SPECIAL ISSUE

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The epidemiology of onset and course of schizophrenia

Abstract Traditionally the heterogeneity of schizophrenia was dealt with by subdividing the syndrome into different subtypes. However, due to lacking standards, the result was an immense variety of subtypes partly based on cross-sectional assessments, partly taken the whole course between onset, resp. first admission and outcome after many years into account. Some solutions were based on symptomatology only, others also relied on social characteristics as the ability to fulfil different roles in family and the world of employment. So it is not surprising that the number of subtypes ranges from two up to more than 70. As one possible solution Carpenter and Kirkpatrick (1988) suggest that attempts to subdivide the schizophrenic syndrome should concentrate on few significant parts of the course thought of to represent specific disease processes.

Based on two epidemiological studies finding about the onset, middle course and late course of schizophrenia are presented. In three quarter of the cases the onset of the first psychotic episode in schizophrenia is preceded by a prodromal phase with a mean length of about five years. The earliest signs of the disorder are depressive and negative symptoms. Early depressive symptoms predict higher overall symptom scores in the first illness episode and lower scores for affective flattening in the medium-term course. There is no decrease in the number of patients with acute symptomatology over fifteen years after first hospital admission, rather there is a tendency of an increase. With respect to social abilities we found a significant increase of disability over time. But the change already takes place during the first five years. Approx. 60 % of those falling ill with schizophrenia become chronic and approx. 25 % will recover during the first five to six years.

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Introduction

When talking about the epidemiology of onset and course of schizophrenia the emphasis is on the identification of generally valid patterns concerning the way in which the illness starts and proceeds over time. Keeping in mind that schizophrenia seems to be a heterogeneous rather than a homogeneous illness group efforts to reduce the complexity of syndrome patterns mainly came about through the formation of schizophrenic subtypes.

Attempts to define schizophrenic subtypes have a long tradition. In the 1899 edition of Kraepelin's textbook three formerly separate disease entities – hebephrenia, catatonia and paranoid dementia – although substantially differing with respect to defining characteristics were combined as subgroups of what he called dementia praecox (Strömgren 1982) on the basis of their common chronic deteriorating course. A few years later a fourth group, 'simple dementia', was added. This division of schizophrenia into different subgroups has even been extended and kept up since then and has become established in the diagnostic system ICD of the WHO as well as in its American counterpart DSM. But, in contrast to the Kraepelinian conceptualisation, since Bleuler, the assignment to a certain subtype above all has been based on the cross-sectionally assessed clinical manifestation of the illness rather than on common characteristics of course and outcome.

While the 'classic' schizophrenic subtypes turned out to be rather instable over time (Goldberg and Weinberger 1995), thus raising doubts about their validity (Fenton and McGlashan 1991; Marengo et al. 1991; Tienari and Wynne 1995), there have been other attempts to subdivide schizophrenia using, for example, the dichotomisation between positive and negative symptoms (Andreasen and Olsen 1982) and linking them to specific pathophysiological processes (type I vs. type II schizophrenia; Crow 1980; 1985).

While these distinctions were also based upon symptoms seen cross-sectionally, longitudinal principles were reintroduced by the comparison between the two basic concepts of acute and chronic schizophrenia, resting upon differences in the constellation of presenting symptoms, type of onset and subsequent course (Tienari and Wynne 1995). An additional approach emerged from empirical studies, using measures from the whole course of the schizophrenic illness (Fig. 1). In contrast to the concepts mentioned above, which were almost completely based on characteristic symptoms, these approaches have often applied di-

verging concepts of course descriptions, including psychopathology as well as personality traits, impairments and measures of social functioning.

