

Unipolar and Bipolar Primary Affective Disorder

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The classification of affective disorders has been a topic of controversy for years. The literature is filled with tentative attempts to order this large group of patients. Such attempts have brought surprisingly little resolution of the issues involved. There are those who would make numerous subdivisions within the affective disorders, and others who see affective illness as a unitary disorder.

Some of the most interesting recent work in the field has focused on the subdivision of primary affective disorder into bipolar and unipolar groups. Investigations carried out by Perris (1966) and by Winokur *et al.* (1969) provide evidence that primary affective disorder, that is affective illness occurring in the absence of other pre-existing psychiatric illness (Robins and Guze, 1969), may be separated as bipolar primary affective disorder in which mania occurs, and unipolar primary affective disorder in which mania is absent. The literature concerning this separation suggests that bipolar illness begins earlier in life and involves more frequent episodes than does unipolar illness. In addition, patients with bipolar illness have more extensive family histories of affective disorder with an increased prevalence of affective disorder among parents or children (two generations affected).

There have also been recent suggestions that important differences exist between patients with early and late onset primary affective disorder. In 1959, Kay reported a study of a large number of patients admitted to the Psychiatric Hospital, Stockholm, in the 1930s. Follow-up and family investigation of those patients indicated that the risk of affective disorder among first-degree relatives was higher for early-onset probands than for late-onset

probands. In the early 1960s, because of Kay's findings, Woodruff, *et al.* (1964) advanced the hypothesis that patients with a family history of affective disorder would show an earlier onset of illness and greater morbidity than patients without a family history of affective disorder. The data did not support that hypothesis. On the other hand, in 1964, Hopkinson published an investigation indicating that early-onset probands with an affective disorder had an increased number of relatives ill with the same disorder compared to late onset probands.

More recently, Winokur *et al.* (1971) have completed investigations of a group of hospitalized unipolar patients and their first-degree relatives. Winokur concludes that at least two forms of unipolar depressive illness exist. One form has as its prototype an early-onset female with a high prevalence of affective disorder among first-degree *female* relatives and an equally high prevalence of alcoholism and sociopathy among *male* relatives. A second form has as its prototype a late-onset male whose first-degree male and female relatives have equal rates of affective disorder, without an excess of alcoholism or sociopathy.

Since 1967, we have operated a research clinic within the framework of the Washington University Psychiatry Clinic, and have collected a group of 500 index cases drawn from the intake of the larger psychiatry clinic so as to provide a representative sample. Each of the 500 patients was studied by means of a systematic research interview. Extensive evaluation of the 500 cases is presently in process, to be followed by a large scale family study. Material from this research clinic provides an opportunity to present descriptive and family data about a sizeable out-patient sample of patients with primary affective disorder. It is possible from these data to explore various possibilities of

* This investigation was supported in part by United States Public Health Service grants MH-13002, MH-09247, and MH-14635.

subdivision within the larger diagnostic group of primary affective disorder; in particular, the separation of bipolar from unipolar patients, and the subdivision of unipolar cases by age of onset can be reassessed.

METHOD

Primary affective disorder is defined as an affective illness occurring in the absence of a pre-existing, diagnosable, non-affective, psychiatric illness. Bipolar primary affective disorder is generally defined by the presence of mania, either at present or in the past. (For the purposes of this study, two patients who did not have a personal history of mania, but who had close relatives with a history of mania, were included in the bipolar group.)

