

Long-term Stability of Subtypes in Schizophrenic Disorders: A Comparison of Four Diagnostic Systems

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Summary. The long-term stability of subtypes of schizophrenic disorders in 148 narrowly defined schizophrenic patients according to four diagnostic systems was compared. The patients were investigated longitudinally for 23 years on average (range 10–50 years). Patients who experienced only one episode and those who were permanently hospitalised were excluded on methodological grounds. Of the remaining 100 patients, a total of 461 episodes were classified into various subtypes according to the criteria of DSM-III-R, ICD-10, the positive/negative dichotomy, and Schneider's first-rank symptoms. It was found that long-term stability of subtype in schizophrenic disorder was not the rule but the exception. The frequency of stable course was found to be depend on the type of the initial episode. In most cases a subtype change occurred within the first few years of the illness with no clear direction. In later stages of the illness the relative frequency of episodes predominated by negative symptomatology increased. The findings were similar for DSM-III-R, ICD-10 and positive/negative dichotomy. Only in patients beginning without first-rank symptoms were more stable than non-stable courses found. The results of this study do not support the assumption that stable subtypes are nosological or etiopathogenetic subentities of schizophrenic disorders.

Key words: Schizophrenia – Schizophrenic subtypes – Long-term course – DSM-III-R – ICD-10

Introduction

The stability or lack of stability of subtypes during the long-term course of the disease may be one of the most relevant external validators of the validity of subclassification in schizophrenic disorders. The criteria of subclassification are based mainly on cross-sectional criteria (Marneros et al. 1992, Marneros and Andreasen 1992), but long-term stability is a *conditio sine qua non* for the correlation of subtypes with biological as well as with other non-symptomatological parameters (Goldstein and

Tsuang 1988, Kendler et al. 1985, Marneros et al. 1992, Strauss and Docherty 1979). As we have shown (Deister et al. 1990, Marneros et al. 1991b, 1992), in terms of the positive/negative dichotomy most patients were bimorphous during course, i.e. they show both positive and negative symptoms during the long-term course. Despite the outstanding clinical and theoretical relevance of "stability", reliable data on the long-term development of subtypes according to modern diagnostic systems are sparse (Gruenberg et al. 1985, Kendler et al. 1985, Fenton and McGlashan 1991). If only a minority of schizophrenic disorders are monomorphic, we must establish whether particular subtypes possibly characterise particular stages of the disease (Deister et al. 1990), or whether stability depends on the duration of the illness.

Various parameters have to be calculated to enable assessment of subtype stability during the long-term course. The most important parameters are: (1) number and annual frequency of episodes in regard to the type of the initial episode, (2) frequency of episodes having the same types as the initial episode, (3) distribution of various subtypes at different stages of the illness, (4) frequency of patients showing only one subtype during the whole course, (5) time and direction of any subtype change and (6) concordance of subtype from one episode to the next.

Material and Methods

Patients

This study is part of the Cologne Study (Marneros et al. 1986, 1988a, 1989, 1991a) on the long-term course and outcome of functional psychotic disorders. Of 402 patients personally examined and investigated longitudinally in this study, 148 were diagnosed as having schizophrenic disorder. The diagnostic criteria used in this study distinguish between "episode" (defined cross-sectionally) and "disorder" or "illness" (defined longitudinally). In order to make the statistical investigation more reliable, an episode was defined as the manifestation or remanifestation of psychopathological symptoms necessitating *inpatient treatment*. The diagnostic criteria for schizophrenic episodes are based on the symptomatological criteria of DSM-III for schizophrenic disorders, ignoring

