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The Course of Affective Disorders

I. Change of Diagnosis of Monopolar, Unipolar, and Bipolar Illness

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Summary. All patients suffering from affective psychoses (ICD 296) who were admitted to the Psychiatric University Clinic of Zurich between 1959 and 1963 were studied in a follow-up investigation until 1975. Of 254 affective psychoses, 95 were bipolar patients (37.4%) and 159 were monopolar (62.6%). The sample of bipolar patients was complemented with all patients who had been admitted in the period 1959—1963 because of manic or mixed manic-depressive syndromes.

This paper describes the change of diagnosis in the two diagnostic groups. In 10% ($N = 20$) of monopolar depression cases there was a change of diagnosis to bipolar affective illness. An analysis shows that the diagnosis of patients with three or more depressive episodes (unipolar depressives) was especially prone to change.

A mathematical correction of some diagnostic errors leads to the conclusion that the ratio of unipolar depression to bipolar illness may be about 1 : 1.

A major source of diagnostic error lies in the change of affective to schizo-affective illness. Up to now, no clinical criterion exists that would exclude this error, which was found in 6% ($n = 12$) of the monopolar but also in 7.5% ($n = 3$) of the bipolar index patients.

It is recommended that studies of affective disorders should be based on truly representative samples of the illness, including patients with one or two episodes, and that the term 'unipolar depression' be used synonymously with the term 'monopolar depression,' originally created by Kleist (1947) and Leonhard (1957).

Key words: Change of diagnosis – Unipolar, bipolar affective disorder – Schizo-affective psychoses.

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1. Introduction

Monopolar depressive illness is defined as a monophasic or recurrent primary depressive disorder. It is, however, well known that this diagnosis is not very reliable, because at any time in the course of the illness a manic syndrome can appear and the diagnosis has then to be changed to bipolar psychosis. Therefore, Perris (1966) based his study of affective illness on 'unipolar depression': a unipolar depression was originally defined as a recurrent endogenous depression with at least three depressive episodes. Perris classified cases with one or two episodes as 'unspecified affective disorder.' The diagnosis of unipolar depression makes sense if it is correct to assume that the diagnosis of a unipolar illness is more reliable than that of a monopolar affective illness and if unipolar illness is representative of recurrent depression. The last question may be answered by comparing the frequency of cases with one or two depressive episodes with that of those with three or more depressive episodes. The question can also be formulated in the following way: is the diagnostic error in terms of a later change to bipolar illness greater in monopolar or in unipolar depression?

Another problem is the change of diagnosis in both depression and bipolar psychoses to schizo-affective illness (ICD 295.7). Schizo-affective psychoses do exist and are a major problem in diagnostic studies of schizophrenia and affective illness (Scharfetter et al., 1976).

A good method of corroborating a diagnosis is a follow-up study. During the last 12—16 years we carried out such a study on a sample of affective disorders which is representative for hospitalized cases. Some results of this study are briefly summarized.

2. Selection of the Sample and Methodology

The patient sample consists of two groups. Firstly we have included all hospital admissions to the Psychiatric University Clinic of Zurich during the years 1959—1963 with a diagnosis of depression in affective psychoses (ICD 296) on admission. This group ($n = 254$) was originally studied during those years and described from clinical and genetic viewpoints in a monograph published in 1966 (English in 1973), which established that monopolar (unipolar) depression differs from bipolar affective illness. This was soon confirmed by an independent investigation (Perris, 1966). In the follow-up study we excluded from our original material 11 patients (eight foreigners, one refusal, two unavailable). Thus, of the original sample of 254 patients (Angst, 1966), 203 monopolar depressives and 40 bipolar patients were left for the prospective follow-up study. Secondly, to this sample has been added another 28 patients admitted to the clinic from 1959 to 1963 with a manic syndrome (25 bipolar and three recurrent manic patients).

A longitudinal study of this kind must necessarily be performed both retrospectively and prospectively, because it has to cover the whole timespan of the natural course of the disorder. The follow-up is based on several types of information: patient records from other institutions (45), from doctors (32), or from other informants (18) by telephone calls or letters. Most of the patients had been readmitted (63%) since they had been examined during their stay in the hospital between 1959 and 1963. In all cases, additional information was obtained not only from the patient, but also from at least one other informant (relative, doctor, social worker). Switzerland is a small stable country with a high telephone density; this makes it relatively easy to follow the patients and to collect additional information. There was also no difficulty in obtaining the records from other institutions for our scientific purpose. Furthermore, the patients and their relatives were very cooperative, especially because most of them had already

been examined personally in the first period of the investigation (1959—1963). The patients got used to the follow-up phone calls, and they frequently called the first investigator spontaneously in cases of relapse. A follow-up examination was carried out in 1964, 1970, and 1975 (the last time by R. Frey).