The criteria for the diagnosis of primary affective disorder were as follows. For a diagnosis of primary affective disorder, depressed type, the patient had to report (a) a dysphoric mood, characterized by the report of any of the following: depressed, sad, low, blue, despondent, hopeless, gloomy, disgusted, discouraged, empty, 'don't care,' worried, fearful, angry, or anxious. (b) In addition to disturbance of mood, the patient was required to have five of the following eight symptoms for a definite diagnosis, and four for a probable diagnosis: 1. Loss of energy or presence of fatigue. 2. Loss of weight or loss of appetite. 3. Loss of sexual interest or loss of general interest. 4. Insomnia or hypersomnia. 5. Slowed or mixed-up thinking or difficulty in concentrating. 6. Feelings of self-reproach or guilt. 7. Thoughts of death or suicide. 8. Either agitation or retardation

For a diagnosis of primary affective disorder, manic type, a patient had to report: (a) Euphoria or irritability plus (b) at least three of the following six symptoms for a definite diagnosis, and two for a probable diagnosis: 1. Hyperactivity (or increased sexual activity). 2. Push of speech. 3. Flight of ideas. 4. Feelings of grandiosity. 5. Insomnia. 6. Distractability.

Among the 500 index cases collected in our research clinic, 158 received the diagnosis of primary affective disorder or probable primary affective disorder. Of these, 139 had no history of present or past mania, nor did they have

first or second degree relatives with a history of mania. These 139 patients received the diagnosis of unipolar primary affective disorder (122 patients) and probable unipolar primary affective disorder (17 patients). Nineteen patients had a clinical history of mania or had a close relative with a history of mania (17 of the 19 patients had a personal history of mania). These 19 patients received the diagnosis of bipolar primary affective disorder. There were no patients with a probable bipolar diagnosis. The 139 unipolar cases were divided into those beginning before age 40 (97 cases) and those beginning at age 40 or later (42 cases). The unipolar cases were also divided into a 'chronic' group of 13 patients who reported long-standing depressions of between seven and 25 years duration without remission (mean 16 years) and an 'episodic' group containing the other 126 unipolar cases.

Comparisons were made between the bipolar and unipolar patients, between the early and late onset unipolar patients, and between the chronic and episodic unipolar patients with regard to a variety of demographic, clinical and familial characteristics. The chi-square test (with Yates' correction) was used for non-parametric data, and the standard error of the difference between the means for parametric data. Both statistics were used as two-tailed tests. Differences were defined as significant when there was one chance in 20 or less that they had occurred by chance ($p \leq .05$).

RESULTS

Twenty-seven per cent of all patients were male, and 27 per cent were also Negro. There were no significant differences in sex or race between any of the subgroups. Data concerning age of onset, age at interview, number of episodes of illness, psychiatric hospitalization, suicide attempts, and family history are summarized in Table I. A number of significant differences were found between the subgroups.

Compared to unipolar patients, bipolar patients reported more affective episodes, more frequent psychiatric hospitalizations, more frequent suicide attempts (at least among men), a more frequent family history of primary affective disorder among first-degree relatives,

TABLE I
Summary of clinical and family data

	All cases N = 158	Bipolar cases N = 19	Unipolar cases N = 139	Unipolar onset <40 N = 97	Unipolar onset ≥40 N = 42	Unipolar chronic N = 13	Unipolar episodic N = 126
Male	27%	47%	24%	23%	29%	15%	25%
Age at onset	32	29	32	—	—	24*	36
Onset ≥40	28%	11%	30%	—	—	8%	33%
Age at interview	39	38	39	32	56	40	39
Mean no. affective episodes	1.9	3.3*	1.5	—	—	—	—
Mean no. depressions	1.7	2.0	1.5	1.8	1.5	1.0	1.1
Ever in psychiat. hospital	37%	68%**	33%	30%	41%	8%	36% 6
Mean no. psychiatric hospitalizations	0.9	1.6 (a)	0.8	0.8	0.8	0.2	0.9
History of suicide attempt	16%	32% (b)	14%	19% (c)	5%	0%	16%
Family history	%	%	%	%	%	%	%
1st degree relative:							
'Nervous breakdown'	32	47	29	32	24	15	31
Primary affective disorder	29	53 (d)*	26	27	24	8	28
Parent or child with affective disorder (2 generations affected)	21	42*	18	21	12	0	20
Alcoholism	27	32	27	31 (e)	17	15	28
Suicide	3	0	3	2	5	8	2
Suicide attempts	8	21	6	10	0	0	7
Psychiatric hospitalizations	24	32	22	24	19	15	23
Prison or jail	11	21	10	11	7	8	10
At least one of the above	57	63	56	56	57	38	58
Family history							
1st or 2nd degree relative:							
'Nervous breakdown'	41	58	39	44	26	15	41
Alcoholism	41	47	40	49**	21	46	40
Suicide	8	11	7	7	10	15	7
Suicide attempts	13	21 (f)	12	18*	0	0	14
Psychiatric hospitalizations	39	47	37	43*	24	15	40
Prison or jail	17	26	16	20	7	23	15
FH entirely negative	15	5	17	10**	31	15	17

