

# The Course of Affective Disorders

## II. Typology of Bipolar Manic-Depressive Illness

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**Summary.** A representative sample of 95 hospitalized bipolar manic-depressive patients was followed up from 1959 to 1975. The mean age of the group at the time of this study was 61 years. It was observed that female bipolar patients demonstrate depression much more frequently than mania, while male patients show a symmetric distribution of both manic and depressive syndromes. The longitudinal occurrence of syndromes remains more or less constant; for instance, individual patients do not tend to go into depression with increasing age. The study shows that even after three episodes 29% of all bipolar patients would still have been misdiagnosed as unipolar depression.

An attempt is made to classify bipolar patients into three subtypes, 'preponderantly manic,' 'preponderantly depressed,' and a 'nuclear' type. Male patients belong mainly to the latter with an equal proportion of the first and third subtype. In contrast, female patients belong mainly to the depressed subtype.

The findings are discussed assuming either a heterogeneity of bipolar disorders or a threshold model of affective disorders suggested by Gershon et al. (1976).

**Key words:** Bipolar manic-depressive disorder – Course – Typology of syndromes – Sex difference – Early and late onset type.

### 1. Introduction

Manic-depressive disorder is generally defined as an affective disorder with the manifestation of mania alone or with an irregular occurrence of manic or hypomanic and depressive episodes. Recurrent mania is not a separate entity as was postulated by Leonhard (1957); the morbidity risk of first-degree relatives of

manic patients is the same in quantity and quality as in relatives of bipolar patients (Perris, 1966; Lee, 1972; Taylor and Abrams, 1973; Angst, 1974). Recurrent mania is a product of the random process in the occurrence of mania and depression (Angst, 1974). For the same reason there exist patients with recurrent depression (unipolar depression) who have not become manic, but who certainly belong to the bipolar group. But how many? This question was discussed in a first paper (Angst et al., 1978). This second study deals with bipolar manic-depressive illness only. The frequency of manic and depressive syndromes in bipolar illness is analyzed.

A longitudinal analysis of the typology of syndromes may also be relevant to the evaluation of heterogeneity of bipolar disorders. Another type of heterogeneity has been suggested, based on genetic marker studies by Winokur et al. (1969) and Mendlewicz et al. (1972).

This paper does not attempt to answer all these questions; its aim is a simple statistical description of what can be observed in a long-term course of bipolar illness.

## 2. Sample and Methodology

The patient sample consisted of 95 cases with a diagnosis of bipolar disorder (ICD 296.3), including three patients with recurrent mania (ICD 296.1). The patients represent all hospital admissions to the Psychiatric University Clinic Burghölzli in Zurich from 1959 to 1963 with the diagnosis of depression or mania in bipolar illness. They were carefully selected from all admissions during these years which had a diagnosis of general affective disorder (ICD 296) or of schizo-affective disorder (ICD 295.7). They represent 37% of all 'affective disorders' diagnosed (ICD 296): in the same years, there were 159 patients admitted with a diagnosis of unipolar (monopolar) depression (ICD 296.2 + 296.0). All the patients have been followed up at least every fifth year from 1959 to 1975 and the diagnosis was confirmed or corrected using the longitudinal approach (Angst, 1977). The methodology has been described in the first paper (Angst et al., 1978).

## 3. Results

### 3.1 *Description of the Sample*

The sample consists of 95 patients (37 males, 58 females) with a mean age of  $61.0 \pm 13.2$  years in 1975. Of these 95 patients, 26 (27%) died with a mean age of  $65.0 \pm 14.9$  years (median 69, range 23–86), 69 patients are alive with a mean age of  $59.5 \pm 12.2$  years (median 61, range 32.84).

Seventy-eight patients were observed both retrospectively and prospectively; in 17 patients the study was purely prospective. The average time of retrospective observation is  $16.8 \pm 11.1$  years ( $n=78$ ) and that of prospective observation  $12.6 \pm 3.8$  years ( $n=95$ ). The average number of episodes observed retrospectively is three (median), prospectively nine (median); therefore most of the episodes belong to the prospective period.