In their book "Schizophrenie – Eine verlaufs- und sozialpsychiatrische Langzeitstudie", Huber et al. (1979) describe a total of 73 different mono- and polyphasic course types, that could be reduced to twelve in combining related types (Fig. 1). Their descriptive categorisation of types was based on data retrospectively collected from 502 patients 9–59 years after index admission into the mental hospital in Bonn (Germany), by applying a com-
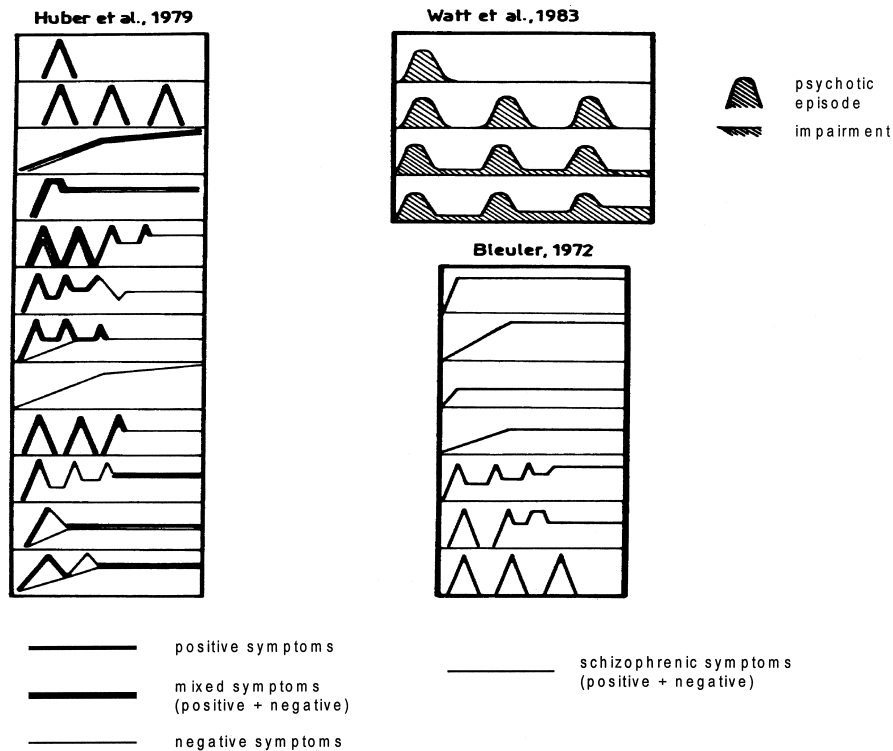
Huber et al. (1979)	
course type	
description	%
monophasic	10
polyphasic	12
chronic pure	4
one manifestation to pure residues	6
phasic to pure residues	10
phasic with 2nd positive bend to pure residues	6
phasic or simple to structural deformities	6
simple to pure residues	5
phasic to pure residues	13
phasic to mixed residues	10
simple to mixed residues	7
phasic or simple to defect psychoses	11

Watt et al. (1983)	
course type	
description	%
one episode – no impairment	16
more than one episode – no/minimal impairment	32
more than one episode – impairments – no return to normality	9
more than one episode – increasing impairments – no return to normality	43

Bleuler (1972)	
course type	
description	%
acute onset - chronic end state	1
chronic onset - chronic end state	12
acute onset – moderate/ mild end state	2
chronic onset – moderate/ mild end state	23
phasic – chronic end state	9
phasic – moderate/mild end state	27
phasic - recovery	22
atypical courses	4

Fig. 1 Course types in schizophrenia

bination of course characteristics and psychopathological measures.

Watt and colleagues (1983) conducted a five-year follow-up study in a cohort of 121 schizophrenic patients – 48 of them were first admissions – diagnosed by means of the PSE (Wing et al. 1974). According to their findings the course and outcome in schizophrenia could be roughly subdivided into four groups: one group, after a single attack, remained symptom-free over the whole period of observation; in a second group further discrete relapses occurred, but between attacks the patient remained symptom-free. In the remaining two groups the patients did not recover between relapses, in the more severe of these groups the residual symptoms increased following each exacerbation.