* = $p < .05$

** = $p < .01$

(a) Male bipolar patients, 1.5; male unipolar patients, 0.6; $p < .05$.

(b) Male bipolar patients, 44 per cent; male unipolar patients, 6 per cent; $p < .05$.

(c) Female early onset patients, 23 per cent; female late onset patients, 0 per cent; $p < .05$.

(d) Each of the 2 bipolar cases included because of relatives with mania also had other 1st degree relatives with primary affective disorder

(e) Fathers of early onset patients, 24 per cent; fathers of late onset patients, 7 per cent; $p < .05$.

(f) Male bipolar patients, 44 per cent; male unipolar patients, 6 per cent; $p < .05$.

and a more frequent pattern of parents or children with primary affective disorder (two generations affected). Bipolar patients also reported a more frequent family history of suicide attempts among first- or second-degree relatives (again among men). An interesting sex difference was observed between bipolar and unipolar patients with regard to personal histories of suicide attempts. Sixty-seven per cent of bipolar patients reporting suicide attempts were male, compared to 15 per cent of unipolar patients ($p < .05$).

Compared to late onset unipolar patients, early-onset unipolar patients were more likely to report suicide attempts (among women), and were also more likely to report a family history of psychiatric hospitalizations, suicide attempts, alcoholism among relatives in general, or specific paternal alcoholism. Completely negative psychiatric family histories occurred with significantly less frequency among early-onset than among late-onset unipolar patients. This last finding was confirmed by a comparison of the 23 unipolar patients with entirely negative family histories and the remaining 116 unipolar cases. The average age of onset of the former group was 42 years; of the latter, 30 years ($p < .001$). Further, 57 per cent of the negative family history patients became ill only at age 40 or older, compared to 25 per cent of the positive family history patients ($p < .01$).

A number of interesting differences were noted between the chronic and episodic cases, but the chronic group was small enough to make statistical comparisons difficult. Only one difference was significant: the chronic cases began much earlier in life.

DISCUSSION

Differences between our bipolar and unipolar cases are consistent with previous reports in the literature, except for the absence of a significant difference in age of onset. If the 13 chronic cases are omitted from the unipolar group, however, and the justification for doing this is discussed further below, the difference in the mean age of onset between the two groups (bipolar and episodic unipolar) becomes seven years, similar to that reported

by other workers. The differences in the clinical course and in the psychiatric family history, particularly with regard to the presence of primary affective disorder among first-degree relatives, argue for the validity of the bipolar-unipolar separation.

Differences between our early-onset and late-onset unipolar patients, showing more positive psychiatric family histories among patients of early onset, are generally consistent with previous reports in the literature.

Winokur reported an increased frequency of primary affective disorder among the relatives of early-onset patients compared to the relatives of late onset patients. He also reported an excess of affectively disordered female relatives of female early-onset probands. In our material, 16 per cent of mothers of early-onset patients and 5 per cent of mothers of late-onset patients had a history of primary affective disorder. Two per cent of fathers of early-onset patients and 2 per cent of fathers of late-onset patients had such a history. A further analysis of primary affective disorder among the parents with probands divided by sex as well as age of proband onset revealed that: 18 per cent of mothers of early-onset male probands had a history of primary affective disorder, 9 per cent of mothers of late-onset male probands, 15 per cent of mothers of early-onset female probands, and 3 per cent of mothers of late-onset female probands had such history. (Only three fathers among all the unipolar cases were reported to have a history of primary affective disorder.) Our data are generally consistent with Winokur's findings, but none of the early-onset : late-onset differences are statistically significant, whether or not probands are divided by sex.