Table 1. Features of population studied

Number of patients	148
Sex	
Male	86 (58.1%)
Female	62 (41.9%)
Sex distribution (m:f)	1:0.7
Age at onset (years)	
Arithmetic mean	27.7
Median	24.0
Standard deviation	10.6
Range	14–64
Length of observation period (years)	
Arithmetic mean	23.0
Median	25.0
Standard deviation	9.9
Range	10–50
Age at the end of observation time	
Arithmetic mean	50.7
Median	51.0
Standard deviation	13.2
Range	27–84
Number of episodes	
Total number (148 patients)	685
Episodes with sufficient informations (148 patients)	630
Episodes not ending in permanent hospitalisation (144 patients)	595
Episodes in patients without permanent hospitalisation (113 patients)	474
Episodes in patients without permanent hospitalisation and more than one episode during course (100 patients)	461

the criteria age at onset and 6 months duration. Of the four classification systems investigated in this study, DSM-III has the narrowest criteria for schizophrenic disorders, so that comparison of the various systems is not influenced by different *diagnostic* criteria. The diagnosis “schizophrenia” was made if only episodes fulfilling the criteria of a schizophrenic episode occurred during the whole observation time, with no affective or schizoaffective episode. That means that during the whole course no melancholic symptomatology (according to the DSM-III-R criteria of “major depression, melancholic type”) and/or manic symptomatology (according to the manic episode of DSM-III-R) occurred (Marneros et al. 1986, 1988a, 1989, 1991a).

The mean observation time was 23 years (Table 1), some 58.1% of the patients were male, and 41.9% female. The mean age at first manifestations was 27.7 years, at the end of observation period 50.7 years.

Methods

All available information about the patients was evaluated for the whole course (additionally to personal interviews with patients and with relatives also case records). For every episode, psychopathological parameters and non-symptomatological features such as sociodemographic variables, life events, treatment and prophylaxis were evaluated. For the evaluation of the psychopathological parameters the AMDP system (Arbeitsgemeinschaft für Methodik und Dokumentation in der Psychiatrie 1981) was used, with additional items from the Scale for Assessment of Negative Symptoms

(SANS, Andreasen 1983) and the Present State Examination (PSE, Wing et al. 1974). The items were assessed as “present” or “not present”. At the end of the observation time all patients were interviewed personally using standardised instruments to assess their long-term course and outcome (Marneros et al. 1991a).

The 148 patients had a total of 685 episodes. Because of the above-mentioned definition, “episode” was identical with “clinical admission”. In 630 episodes (92.0%, Table 1) the clinical data were sufficient to classify the episode. Thirty-five patients became permanently hospitalised (length of stay more than 3 years) and on methodological grounds they were excluded from all calculations regarding long-term course. Another 13 patients with only one manifestation of the illness (monoepisodic cases) were also excluded. The following results are therefore based on 100 patients, who had 461 episodes for which sufficient information was gathered during the total course of the illness (Table 1). The retrospective classification of episodes proved to be reliable if all available sources of information (case records, personal interviews of patients and relatives etc.) were used. Homogeneity of the material and of the case documentation was ensured (Marneros et al. 1991a). For every one of the investigated patients frequency, time, and direction of subtype change were ascertained. *Subtype change* was defined as change from one subtype to another within the same diagnostic system. Courses showing no subtype change were described as *stable*, i.e. in these cases all episodes occurring during course were of the same subtype as the initial episode. To estimate the distribution of the subtypes in different stages of the illness, the total course was divided in periods of 5 years. To investigate stability and subtype change from one episode to the next the kappa values were calculated.

For statistical evaluation the SPSS software was used.

Diagnostic Systems and Subtypes

The episodes were classified according to the criteria of four diagnostic systems: DSM-III-R (APA 1987), ICD-10 (WHO 1991), the positive/negative dichotomy (Andreasen and Olsen 1982) and Schneider’s first-rank symptoms (Schneider 1946–1980). The symptomatology occurring during the whole episode was assessed. Every episode was classified by the same clinical expert. “Pre-episodic alterations” (i.e. states usually called “prodromal states”), and “persisting alterations” (usually called “residual states”) were excluded from the evaluation; theoretical considerations on these two terms can be found in Marneros et al. (1991a).

For methodological reasons only the symptomatological criteria of the subtypes were considered; *time criteria were ignored*. This was the case especially in the residual type (DSM-III-R) and in the schizophrenic residuum (ICD-10). The aim of this study is the investigation of “stability” of subtypes during long-term course. If time criteria were included as an aspect of classification, investigation of stability would not be possible.