In his Burghölzli study, M. Bleuler (1972) separated four simple and three phasic course types (adding other groups of atypical courses) based on clinical observations from 208 patients over a period of 20 years. The assessment was realised on the basis of psychopathology and single symptoms as well as social, occupational and family conditions.

Similar attempts to classify courses of schizophrenia were made by Changhui et al. (1995), Ciompi and Müller (1976), Harding (1988), Hutter (1940), Johanson (1958), Leon (1989), Marengo et al. (1991), Marneros et al. (1991), Mason et al. (1995), Müller (1951), Rey and Bailer (1996) and Thara et al. (1994), to mention just a few.

Although at least the graphical representation of course patterns in these studies suggests a few similarities, the differing number of course types and their relative frequencies imply different explanations. It is obvious that the question whether one type corresponds to another cannot be answered without clearly defined definitions of trends and course patterns and comparable definitions of symptoms. However, studies differ with respect to study populations, periods of observation, operationalisations of course and outcome criteria, sources of follow-up data and number of cross-sectional assessments (for more details also see Harding et al. 1987; Marengo 1994; an der Heiden 1996). Therefore, attempts to 'synchronise' course prototypes from different studies (Bleuler et al. 1976; Harding 1988) remain problematic.

To overcome at least some of the difficulties, Carpenter and Kirkpatrick (1988) suggest restricting the definition of putative course subtypes to certain 'epochs'. In fact, many factors associated with certain stages in illness development – such as age or type of onset, early morbid or premorbid syndromes/symptoms/signs, interepisode residual impairments, long-term outcome, late course improvement – show so many differences between patients that they may equally well serve as criteria for subdividing the syndrome of schizophrenia. For Carpenter and Kirkpatrick, the three epochs of main interest are onset, middle course and late course. Within this approach, instead of presuming that, for instance, the combination of insidious onset, prolonged psychosis and severe outcome defines a certain subtype, one could view each of these factors as an important tool that may represent a specific disease process; one would make no a priori assumption about the relationship of each feature to those of other epochs.

In applying Carpenter's and Kirkpatrick's approach, the purpose of the present paper is to summarise some of the results we were able to work out with respect to the main epochs of schizophrenia while conducting two epidemiological studies on onset, course and outcome of the illness.

Samples

Concerning onset and early/middle course of schizophrenia we assessed a large, population-based sample of broadly defined cases of schizophrenia (ICD 295, 297, 298.3/4) from a semi-rural, semi-urban German population of about 1.5 million inhabitants in the south-western part of Germany (for greater detail see Häfner et al. 1993).

The sample comprised 232 subjects with first episodes (ABC study sample), that is 84 % of 276 first-admission cases screened for interview in the age range 12–59 years. The inclusion criterion for the first-episode sample was absence of positive symptoms of more than 13 days' duration before the index episode.

On the basis of internationally accepted instruments, we have developed a semi-structured interview for the retrospective assessment of the onset and early course of schizophrenia, the so-called IRAOS (Häfner et al. 1992; Häfner et al. 1999), that might provide information on indicators of the onset of schizophrenia at four different levels: (a) specific and non-specific symptomatology; (b) psychological impairments, cognitive and social deficits; (c) changes in social life; and (d) help seeking behaviour.