An increased prevalence of alcoholism among the fathers of early-onset cases as well as among all first- and second-degree relatives taken together is also consistent with Winokur's hypothesis (see introduction). However, in our material, significant differences in prevalence related to the sex of index cases were not found for alcoholism, as they were not found for primary affective disorder. Our early-onset male probands reported a history of alcoholism among 18 per cent of their fathers, as compared

to such history among 9 per cent of fathers of late-onset male probands. Early-onset female probands reported alcoholism in 25 per cent of their fathers, as compared to 7 per cent of the fathers of late-onset female probands. While the ratio of early-onset to late-onset alcoholism was somewhat higher among female probands than among male probands, this sex difference was not significant. (In addition to the higher risk of alcoholism among the fathers of early-onset cases, four mothers among the unipolar patients were reported to be alcoholic, all of early-onset cases, two male and two female.)

We could not estimate the risks of primary affective disorder and alcoholism among siblings with accuracy because we did not have specific information concerning the ages of all siblings. It was not possible to determine how much of the age of risk for affective disorder or alcoholism had been completed by each sibling. (Among parents, consideration of age was not critical, since nearly all parents had passed well into the age of risk for affective disorder.) Data concerning parents are probably the most useful among first-degree relatives. It is likely that index patients identified alcoholism more reliably among parents than among siblings. Alcoholism in a parent was usually evident while the index subject was growing up at home. Alcoholism among siblings was generally evident only after the sibling had left the parental home. (A similar though less impressive argument can be made with regard to affective disorder). We also had reservations concerning age of risk and problems of detection of alcoholism and affective disorder among the children of index patients. The small number of index patients whose children had reached adulthood made analysis of risk among children inappropriate.

In summary, the data concerning the risk of psychiatric disorder, especially alcoholism among fathers of unipolar cases, are generally consistent with previous work indicating that early onset cases are associated with an increased risk of illness among close relatives. Our data do not indicate any differential risk of alcoholism or affective disorder among relatives when the index subjects are divided according to sex.

It is unfortunate that the number of chronic cases was so small that satisfactory statistical

comparisons were not possible. The results suggest that these patients represent a distinct group. They seem to have an earlier age of onset, a reduced risk of psychiatric hospitalization, a reduced risk of suicide attempt, and an apparently reduced frequency of psychiatric disorder (including primary affective disorder) among first-degree relatives. More cases will need to be studied before this group is adequately evaluated.

The results indicate that valid subdivisions of primary affective disorder are possible and appropriate. Distinctions between bipolar and unipolar groups, and between early-onset and late-onset unipolar groups are warranted in further studies of aetiology, treatment, and prognosis. A follow-up study of our patients will be undertaken to provide data about response to treatment and prognosis. With that information we can continue evaluation of the validity of this subclassification of primary affective disorder.

SUMMARY

One hundred and fifty-eight patients with primary affective disorder, all seen in an outpatient setting, were investigated with regard to bipolar versus unipolar illness, early onset versus late onset unipolar illness, and chronic versus episodic course among unipolar patients. Statistically significant differences, particularly in family history data, serve as evidence of the validity of separating bipolar from unipolar cases, as well as the validity of separating early-onset unipolar cases from those of late onset. The number of chronic cases available for investigation was small, and statistical comparisons were not possible. The results, however, suggest that patients with chronic, unremitting depression over a period of many years may form a distinct group.

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A synopsis of this paper was published in the *Journal* for December 1970.

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(Received 7 September 1970)