The total length of observation (since onset of the disorder) is 26.5 years in those who died and 26.3 years in those who remained alive.

The average age of the total sample of 95 patients at the first episode was  $34.7 \pm 13.9$  years. In a minority of 12% no further episode was observed during the last five years of the follow-up; in all others (88%) the process was still going on at a mean age of 61 years. At the time of the last follow-up the average length of the illness was  $23.8 \pm 12.5$  years (range 25—705 months). For the dead patients ( $n=26$ ) the length of illness was calculated as  $25.1 \pm 14.6$  years, in the group still alive ( $n=69$ ) it was now up to  $23.3 \pm 11.7$  years. The length of illness was defined as the time between the onset of the first and the end of the last episodes observed.

### 3.2 Episodes

An episode is defined as a change of mood to depression, mania, or a mixture of both; it requires ambulatory or inpatient treatment or leads to such a change of behavior that the patient himself feels ill and incapacitated or the relatives suffer (the latter especially in the case of hypomanic or manic patients not willing to be treated). A free interval of at least four weeks is required to accept the existence of a subsequent episode. Manic and depressive syndromes linked together without free intervals are considered to belong to the same episode.

Table 1 gives an approximate distribution of the total number of episodes observed in males and females. It is apparent that there is no difference between the sexes in the frequency of the observed episodes. A median of nine episodes were registered in a period of 26.3 years of observation.

**Table 1.** Distribution of the total number of episodes

Total number of episodes	Number of patients by sex		
	m	f	m + f
1—5	9	16	25
6—10	14	16	30
11—15	4	12	16
16—20	6	3	9
> 20	4	11	15
Total	37	58	95

$df=4$ ;  $\chi^2=6.0016$  NS

### 3.3 Typology of Syndromes

Episodes may be classified using a simple typology. The elements of this typology are defined as follows:

M=manic syndrome requiring hospitalization

m=hypomanic syndrome not requiring hospitalization

D=depression requiring hospitalization

d=depression not requiring hospitalization

In this selection, for instance, 'Dm' means that the patient was suffering from a depression requiring hospital treatment and the depression was immediately

**Table 2.** Frequency of syndrome patterns in bipolar psychoses and sex (95 patients, 1176 episodes)

Pattern of syndromes	Males		Females		Males %	Females %
	<i>n</i>	%	<i>n</i>	%		
D	80	18.3	194	26.3	35.5	60.0
d	75	17.2	246	33.7		
M	127	29.1	75	10.1	35.3	13.6
m	27	6.2	26	3.5		
DM	5	1.1	15	2.0	15.3	16.6
Dm	23	5.3	66	8.9		
dM	7	1.6	4	0.5		
dm	32	7.3	39	5.2	12.6	9.2
MD	2	0.5	11	1.5		
Md	19	4.3	18	2.4		
mD	3	0.7	11	1.5		
md	31	7.1	28	3.8		
Questionable, unknown	6	1.4	6	0.8		

D = severe depression (requiring hospitalization)

d = mild depression (not requiring hospitalization)

M = mania (requiring hospitalization)

m = hypomania (not requiring hospitalization)

followed by hypomanic swing; d means, for instance, that the patient was suffering from a depression which received ambulatory treatment or was left untreated.

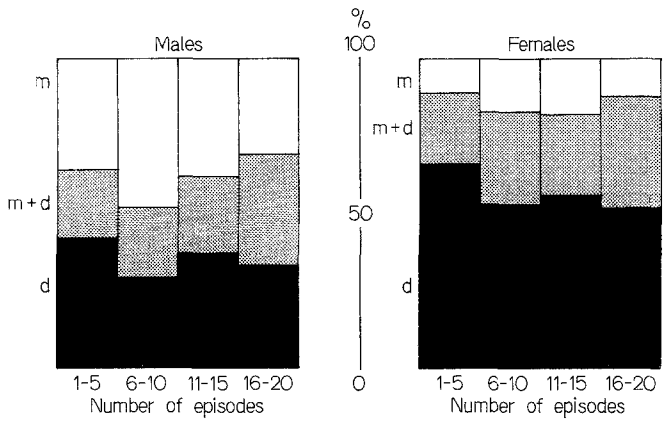
In each episode the sequence of these syndromes was recorded. In most of the episodes (99%) a sequence of two elements was sufficient to describe the change of syndromes; in 1% ( $n = 12$ ) there were more than two subsequent syndromes observed during the same episode.