A subsample of 115 patients of the ABC study sample was followed-up prospectively for a period of five years after first hospital admission with cross-sectional assessments at 0, 6 and 12 months, 2, 3 and 5 years.
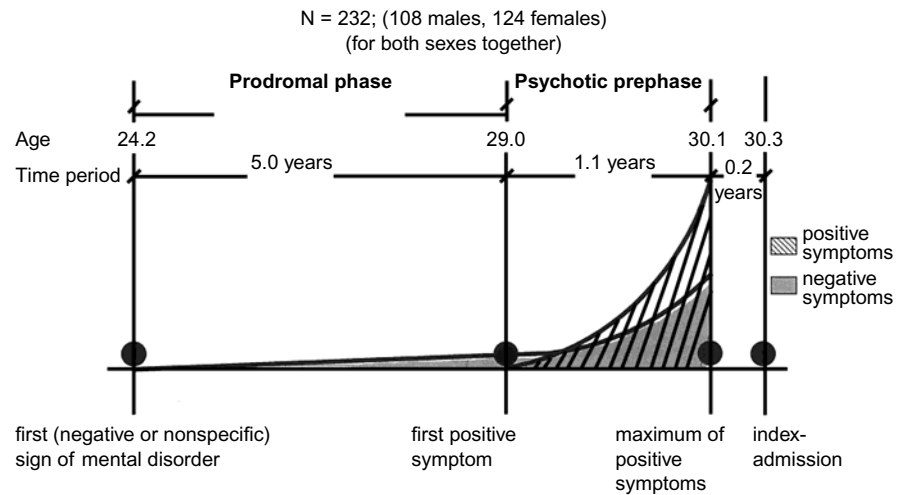
Additionally, to learn more about long-term course and outcome of schizophrenia we have carried out a 14/15, five-year follow-up of patients of the Mannheim cohort of the former WHO 'Disability' Study (an der Heiden et al. 1996; Jablensky et al. 1980). This study is also part of the WHO ISoS study (Sartorius et al. 1996).

In the beginning the study population consisted of a representative first-admission sample of 70 patients with residence in Mannheim, Heidelberg, and the Rhine-Neckar County – an area that is also part of the catchment area of the ABC study – with a total population of approx. 900 000 inhabitants; 56 of them could be traced and interviewed 14 years after index admission.

In contrast to most of the other investigations on this subject our study has some features that seem to be better suited to learn more about long-term course and outcome of schizophrenia (an der Heiden et al. 1995):

– It was designed as a real prospective first admission study. The project started in 1978, involving seven cross-sections during the first five years from first hospital admission and first assessment on. So, when we started with the long-term follow-up of the cohort, data

Fig. 2 The prephases of schizophrenia from first sign of mental disorder to first admission

N = 232; (108 males, 124 females)
(for both sexes together)

Onset of schizophrenia

Traditionally, type of onset has played an important part in the epidemiology of schizophrenia. Schizophrenics with an acute onset seem to have a more favourable course than schizophrenics with an insidious onset (Hubschmid and Ciompi 1990). There have been lots of studies to validate the importance of type of onset by assessing short- and long-term outcome, prediction of treatment response and other course relevant data. From that point of view, type of onset seems to be well suited for the classification of schizophrenic patients from an epidemiological point of view.

However, the exact determination of the onset of schizophrenia is one of the most difficult tasks (Häfner and Maurer 1993; Zedlick et al. 1993). This is because the very onset of the disease is often not marked by psychotic symptoms in a narrow sense but rather by unspecific symptoms like irritability, restlessness and moodiness. Until recently there was hardly any agreement as to which symptoms characterise the beginning of schizophrenia nor how to operationalise type of onset.

on short- to medium-term course were already available and did not have to be collected retrospectively.
– Instead of relying on a single assessment for outcome assessment 14 years after index-admission, we carried out another two cross-sectional assessments 9 and 18 months after the 14-year follow-up. So, in total, data from ten cross-sectional assessments were at our disposal, prospectively collected and covering a period of 15.5 years.
– The main construct variables – signs and symptoms, impairments and disabilities – were collected with the same instruments at each of the ten cross-sections. In addition, to fill the gap between the 5-year and the 14-year assessment, an adaptation of the IRAOS interview (Häfner et al. 1992; Häfner et al. 1999) from the ABC-study was administered.

The prephases of schizophrenia from first sign to first admission

With the help of the IRAOS we were able to identify different milestones in the early development of schizophrenia, thus subdividing the period between the first sign of the illness until first hospital admission into several phases.

