probands' clinical status for major depression						Significance of differences	
	Delusional		Nondelusional		Overall		Delusional vs. Nondelusional	Overall
Description by health professional	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%		
Hyperactive	3	(6.5)	2	(2.2)	0	(0.0)	<sup>a</sup>	<sup>a</sup>
Attention problems	4	(10.8)	3	(4.0)	1	(1.2)	NS	<sup>a</sup>
Learning disability	7	(15.2)	6	(6.6)	3	(3.6)	NS	<sup>b</sup>
Global Assessment	Mean	(SD)	Mean	(SD)	Mean	(SD)		
Psychiatrist best estimate (range 1–100; higher score, better functioning).	60.5	(2.1)	66.2	(1.5)	73.6	(1.6)	<sup>b</sup>	<sup>d</sup>
Social Adjustment Global Score (range 1–4; higher score more impairment).								
Child's report	1.8	(0.08)	1.5	(0.05)	1.4	(0.05)	<sup>c</sup>	<sup>d</sup>
Mother's report	1.7	(0.07)	1.5	(0.05)	1.4	(0.05)	<sup>b</sup>	<sup>c</sup>
Age of onset of major depressive disorder (yr)	12.1	(4.6)	13.2	(3.6)	16.7	(2.9)	NS	<sup>c</sup>

<sup>a</sup> *p* < 0.10.<sup>b</sup> *p* < 0.05.<sup>c</sup> *p* < 0.01.<sup>d</sup> *p* < 0.001.

previous research indicated that earlier age at onset of major depression was related to increased risk of major depression in adult relatives and may be related to bipolar disorder, which has an earlier age at onset than major depression (Weissman et al. 1984c). We also examined the effect of age of onset on rates of cyclothymia in the children using a proportional hazards analysis in the first model that included delusional major depression and age at onset of depression in probands as a continuous variable, and age and sex of child (data not shown). Cyclothymia in the child was the outcome. Although none of the coefficients were significant, delusional as compared to nondelusional depression had an adjusted relative risk of 2.36. When age at onset was dropped from the model, the coefficient changed marginally, indicating that age at onset of major depression in the depressed parent was independent of the effect of delusional depression. The coefficient for delusional depression was marginally significant ( $p < 0.1$ ). When delusional depression was dropped from the model there was no significant effect. Thus, the effects of delusional depression on rates of cyclothymia in the children were still significant after controlling for probands' age at onset of depression and children's age and sex.

#### The Effects of Chronicity of Parental Depression

As shown in Table 1, probands with delusional as compared to nondelusional depression more often had been in continuous treatment and had more episodes, suggesting that this was a more chronically ill group. Keller et al. (1986) showed that chronic depression in a parent increased risk of depression in the offspring. Although Keller et al. (1986) did not have a specific hypothesis about the effects on rates of cyclothymia in offspring, a more chronic parental illness could be producing differential rates of cyclothymia in children. We found that the rates of cyclothymia in children did not differ significantly by parental treatment history, number of episodes, or parental diagnosis of depressive personality (another possible reflection of chronicity in the parent).

### DISCUSSION

These results in the offspring of delusionally depressed probands are consistent with our previous findings in adult relatives that suggest an association between delusional depression and bipolar disorder or spectrum. More specifically, we found that the offspring of delusional as compared to nondelusional proband parents with major depression were at in-

creased risk for cyclothymia and anxiety disorder, were more often described by health professionals as hyperactive, and had significantly more school and social impairment reported both by their mother and by themselves. The results could not be explained by an earlier age at onset of major depression in the parent or in the offspring, or by chronicity or recurrence in the parent.

The findings must be considered as suggestive, because of the study limitations. Although based on a best estimate of diagnosis from multiple informants, the diagnosis of delusional depression in the proband was retrospective. Moreover, the sample of children of delusionally depressed parents was small ( $n = 46$ ) for a low-prevalence disorder such as bipolar disorder or its spectrum, and many offspring had not entered the age of risk for bipolar disorder.

#### The Spectrum of Bipolar Disorder

Evidence for a spectrum of bipolar disorder that includes cyclothymia and possibly other early behavioral manifestations is receiving increasing support from empirical research. Several investigators studying early presentations of bipolar disorder in hospitalized adolescents have noted the presence of cyclothymia, a history of hyperactivity, and poor school and social functioning (Strober and Carlson, 1982; Gammon et al. 1983; Klein et al. 1986; Ballenger et al. 1982; Rogeness et al. 1982; Carlson and Strober 1981; Preodor and Wolpert 1979). Additional support has come from family studies where the first-degree relatives of bipolar probands show increased rates of cyclothymia (Akiskal et al. 1983; Klein et al. 1986; Weissman et al. 1984a). Finally, the recent report of linkage of bipolar disorder to chromosome markers for color blindness and glucose-6-phosphate dehydrogenase deficiency in five Israeli pedigrees first included relatives with cyclothymia as affected (Baron et al. 1987). When a narrower definition of the affected phenotype was used and the relatives with cyclothymia were classified as normal, the lod scores were smaller than those obtained using the wide definition of the phenotype. This finding is partial evidence that cyclothymia was contributing to the linkage effect for bipolar disorder. In light of the emerging data on the spectrum of bipolar disorder, the recent revision of DSM-III (DSM-III-R) includes cyclothymia as part of Axis I bipolar disorders.