The results of the analyses of 1176 registered episodes are shown in Table 2. There is a marked difference in the typology of syndromes between the sexes. Males show a symmetric distribution of both syndromes, manic and depressive, with 35% of each, and an equal occurrence of biphasic episodes (DM = 15%, MD = 13%). Therefore, the occurrence of the two syndromes can be understood as the result of a random process. In females, there is a high preponderance (60%) (males 35.5%) of pure depressive syndromes, and manic syndromes are under-represented (13.6% in females, 35.3% in males). There is also a trend toward more frequent occurrence of the depression-mania sequence (16.6%) rather than toward the reverse mania-depression (9.2%).

A second finding of great interest is the frequency of the constellation Dm/DM or dm/dM, which means the probability of a change from a hospitalized depression (D) or a nonhospitalized depression (d) to hypomania (m) or mania (M). In hospitalized patients the observed frequency was 6.4% in males and 8.9% in females. The figures cannot be considered as indicating spontaneous change, because most of these episodes were treated by antidepressant drugs.

**Table 3.** Frequency of depressed (D) and manic (M) syndromes in subsequent episodes

Number of episodes	Males						Females						T
	D		M + D		M		D		M + D		M		
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	
1—5	75	42	40	22	64	36	178	66	62	23	31	11	
6—10	33	29	27	23	55	48	93	53	52	30	30	17	
11—15	24	37	16	25	25	38	58	56	27	26	19	18	
16—20	11	33	12	36	10	31	29	52	20	36	7	12	
> 20	11	26	28	65	4	9	83	69	28	23	10	8	
Total	154		123		158		441		189		97		1
$\chi^2 = 9.134; df = 6; P < 0.20$ (NS)							$\chi^2 = 11.356; df = 6; P < 0.10$ (NS)						



**Fig. 1.** Cross-sectional proportion of depressive (d), manic (m), and manic-depressive (m+d) syndromes during the first 20 episodes

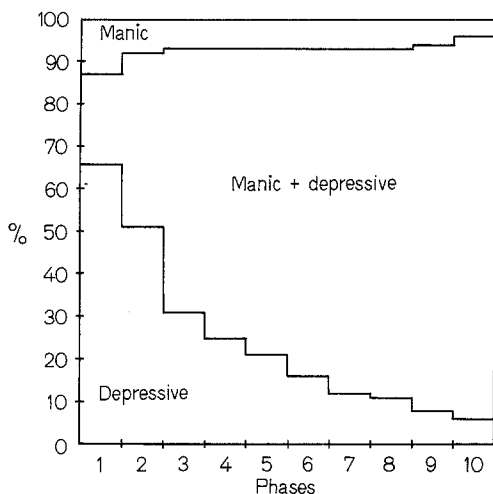
### 3.4 The Longitudinal Occurrence of Syndromes

Is there a longitudinal change in the ratio of manic and depressive syndromes? For instance, is there a shift from mania to depression correlated with age? Do patients therefore become more and more depressed?

Table 3 and Figure 1 give the cross-sectional proportion of depression and mania for the first 20 episodes divided according to sex. They show in general a preponderance of depressive manifestations in bipolar disorder, a preponderance of depression among female patients, and amazingly little change with age. At the beginning (first episode) there are a few more depressive episodes; this is probably due to an underreporting of first manifestations of hypomania. Therefore, the reported age at the first episode may also be higher than actually occurs.