As illustrated in Fig. 2, the early phase of schizophrenia may be separated into a prodromal and a psychotic prephase. Endpoint of the psychotic prephase is the maximum of the psychotic episode. On average, there is another short gap between the maximum of the psychotic episode and the first hospital admission, but considerable time can still elapse in individual cases until first professional help starts.

Schizophrenia begins with the first sign, no matter what type (positive, negative or non-specific), indicative of the disorder and is followed by the first negative and first positive symptom, the latter marking the end of the prodromal phase.

This earliest illness phase in our study had a mean length of 5 years. The psychotic prephase from the first positive symptom to the climax of the first episode – operationalised by a maximum of positive symptoms – lasted on average 1.1 years. First admission took place on average some 2 months later.

How does schizophrenia begin and what are the first signs of the illness?

In 77 % of all cases the first sign of the disorder appeared before the age of 30, in 41 % before the age of 20 and in 4 % as early as before the age of 10 (Fig. 3). The main period of risk for the onset of schizophrenia extended from ages 15 to 30 years, thus coinciding with the main period of social achievement in life.

At 68 % the insidious type of onset (= earliest continuous sign of the illness more than one year before maximum of psychotic symptoms) was most frequent. The acute type

ABC first episode sample:

	N = 232	males N = 108	females N = 124
	%	%	%
Age at onset of the earliest sign			
< 30 years	77	82	73
< 20 years	41	46	37
< 10 years	4	7	2
type of onset			
insidious / chronic (> 1 year)	68	70	65
subacute (> 1 month ≤ 1 year)	15	11	18
acute (≤ 1 month)	18	19	17
type of first symptom			
negative / unspecific	73	70	76
positive	7	7	6
both	20	22	19

Note: no significant gender differences in all the variables listed above

Fig. 3 Onset of schizophrenia

(= maximum of psychotic symptoms within one month after earliest sign of the disorder) was observed in 18 % and the subacute type (= earliest sign more than one month but less than one year before the maximum of psychotic symptoms) in about 15 %.

In 73 % of all cases schizophrenia began with a negative or a non-specific symptom and only in 7 % with a positive symptom. In 20 % symptoms of both categories appeared more or less simultaneously, that is, within the same month. From the 232 patients of the first episode sample, only 27 % showed no prodromal phase.

When asking for the first ever symptom, most often, with some 19 %, patients reported *restlessness* and *depression* (Table 1). *Anxiety* and *troubles with thinking and concentration* were rated next with some 18 % and 16 %, respectively, followed by *worrying* and *lack of self-confidence* and *energy*. In total, this finding indicates that schizophrenics tend to develop symptoms associated with a risk of social impairment as soon as onset has occurred and, thus, well before the first psychotic episode and first admission take place.

As it can be seen from Table 1 there were no positive symptoms among the first ever rated symptoms. Instead, the majority of those symptoms belong to one of two dimensions:
– Negative symptoms, partly indicative of social impairment, such as loss of energy, slowness, difficulties in thinking and concentration.
– Affective symptoms, such as depressive mood, lack of self-confidence and anxiety.
This means that the onset of schizophrenia is frequently

Table 1 The ten most frequent earliest signs of schizophrenia (independent of the course) cited by the patients

IRAOS signs and symptoms[1]	Total (n = 232) %	Men (n = 108) %	Women (n = 124) %
Restlessness	19	15	22
Depression	19	15	22
Anxiety	18	17	19
Trouble with thinking and concentration	16	19	14
Worrying	15	9	20*
Lack of self-confidence	13	10	15
Lack of energy, slowness	12	8	15
Poor work performance	11	12	10
Social withdrawal, distrust	10	8	12
Social withdrawal, communication	10	8	12

[1] based on closed questions; multiple counting possible
* $p < 0.05$

characterised by two symptom categories that are not specific to the disorder, but which are of decisive importance for the later course and the patient's quality of life.