DSM-III-R

According to the DSM-III-R criteria for subtypes of schizophrenic disorders (APA 1987), the episodes were classified as disorganised type (295.1), catatonic type (295.2), paranoid type (295.3), residual type (295.6), or undifferentiated type (295.9, Table 2). An episode was classified as “residual type” if the symptomatological criteria of this type were fulfilled, regardless of the duration of the symptoms. For this reason, the term “residual” is enclosed in quotation marks throughout this paper.

ICD-10

According to the ICD-10 criteria for subtypes of schizophrenic disorders (WHO 1991), the episodes were classified as paranoid schizophrenia (F20.0), hebephrenic schizophrenia (F20.1), catatonic schizophrenia (F20.2), or undifferentiated schizophrenia

Table 2. Duration of observation time, number and annual frequency of episodes ($n = 100$)

Initial subtype	Number of patients	Duration of observation period (years, arithm. mean)	Number of episodes (arithm. mean)	Annual frequency of episodes (arithm. mean)
<i>DSM-III-R</i>				
Paranoid type	31	18.1	4.3	0.27
Disorganized type	7	18.4	5.3	0.43
Catatonic type	6	27.3	7.2	0.31
Undifferentiated type	33	22.9	5.4	0.27
"Residual" type	23	21.7	4.9	0.30
<i>ICD-10</i>				
Paranoid schizophrenia	48	18.7	4.5	0.29
Hebephrenic schizophrenia	7	18.4	5.3	0.43
Catatonic schizophrenia	6	27.3	7.2	0.31
Undifferentiated schizophrenia	28	24.4	5.5	0.26
"Residual" type	11	21.3	5.0	0.29
<i>Positive-Negative-Schizophrenia</i>				
Positive schizophrenia	50	19.0	4.8	0.30
Mixed schizophrenia	20	26.4	5.9	0.23
Negative schizophrenia	30	20.9	5.0	0.33
<i>First rank symptoms</i>				
First rank schizophrenia	24	22.0	5.4	0.28
Non-first rank schizophrenia	76	20.8	5.0	0.30

(F20.3). An episode was classified as "schizophrenic residuum" (F20.5) if the symptomatological criteria of this subtype were fulfilled, ignoring the time criteria. Post-schizophrenic depression (F20.4) and schizophrenia simplex (F20.6) were not considered in this study. Post-schizophrenic depression can be diagnosed only if during the last 12 months a schizophrenic symptomatology was present and if the symptomatology fulfilling the ICD-10 criteria of depressive episode was prominent. The ICD-10 subtype 'schizophrenia simplex' is based on insufficiently clearly defined symptoms.

Positive Versus Negative Schizophrenia

The episodes were classified according to the criteria of Andreasen and Olsen (1982) as "positive", "negative" or "mixed". The classification was made using the global ratings of the Scale for the Assessment of Negative Symptoms (SANS, Andreasen 1983) and the Scale for the Assessment of Positive Symptoms (SAPS, Andreasen 1984). The reliability of these scales is well documented (Andreasen 1989). "Negative symptoms" were the following: alogia, affective flattening, anhedonia-asociality, avolition-apathy and attentional impairment. An episode was categorized as "negative" if at least two of the negative symptoms were present to a marked degree (score 4 or higher). An episode was classified as "positive" if at least one of the positive symptoms (hallucinations, delusions, positive formal thought disorder, bizarre or disorganised behaviour) was a prominent part of the episode and none of the negative symptoms was present to a marked degree. A "mixed" schizophrenic symptomatology was diagnosed if the criteria for neither positive nor negative episodes or the criteria for both types of episodes were fulfilled. The classification of the schizophrenic episodes into positive, negative and mixed was made according to the most prominent symptomatology rather than according to the presence or absence of symptoms. In other words, a positive episode could include some negative symptoms which, however, were discrete, not prominent or not intensive; and

equally a negative episode could include some positive symptoms which also were not prominent, intensive or severe. The retrospective classification of the episodes proved to be reliable if only the five global ratings (such as 'affective flattening'), but not every one of the single sub-items was considered (Marneros et al. 1992).