But there still remain many sources of error: a follow-up every fifth year may miss quite a few milder episodes, because the patients or the informants may have forgotten them; in particular there may be an underreporting of mild short mood swings, for instance, hypomania. But such errors may be distributed by chance over the total sample so that they may be ignored in an analysis of subgroups. Anyhow, the reported figures may be minimal figures of morbidity.

3. Results

3.1 Change of Diagnosis in Monopolar Depression

The original sample of 203 monopolar depressive patients consists of both early and late onset depressives (ICD 296.2 and 296.0). At the time of the first investigation from 1959 to 1963 (published 1966), ten of these 203 patients had already shown some signs of hypomania, mainly at the end of the episode during a drug treatment. Originally they were subsumed to the group of monopolar depression, because we did not feel sure about their nosologic identity, in the meantime, we decided to count them as bipolar manic-depressive patients. Figure 1 gives the subgroups of patients whose diagnosis has changed. With ten patients there was, as already mentioned, not a true change of diagnosis but a change of concept. With another 20 patients (10%) the follow-up showed some kind of hypomania or clear mania; therefore, we definitively had to change the diagnosis in 10% of monopolar depression to bipolar illness. In another 6% ($n = 12$) we found schizophrenic syndromes or mixed syndromes of schizophrenia and affective disorders, suggesting the diagnosis of a schizo-affective psychosis (ICD 295.7). We had therefore to change the diagnosis in 32 of 203 cases (16%) (Fig. 1).

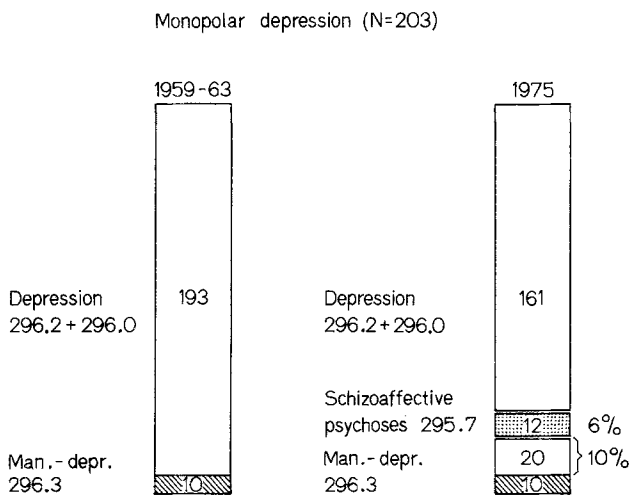

Fig. 1. Change of diagnoses 1959—1975

Table 1. Change of diagnosis and number of previous depressive episodes

Original diagnoses	Number of episodes at which the diagnosis changed to bipolar illness (ICD 296.3)	
	2—3	Unipolar depression 4 and more
ICD 296.2	4	13
ICD 296.0	2	1
Total	6 (30%)	14 (70%)

Table 2. Error of classification of unipolar and bipolar affective psychoses

Episodes	d_k Diagnosis 296	r_k Drop-out total	r_{3k} Drop-out 296.3	d_k Diagnosis 296.3	ρ_k Relative error o	a_k Absolute error ×	$\frac{d_k - d_k + 1}{d_k}$	$\frac{r_{3k}}{r_k}$
1	254	—	—	32	0.67	0.67	0.09	—
2	230	24	—	15	0.76	0.50	0.16	0.00
3	193	37	2	19	0.60	0.30	0.13	0.05
4	168	25	6	5	0.83	0.25	0.17	0.24
5	140	28	7	4	0.83	0.21	0.14	0.25
6	121	19	10	4	0.80	0.17	0.14	0.53
7	104	17	4	5	0.69	0.12	0.20	0.24
8	83	21	11	1	0.91	0.10	0.08	0.52
9	76	7	3	2	0.80	0.08	0.09	0.43
10	69	7	5	2	0.78	0.06	0.19	0.71
>10	56	13	7	6				0.54
		$\Sigma = 198$	$\Sigma = 55$	$\Sigma = 95$	$\rho = 0.767$			

In contrast to Perris' study (1966), our original sample included not only unipolar patients, suffering from at least three depressive episodes, but also patients with only one or two depressive episodes. The question arises whether the change of the diagnosis would have been minor if the investigation had been based on the strict diagnostic concept of 'unipolar depression' which assumes that patients, who have already had at least three depressive episodes, have a lower chance of becoming bipolar. Our 20 patients, who switched from monopolar to bipolar psychoses, can be subdivided into those with one or two previous episodes and those with three or more. Therefore, the switch to bipolar affective illness occurs in episodes number 2—3 or 4 or later. Table 1 shows the frequency of changes in the two subgroups. As can be seen, most of the changes were found in patients who fulfill the strict criteria of unipolar illness (in 14 cases which is 70% of those

that changed). If our investigation had been based on unipolar depressives, we would have avoided only 30% of the diagnostic change.