Early depression

A high prevalence of depressive symptoms in patients with schizophrenia was also found in some other studies (e. g. McGlashan and Carpenter 1976; Möller and von Zerssen 1986; Plasky 1991; Siris 1991).

There are several possible explanations for the relationship between depressive symptoms and schizophrenia: (1) depression is a component of the schizophrenic syndrome (Bleuler 1911; Knights and Hirsch 1981; Koreen et al. 1993) and might, therefore, be a direct expression of the illness; (2) depression may be interpreted as a reaction of the ill person to schizophrenic symptomatology; and (3) depression is a side effect of neuroleptic treatment (Floru et al. 1975; van Putten and May 1978).

The second hypothesis seems less probable – at least in the early illness phase – because, as we have shown, in most cases depressive symptoms occur long before psychotic symptoms. Neuroleptically induced depression also seems not very plausible as in our cohort only 19 % of the patients reported a neuroleptic treatment before hospital admission. As the possibility of a misdiagnosis of depressive symptoms can be excluded to a large extent because of the design of our study, we consequently presume a strong connection between depressive symptoms with the symptoms of the illness in schizophrenia.

After depressive symptoms obviously turned out to belong to the earliest signs of schizophrenia, we tried to determine its overall frequency and development in the early phase until first admission. We based our analysis on four diagnostically relevant symptoms in the IRAOS with presumably small overlap with the negative syndrome: *de-*

Table 2 Comparison of four depressive IRAOS items in patients and controls – lifetime prevalence by age at first admission of schizophrenic patients

IRAOS item	schizophrenics (N = 57) %	controls (N = 57) %	Chi^2 test	relative risk
Depressive mood	70.2	19.3	***	3.6
Feelings of guilt	33.3	10.5	**	3.2
Lack of self-confidence	59.4	12.3	***	4.8
Suicide attempt	12.3	8.8	n. s.	1.4

n. s. = not significant, ** = $p < 0.01$, *** = $p < 0.001$

pressive mood, *feelings of guilt*, *lack of self-confidence* and *attempted suicide*. 83 % of the total first-episode sample (N = 232) suffered from depressive mood for at least two weeks before first admission.

Continuously persisting depressive symptoms were most frequent with 39 %, while the recurrent type was in second place with 34 %. Occurrences of a single depressive episode were rather rare (8 %). On average, depressive mood appeared for the first time some 52 months before first hospital admission; feelings of guilt and lacking self-

confidence were noted for the first time on average 34 and 35 months before, respectively.

A comparison of a representative subsample of 57 schizophrenic patients from our ABC sample with 57 controls matched for age and sex and drawn from the city of Mannheim's population register shows that the cumulative prevalence of depressive symptoms, except attempted suicide, is three to almost five times higher for schizophrenics than in controls (Table 2). Attempted suicide shows an excess of nearly 50 % in schizophrenics, not significant because of the small case numbers. However, it points to an early suicide risk before the first treatment contact in schizophrenia.

To study the predictive power of early depressive symptoms on the first illness episode and 5 years later, we formed two groups: patients with and without depressive mood in the early course of schizophrenia.

The group experiencing depressive mood in the prephase has also a significantly elevated depression score (PSE-CATEGO; Wing et al. 1974) in the first psychotic episode as well as a higher level in global psychopathology (PSE-CATEGO total score), the latter accounted for by the specific and non-specific neurotic syndromes (PSE-CATEGO NSN and SNR) and the psychosis-specific syndromes (PSE-CATEGO DAH). But, as Fig. 4 shows, early depression has no predictive power beyond the first psychotic episode.