Schneider's First-Rank Symptoms

The episodes were classified into those with and those without first-rank symptoms according to the definitions of Kurt Schneider (1946-1980). First-rank symptoms are the following: (1) delusional perceptions, (2) auditory hallucinations in which a voice keeps up a running commentary on the individual's behaviour or thoughts, (3) auditory hallucinations in which two or more voices converse with each other, (4) auditory hallucinations in which the patient hears his own thoughts spoken aloud, (5) thought broadcasting, (6) thought insertion, (7) thought withdrawal and (8) other feelings of being influenced by outside forces.

An episode was classified as "first-rank schizophrenia" if at any time during the episode one or more of these symptoms were present, independent of their duration intensity or combination with other symptoms. An episode was classified as "non-first-rank schizophrenia" if none of the above-mentioned symptoms was found at any time during the episode.

Results

Number and Annual Frequency of Episodes

Table 2 shows the duration of observation time and the number and annual frequency of episodes by the type of the initial episodes. The average number of episodes during the course varies from 4.3 in patients beginning with a DSM-III-R paranoid episode to 7.2 in patients

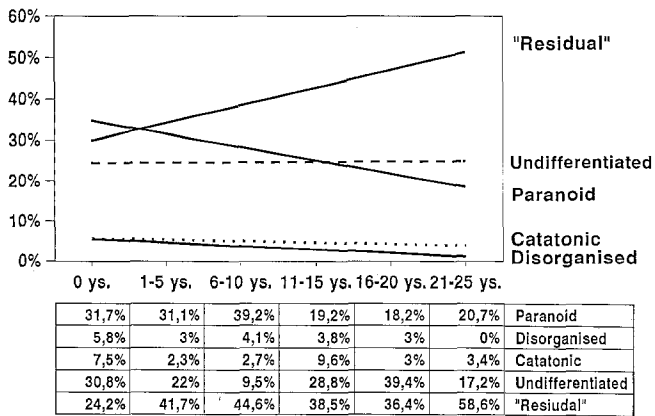


Fig. 1. DSM-III-R: frequency of various subtypes in 5-year periods (relative numbers and regression lines)

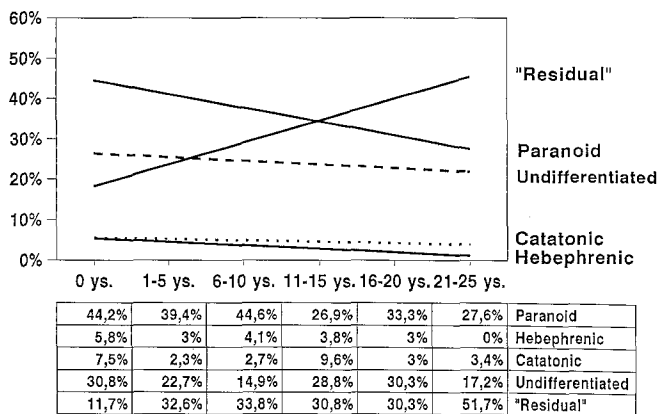


Fig. 2. ICD-10: frequency of various subtypes in 5-year periods (relative numbers and regression lines)

initially having a catatonic episode. In interpreting these results one has to remember that patients having only one episode during the course were excluded from evaluation. To achieve better comparability among the various subtypes, for every patient the annual frequency of episodes (total number of episodes divided by duration of illness in years) was calculated (Marneros et al. 1988a). According to DSM-III-R, the lowest annual frequency of episodes was found in patients whose first episode was a paranoid or an undifferentiated one (mean 0.27), the highest in those with initial disorganised episode (mean 0.43). According to ICD-10, patients with a hebephrenic initial episode had the highest annual frequency of episodes (mean 0.43). Patients with positive and patients with negative first episodes had similar annual frequencies (0.30 and 0.33 respectively). In this system, patients with a mixed initial episode had the lowest annual frequency of episodes. Patients with and without first-rank symptoms during the initial episode did not differ with regard to the annual frequency of episodes.