#### Links Between Delusional Depression and Bipolar Disorder

Several clinical, follow-up, and treatment studies have also suggested a relationship between delusional depression and bipolar disorder.

**Clinical Studies** Coryell et al. (1984b), in a study of 65 patients with major depression and psychotic features compared to 192 patients with major depression and no psychotic features, found that patients with psychotic depression were more likely to have bipolar disorder.

Guze et al. (1975), in a study of 253 patients with affective disorders, found a significantly increased history of delusional depression in the bipolar as compared to the unipolar patients.

Garvey et al. (1982) found an increased history of mania in the mothers of 16 patients with a history of psychotic depression as compared to 74 with non-psychiatric disorder.

Andreasen et al. (1986) examined 2942 first-degree relatives of 566 individuals diagnosed as having unipolar major depression. The relatives of patients with autonomous as compared to nonautonomous depression had significantly increased risk of mania and bipolar disorder. The autonomous depression criteria includes depressive delusions as one of the symptoms.

Coryell et al. (1985), in a study of 473 patients with nonpsychotic and 76 patients with psychotic depression, found that a significantly higher percent of the probands with non-mood-congruent psychotic depression had a history of mania.

**Follow-up Data** Akiskal et al. (1983), in a follow-up study of 206 depressed adolescents, found that psychotically as compared to nonpsychotically depressed patients were more likely to become bipolar at follow-up.

Strober and Carlson (1982), in a 3- to 4-year follow-up study, found that depressed adolescents who had delusions at initial interview were more likely to later develop a bipolar illness. Strober (personal written communication, May 8, 1986), in a prospective 8- to 44-month follow-up of depressed adolescents, found that 9 of the 15 (60%) delusionally depressed and none of the 50 nondelusionally depressed adolescents developed bipolar disorder over the follow-up period. Moreover, he found a significant aggregation of bipolar disorder in the first- and second-degree relatives of delusionally as compared to nondelusionally depressed adolescents.

**Treatment Studies** Price et al. (1983) reported on the usefulness of lithium augmentation of tricyclic antidepressants to treat delusional depression in patients who did not respond to the combination of tricyclics and neuroleptics. Similar findings have been reported by Weaver (1983) and by Pai et al. (1986) in clinical reports. However, Nelson and Mazure (1986) found lithium augmentation useful for psychotic depression in bipolar but not in unipolar patients. Sam-

pling variability may account for these inconsistent results.

### Age of Onset and Sampling Selection

We have described delusional depression with onset in adolescence or young adulthood as a possible early form of bipolar disorder that first manifests as cyclothymia, hyperactivity, and poor social functioning. This description contradicts the classic description of the delusional depressed patient as a middle-aged or elderly patient with good premorbid functioning. Until the recent systematic studies of psychiatrically ill children and adolescents, the studies of psychotic depression derived primarily from adult inpatient units where the average age of first onset, if noted at all in published reports, was ages 45 to 60 (Glassman and Roose 1981; Price et al. 1983; Healy et al. 1986; Thase et al. 1986; Charney and Nelson 1981; Frances et al. 1981). A difficulty that arises in interpreting the older literature is the failure of many investigators to note the age at first episode of depression and to distinguish between age of first episode of the disorder and the age of the patient when studied. It is quite likely that delusional depression with onset in adolescence and young adulthood is different from delusional depression with first onset after middle age. If a large proportion of adolescents with delusional depression go on to develop bipolar disorder, when these adolescents age they will be diagnosed and treated as bipolar patients and would not be included in samples of delusionally depressed patients. Thus, samples of older psychotically depressed patients may be a quite different subgroup from younger patients with early onset delusional depression.

Obviously, longitudinal studies of early and late-onset delusional depression in samples of patients selected and followed from the first episode would resolve this issue. Just as we have found that early onset delusional depression is familial and possibly linked to bipolar disorder, late-onset delusional depression may not be familial and may be linked to physical illness such as early dementias, Parkinson's disease, side effects of antihypertensive medication, or unresolved grief.

### CONCLUSIONS

In summary, our findings, taken in the context of a diverse literature, suggest that delusional depression may be linked to bipolar disorder and that early manifestations in children and adolescents are cyclothymia and hyperactivity. Delusional depression

with an onset in adolescence and young adulthood may be quite different than later-onset delusional depression, although the precise age cutoff is not clear. Research studies of delusional depression should include the age at onset of first episode of depression in order to examine a possible source of heterogeneity. Age of onset should be considered in selecting patients with delusional depression for psychopharmacologic trials. Inclusion of delusionally depressed patients with early and late onsets could obscure findings. If our findings on the association between the spectrum of bipolar disorder and delusional depression are replicated, alternative treatment strategies for the delusionally depressed patient with early onset are suggested. Moreover, the recent attention to genetic linkage studies of bipolar disorders (Egeland et al. 1987) increases the importance of questions about which types of major depression to include as affected phenotypes aggregating with bipolar disorder.

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