Another way of dealing with the data is to analyze the total material of 254 affective psychoses (ICD 296) to find out at which episode a manifestation of hypomania or mania identified the illness as a bipolar psychosis.

Starting with $n_0 = 254$ depressive patients (Table 2) we can estimate retrospectively the size n_2 of the bipolar subgroup as well as the risk of a change in diagnosis at any given point in time (number of episode). In doing so we have to consider that there might be patients among the dropouts with an undiagnosed bipolar illness; this must be taken into account as a correcting factor in connection with the estimate of n_2. The effect of this factor should also be analyzed in order to get an upper limit of the error under worst-case conditions.

The sum of the actual bipolar diagnoses at the time κ results in

$$n_2 = |2.96.3| \geq \sum_{\kappa} d_{3\kappa}.$$

$\kappa = 1, 2, \ldots$ episodes;
$d_{3\kappa}$ = number of changes in diagnosis at the time κ.

Equality holds if there is no misclassification among the dropouts. In that case we find a nearly constant relative error of classification and an exponential decrease of the absolute error (a_κ) in Figure 2:

$$\rho_\kappa = 1 - \frac{d_{3\kappa}}{n_2 - \sum_{i<\kappa} d_{3i}} \quad \text{relative error}$$

$$a_\kappa = a_0 \cdot e^{\beta(\kappa - 1)} \quad \text{absolute error}$$

For the constant β in the exponent we find $\beta \approx \log \rho \approx -0.3$ where ρ is the average relative error and the other constant is intended to be $a_0 \approx 1 - d_{31}/n_2$.

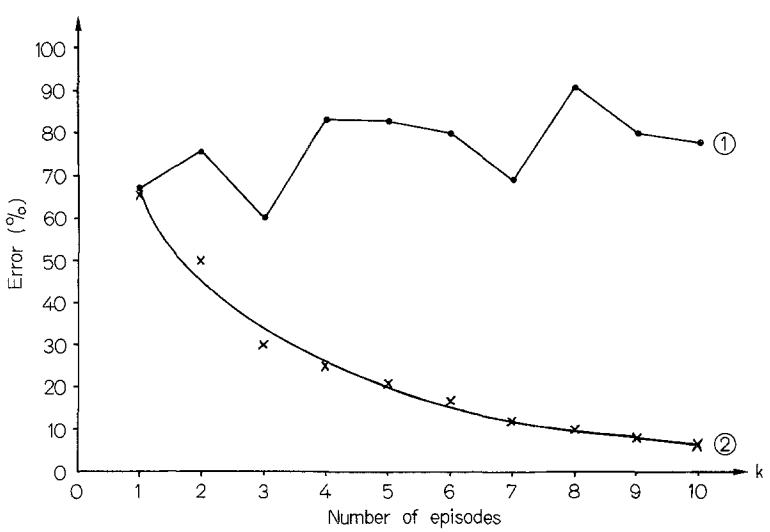

Fig. 2. Relative error ρ_k ① and absolute error a_k ② of classification as a function of the number of episode k

This shows directly that the misclassifications among the dropouts increase the relative error (because n_2 increases) and that the absolute error decreases more slowly. From the equation for the relative error we also get an estimation of n_2 as a function of the average relative error:

$$n_2 = \frac{d_{3\kappa}}{1-\rho} + \sum_{i<\kappa} d_{31i}$$

Thus with the worst case condition $\rho = 0.85$, n_2 can be calculated as the mean of $n_{2\kappa}$, in detail:

ρ (relative error)	0.75	0.80	0.85
n_2 (bipolar)	99	107	122
σ (variance)	14.4	24.2	39.5

Taking into account the high rate of the relative error we may estimate that the ratio of unipolar to bipolar affective disorder may be $\approx 1:1$.

Beyond that there are other independent estimations for the approximate size of n_2:

1. From the relation between both subgroups $(n_0 - n_2)/n_2 \approx 1$ we find $n_2'' \approx 125$;

2. From the dropouts one can calculate

$$n_2'' \approx n_2 + (\sum_{\kappa} r_\kappa)/2 - \sum_{\kappa} r_{3\kappa} = 135.$$

Here it is implied in our assumption that the process in the subgroups is similar to that of the whole group. This is not correct (Fig. 3): the relative change $(d_{\kappa+1} - d_\kappa)/d$ is nearly constant, but the fraction $r_{3\kappa}/r_\kappa$—that is the bipolar part of the dropouts—increases continuously, therefore n_2'' is not a valid estimation of n_2. On the contrary it is obvious that there are important fluctuations from 296.2 to 296.3 within the dropouts. A great deal of the decrease of the absolute error is due to this.