Distribution of Subtypes During Long-term Course

The distribution of the various subtypes was calculated for each 5-year period of the course (Figs. 1-4). Only

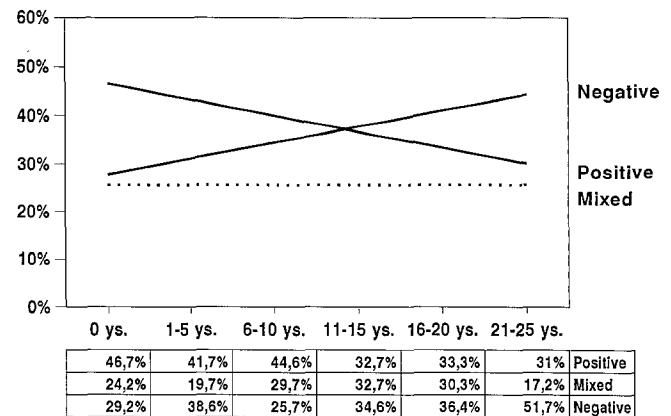


Fig. 3. Positive-negative-schizophrenia: Frequency of various subtypes in 5-year periods (relative numbers and regression lines)

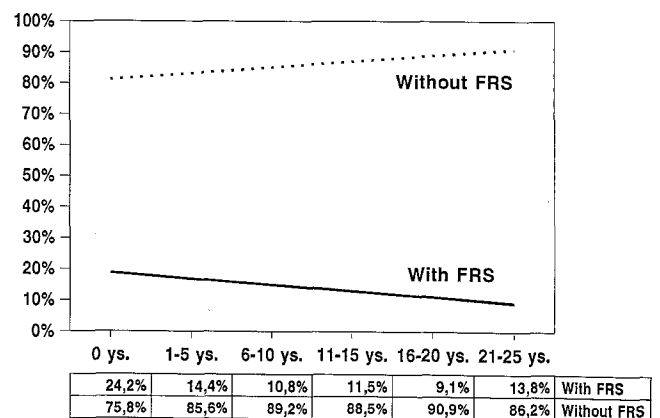


Fig. 4. First-rank schizophrenia: frequency of various subtypes in 5-year periods (relative numbers and regression lines)

episodes occurring in the first 25 years of the illness were considered. For each subtype, the tendency (linear regression) over the course was estimated. Using the DSM-III-R criteria, it was found that paranoid episodes decreased in frequency over time while episodes with "residual" symptomatology increased (Fig. 1). The proportions of undifferentiated, catatonic and disorganised episodes remained rather stable during the long-term course.

Similar results were found for ICD-10: paranoid episodes became less frequent and "residual" episodes became more frequent during the long-term course (Fig. 2).

Positive schizophrenic symptoms were found to be more frequent in the earlier stages of the course, while negative schizophrenic episodes more often occurred in the later stages (Fig. 3). The percentage of episodes with and without first-rank symptoms showed no relevant variation during the course (Fig. 4).

Frequency of Subsequent Episodes Having the Same Type as the Initial Episode

For DSM-III-R, ICD-10 and positive/negative dichotomy, only in one subtype (ICD-10 paranoid type) were more than half of the subsequent episodes of the same

Table 3. Parameters of stability and syndrome change during long-term course ($n = 100$)

Initial subtype	Patients with stable course	Frequency of episodes with the same type as initial	Most frequent direction of first change	Year of first change (arithmetic mean)
<i>DSM-III-R</i>				
Paranoid type ($n = 31$)	14 (45.2%)	50.6%	"Residual"	7.5
Disorganized type ($n = 7$)	—	22.7%	"Residual"	1.9
Catatonic type ($n = 6$)	—	16.2%	"Residual"	5.8
Undifferentiated type ($n = 33$)	3 (9.1%)	22.7%	"Residual"	7.3
"Residual type" ($n = 23$)	4 (17.4%)	53.0%	Undifferentiated	4.9
<i>ICD-10</i>				
Paranoid ($n = 48$)	18 (37.5%)	54.8%	Undifferentiated	6.2
Hebephrenic ($n = 7$)	—	22.7%	Undifferentiated	1.9
Catatonic ($n = 6$)	—	16.2%	"Residual"	5.8
Undifferentiated ($n = 28$)	7 (25.0%)	36.6%	Paranoid	8.9
"Residual" ($n = 11$)	—	45.5%	Paranoid	5.2
<i>Positive-negative-schizophrenia</i>				
Positive schizophrenia ($n = 50$)	18 (36.0%)	52.4%	Negative	2.8
Mixed schizophrenia ($n = 20$)	2 (10.0%)	28.6%	Negative	8.8
Negative schizophrenia ($n = 30$)	6 (20.0%)	46.2%	Positive	4.1
<i>First rank symptoms</i>				
First rank schizophrenia ($n = 24$)	3 (12.5%)	13.2%	—	6.8
Non-first rank schizophrenia ($n = 76$)	55 (72.4%)	87.8%	—	8.2