### 3.5 'Unipolar' Manifestations of Bipolar Disorder

A bipolar disorder can fortuitously manifest itself for a certain period of time as a 'unipolar' illness. We therefore observed recurrent manic and recurrent depres-



**Fig. 2.** Unisyndromal course of bipolar psychoses

sive types of bipolar disorder. Recurrent mania can easily be classified as true bipolar disorder, but recurrent depressive illness cannot be distinguished from the true unipolar depression. Therefore, we lack the depressed phenotype of bipolar illness in our material. From a methodological viewpoint, it is of interest to know something about the diagnostic error, arising from a syndrome change from depression to mania.

Figure 2 gives the frequency of 'unipolar' courses of bipolar patients until their psychopathology changed polarity. It is certainly of practical interest that 29% of all bipolar patients are still misdiagnosed after three depressive episodes as unipolar depression. In the first paper we analyzed the question of these diagnostic errors (Angst, 1978).

### 3.6 Typology of Bipolar Patients

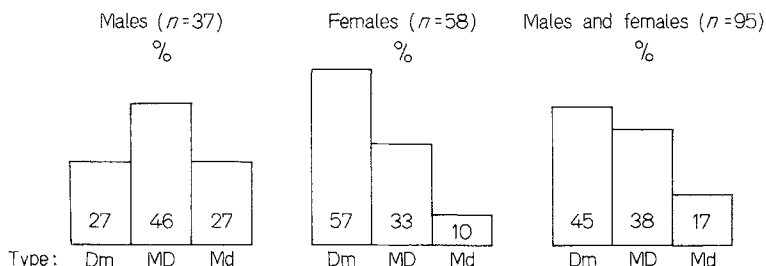
Patients (compare syndromes, 3.3) were classified into three different groups: Type 'MD': The patient showed both mania and depression requiring hospital admission (nuclear type).

Type 'Md': During his life the patient suffered once or several times from mania, requiring hospitalization, but he showed only mild or no depression. This is called the predominantly manic type.

Type 'Dm': The patient required hospital admission for depression, but showed only hypomania (predominantly depressed type).

Figure 3 shows the frequency of the three types according to sex. Again the findings of Section 3.3 are confirmed with amazing accuracy: male patients belong preponderantly to the nuclear (MD) type with both severe mania and severe depression. The frequencies of the other two types (Md, Dm) are equal. It makes sense to assign the recurrent pure manic type ( $n=3$ ) to this group.

In female patients there is a high preponderance of the depressed subtype in not less than 59%, whereas the nuclear mixed type 'MD' is found in about the



**Fig. 3.** Typology of bipolar patients. *Type MD:* The patient suffered at least once from a severe manic and a severe depressive syndrome—the *bipolar type*. *Type Md:* The patient suffered at least once from a severe manic syndrome, but showed only mild depressive symptomatology—the *prevailing manic type*. *Type Dm:* The patient suffered at least once from a severe depressive syndrome, but showed only hypomanic symptoms—the *prevailing depressive type*.

**Table 4.** Frequency of subtypes of bipolar disorders

	Clinical subtypes	$p_1(x)$ males	$p_2(x)$ females
$x_1$	M	2	1
$x_2$	Md	8	6
$x_3$	MD	17	19
$x_4$	mD	10	33
$x_5$	D	—	—

M = mania

D = depression unipolar

same proportional frequency (33%) as in males (46%). Therefore, we find type 'Md' underrepresented in female patients and more type 'Dm.'

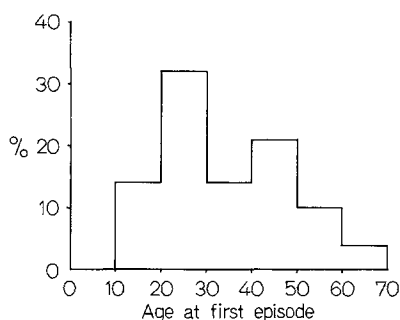
### 3.7 Heterogeneity of Bipolar Illness

The finding of a remarkable difference in the proposed typology of syndromes and patients in each sex is of interest. It leads to the hypotheses that bipolar illness is heterogeneous or that an unspecific sex-dependent factor modifies the manifestation of the illness in females in favor of depression. The latter hypothesis is supported by epidemiologic and clinical findings that show a preponderance of female depressives (ICD 296, 300.4) over male depressives in epidemiologic, clinical, and genetic studies (Angst, 1966).