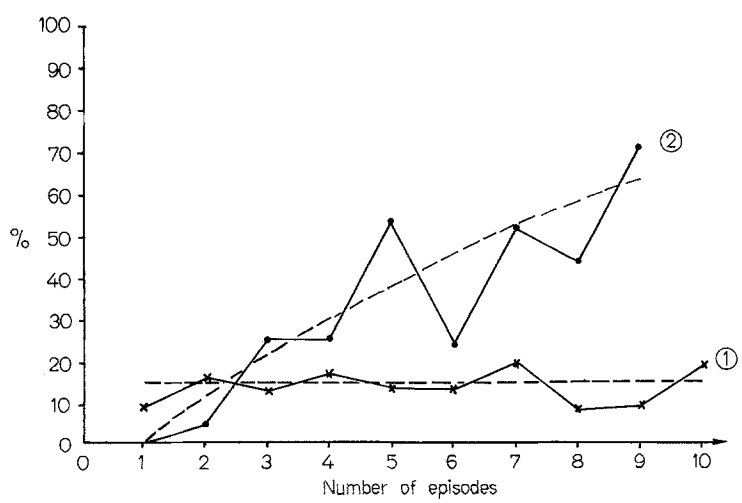

Fig. 3. Relative change of the size of the total sample ① and of the bipolar subgroup ②

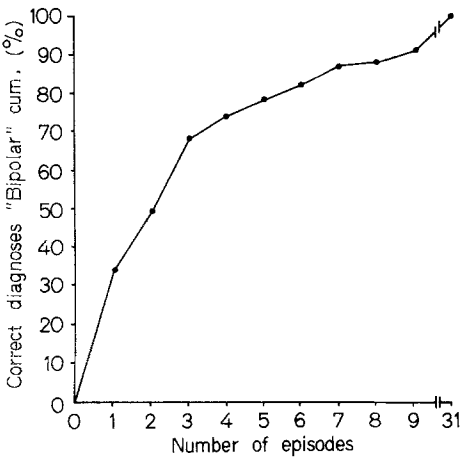

Fig. 4. Cumulative percentage of correct diagnosis of bipolar disorder as a function of episodes (empirical data $n = 95$)

Figure 4 summarizes the results obtained on the relationship between the number of the episode and correct diagnosis of bipolar disorder.

After three depressed episodes only 70% of all bipolar patients were recognized, after six episodes 83%. Therefore, we conclude that in general representative investigations should not be based on unipolar affective illness, excluding patients with one or more depressive episodes, because a diagnosis of unipolar depression (defined as a patient having three or more episodes) excludes 37% of the material and such a sample cannot be representative. Therefore we suggest that future studies should be based on the course and the genetics of affective illness and not only on a restricted class of the classical unipolar depressive index cases as stated by Perris (1966). If the term 'unipolar depression' is used synonymously with the original term 'monopolar depression' (designating every primary depression with one or more episodes), Perris' (1966) original definition has to be given up.

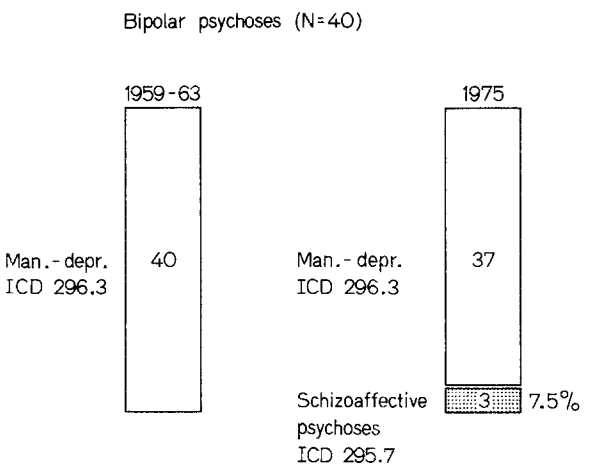

Fig. 5. Change of diagnoses 1959—1975

3.2 Change of Diagnosis of Bipolar Psychoses

A bipolar psychosis cannot change to monopolar but can change to a schizo-affective psychosis. We found such a change in three of 40 cases (7.5%) (Fig. 5).

Even in bipolar psychoses, which seem to form a nuclear group of affective illness, the future course of the illness may show the original sample to have been heterogeneous. The error of 7.5% is still remarkable and has to be taken into account in biochemical studies in this field.

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