subtype as the initial episode (Table 3). The lowest frequency of subsequent episodes of the same subtype as the initial episode (16.2%) was found in patients beginning with a catatonic episode. In patients beginning with non-first-rank schizophrenia, only 12.2% of subsequent episodes featured first-rank symptoms. However, subsequent first-rank symptoms are equally rare (12.1%) in patients beginning with first-rank schizophrenia.

Frequency of Stable Courses in Relation to the Type of Initial Episode

Most of the patients had episodes of more than one subtype in the long-term course. The frequency of patients with a "stable" course differs among the subtypes (Table 3). Patients beginning with a DSM-III-R paranoid episode showed stable courses in 45.2% of cases, those beginning with an ICD-10 paranoid subtype in 37.5%. In some subtypes (DSM-III-R: disorganised and catatonic; ICD-10: hebephrenic, catatonic and "residual") no instances of stable course at all were found. Patients beginning without first-rank symptoms again were an exception: 72.4% of them had no first-rank symptoms during the whole course (Table 3).

Stability in Regard to the Number of Episodes

The type of every episode was compared with the type of the following episode. Because of the varying numbers of episodes, successively decreasing numbers of patients were available for these comparisons. No clear relation-

ship between kappa values and number of episodes was found during the long-term course (Table 4).

Time and Direction of Subtype Change

Table 3 shows the most frequent direction of the first subtype change, and the average interval between onset of the illness and first subtype change, for each initial subtype. In DSM-III-R, for all groups of initial subtypes as a whole, the most frequent direction of first subtype change was to "residual" symptomatology. Patients beginning with a "residual" episode most commonly changed to an undifferentiated episode. The first change occurred earliest in patients beginning with a disorganised subtype (average 1.9 years), while in patients with a paranoid initial episode the first subtype change occurred significantly later (mean 7.5 years).

For ICD-10 no clear pattern of first subtype change was found (Table 3). Patients beginning with a paranoid or a hebephrenic subtype mostly changed to undifferentiated types, undifferentiated and "residual" types to paranoid types, and catatonic subtypes in most cases firstly changed to "residual" episodes. Patients beginning with the undifferentiated subtype showed the latest change of all investigated subtypes (average 8.9 years after onset). As for the positive/negative dichotomy, patients with a positive initial episode were found to change to another subtype significantly earlier (mean 2.8 years) than patients beginning with a mixed schizophrenic symptomatology (mean 8.8 years). Patients beginning with and without first-rank symptoms showed no relevant difference in the time to first change.

Table 4. Kappa-values during long-term course ($n = 100$)

Episodes	DSM-III-R	ICD-10	Positive-negative	First rank symptoms
1st vs 2nd ($n = 100$)	0.24	0.30	0.21	0.05
2nd vs 3rd ($n = 71$)	0.17	0.29	0.23	0.41
3rd vs 4th ($n = 49$)	0.49	0.50	0.56	0.69
4th vs 5th ($n = 37$)	0.54	0.54	0.59	0.52
5th vs 6th ($n = 26$)	0.62	0.50	0.25	0.63
6th vs 7th ($n = 18$)	0.43	0.54	0.66	0.43
7th vs 8th ($n = 15$)	0.51	0.40	0.42	0.43
8th vs 9th ($n = 12$)	0.62	0.68	0.26	1.00
9th vs 10th ($n = 7$)	0.55	0.41	-0.09	1.00

Discussion

The investigation of longitudinal development of subtypes is plagued by methodological problems (Marneros et al. 1992, Carpenter et al. 1991, Deister et al. 1990, Marneros and Andreasen 1992, Häfner and Maurer 1991). Despite the outstanding clinical importance of this research, there are no reliable results in the literature.