On the other hand, the unequal distribution of depressive and manic syndromes in bipolar females may also be due to some kind of heterogeneity in this sample. An analysis, based on the age at the first episode of bipolar illness and on the three subtypes, is given in Table 5 and Figure 4. The histogram (Fig. 4) shows a bimodal distribution with early (20–30 years) and late onset (40–50 years) groups. The figures for the three subtypes of bipolar illness show a unimodal distribution of the age at onset for the prevailing manic type 'Md' and a bimodal one for the two others 'MD' and 'Dm.'

**Table 5.** Age at onset in subtypes of bipolar illness

Subtypes	Age at first episode					
	10—19	20—29	30—39	40—49	50—59	60—69
Md	3	6	3	1	2	1
MD	6	14	4	10	2	—
Dm	5	12	7	10	6	3
Total	14	32	14	21	10	4

**Fig. 4.** Heterogeneity of bipolar illness, bipolar psychoses ( $n=95$ )**Table 6.** Age at first episode and sex

Sex	Age at first onset					
	10—19	20—29	30—39	40—49	50—59	60—69
m	6	13	7	7	3	1
f	8	19	7	14	7	3

Dividing the material according to sex we arrive at the figures given in Table 6, which shows a clear bimodal distribution of the age of onset for females with a second peak in the fourth decade (mainly between 45 and 49 years); in males, a similar trend may be present but is doubtful. The difference might be explained by the effect of endocrine menopausal changes in women. But our small group of males does not exclude the existence of an early and late onset group here too. The question must be kept in mind for future studies.

The different ages at first episode in the proposed subtypes with an earlier manifestation in 'MD' ( $31.6 \pm 11.6$  years) and 'Md' ( $32.6 \pm 15.3$  years) than in the preponderantly depressed group 'Dm' ( $38.0 \pm 14.6$  years) does not prove the heterogeneity of bipolar illness. The different subtypes could also be explained by the different degrees of severity of the disorder. This hypothesis would assume that the recurrent manic and the preponderantly manic type 'Md' are the most severe forms of bipolar illness, followed by the nuclear type 'MD' and the preponderantly depressed type 'Dm.' Differences in the age at onset would be a



consequence of severity and penetrance. The same would be true for the whole spectrum of bipolar illness, assuming a normal distribution and including some cases of unipolar 'depression,' suicide, and neurotic or reactive depression. On the other hand, differences in the age at first onset would not be completely compatible with this model. Milder neurotic and reactive depressions tend to manifest themselves earlier than severe bipolar disorder and unipolar depressive disorders. The question of a heterogeneity of bipolar illness has to be analyzed in future studies in more detail, based on bigger samples of patients.

In this connection we must consider whether, despite the supposed spectrum of bipolar affective illness (*Morbus bipolaris*) including different types of depression, unipolar depression does actually exist as a separate entity. The consequence of the classification presented here is that an important proportion of depressive syndromes, diagnosed as unipolar, neurotic or reactive, or suicidal, belong to bipolar illness. On the other hand, the hypothesis of the existence of a separate unipolar depressive disorder is based on different criteria that distinguish it from bipolar disorder (genetic background without special risk for mania or manic-depressive disorder, sex ratio with a preponderance of females, later age at onset, low recurrence, different premorbid personality).

The threshold model (Gershon et al., 1976), which assumes a milder type of affective disorder with pure depression and a more severe type with bipolar syndromes, is also of great interest. It would be compatible with a later age of onset for the milder disorder (depression) and would also fit the observed later age at onset of the depressed subtype (Dm) of bipolar disorder. Why women have a higher risk of acquiring an affective disorder, especially depression, is still an open question which has perhaps to be explained by endocrine factors. For the same reason, women seem to be more vulnerable to the milder form of disturbance, namely, depression.

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