As we had already shown for positive vs. negative schizophrenia (Marneros et al. 1991b, 1992), commonly more than one DSM-III-R and ICD-10 subtype occurred during the long-term course. Although this was true for all subtypes of initial episode – with the exception of patients beginning without first-rank symptoms – relevant differences were found for different subtypes. Stable courses, i.e. courses having only one type of episode, were found most frequently in patients with an initial paranoid episode, while in initially catatonic, hebephrenic and disorganised subtypes of courses were stable, i.e. none featured only one type of episode (Marneros et al. 1988b). This fully agrees with the results of Kendler and co-workers (1985).

These differences could be an effect of different numbers of episodes or different annual frequency of episodes. It was found that the annual frequency of episodes varies from 0.23 episodes per year for mixed schizophrenic episodes, i.e. about one episode every 4 years, to 0.43 episodes per year in hebephrenic/disorganised type, i.e. about one episode every 2 years. In interpreting these results, one must remember that on methodological grounds monoepisodic patients and permanently hospitalised patients were excluded. The highest discrimination with regard to annual frequency was found for ICD-10. The proportion of total episodes having the same subtype as the initial episode also differed. The highest frequencies were found for paranoid and “residual” subtypes, the lowest in patients with catatonic initial episodes. These results show that stability is not a function of number of episodes.

Not only frequency of subtype change was found to differ among the groups investigated but also time and direction of syndrome change. Patients beginning with a hebephrenic or a disorganised episode experienced another type of episode, mostly an undifferentiated one (ICD-10) or a “residual” one (DSM-III-R), after only 2

years on average. Patients with a paranoid initial episode experienced their first episode of another type significantly later in the course of the disease, but mostly in the same direction as patients with hebephrenic initial episode. Despite this, first and subsequent changes of subtype could, in principle, be in any direction, and no clear patterns were found.

The direction of changing was interchangeable in some cases; ICD-10 paranoid schizophrenia most frequently changed to the undifferentiated subtype, and vice versa.

We also proved the hypothesis that specific subtypes characterise specific stages of the illness, that means whether paranoid or positive episodes are typically for the earlier stages of a schizophrenic disorders, whereas in later stages negative or “residual” types predominate. Episodes with mainly negative schizophrenic symptomatology increased in frequency as the disorder went on, while the frequency of episodes with only or predominantly productive psychotic symptomatology decreased. This was true for all four diagnostic systems investigated. It must again be pointed out that in the present study only symptomatology during narrowly defined episodes of the illness was investigated. The occurrence and the nature of persistent alterations (so-called “residual states”; Marneros et al. 1991a), which are frequently characterised by the predominance of negative schizophrenic symptomatology were not considered for methodological reasons.

Given that negative symptomatology is more common in later stages of the illness than in earlier stages, the concordance of subtypes from one episode to the next – calculated using kappa statistics – might be expected to become higher for higher numbers of episodes. However, this was not consistently the case; there was no clear tendency to more stability later in the course. It was found, however, that in all four diagnostic systems the lowest kappa values were found in the first three episodes of the illness. The validity of the kappa values for concordance between the eighth and ninth episodes and between the ninth and the tenth episodes is limited by the small number of patients with such a high number of episodes.

All in all, it can be concluded that long-term subtype stability in schizophrenic disorders is not the rule but the exception. In most cases, there is a change of subtype in

the first early years of the illness, with no clear direction of change. Patients with an initial episode characterised by productive psychotic symptomatology were the most likely to display a stable long-term course. In later stages of the illness the frequency of episodes dominated by negative symptomatology increased. The results of this study therefore do not support the assumption that stable subtypes are nosological or aetiopathogenetic subentities of schizophrenic disorders.

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