The course of depressive CATEGO syndrome over 5 years in patients with and without early-course depressive mood

(n = 115)

t-tests: *** $p < 0.001$
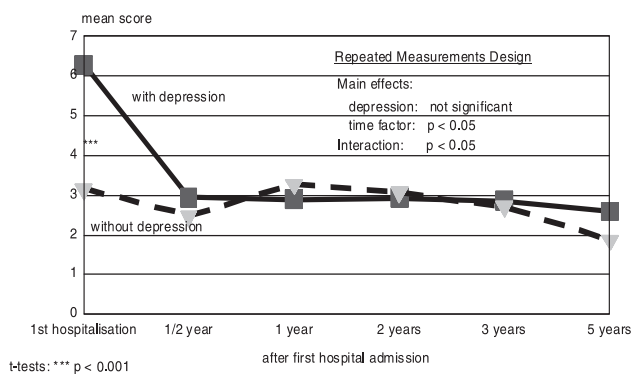
The course of symptoms (CATEGO total score) over 5 years in patients with and without early-course depressive mood
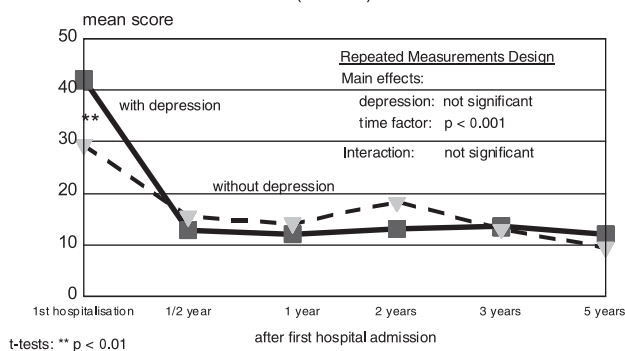
(n = 115)

t-tests: ** $p < 0.01$

Fig. 4 The course of symptoms (CATEGO depressive/total score) over 5 years in patients with and without early-course depressive mood

The middle course of schizophrenia

Although onset characteristics constitute the main field of presentation in the last section, we already entered the domain of course descriptions. The investigation of the course of schizophrenia has to face three problems: a conceptual, a methodological and a content-related problem.

Conceptually, the investigation of the 'natural' course of schizophrenia seems almost impossible to carry out under the ethic conditions of modern mental health care. Due to the severity of the illness it is to be expected that the vast majority of the subjects will be treated within the health care system at some time or some stage of the disorder. While treatment measures may significantly alter psychotic episodes and psychotic episodes mark the course of the disease, the description of the course will always reflect therapeutic influences to an unknown extent.

The middle course of the illness is often a neglected

topic in schizophrenia research. From a methodological point of view, one of the reasons is that longitudinal studies are far too often restricted to just a few cross-sectional assessments, forcing us to find answers about course characteristics only by a retrospective data collection on the basis of fuzzy working models over long periods of time. Therefore, most of these studies are limited to only crude statements about the course of schizophrenia, a situation that is also reflected in the discussion of course types, as mentioned before.

In a meta-analysis of studies on the long-term course and/or outcome of schizophrenia (an der Heiden 1996), it turned out that in 38 from 64 studies there was only one follow-up assessment after index measurement, another 13 studies had up to at least three cross-sectional assessments within the whole period of observation. Consequently, it is almost a matter of luck as to whether the course in different studies is described in terms of 'episodes', 'relapses', 'exacerbations' or hospital readmissions.

With respect to the content of what constitutes the course of schizophrenia, the reliable and valid description requires a thorough operationalisation of the dimensions used. Although the boundaries are often not sharply delineated, concepts like symptoms, signs, impairments and disabilities differ with respect to specificity and also by the extent to which they may be influenced by extrinsic factors.

So, at least two prerequisites must be fulfilled:

1. The description of the course of schizophrenia should be carried out by means of signs and symptoms thought to be specific and characteristic for schizophrenia.

While measures like 'quality of life' or the ability to fulfil different roles in the family or at work are important indicators of well-being or functioning, they must be looked at as consequences of the disease (WHO 1980) rather than being intrinsic to the disease.

Although the specific symptoms felt to characterise schizophrenia have varied widely over time and across cultures, as has the diagnostic and prognostic importance placed on these symptoms, today there is an agreement that a comprehensive description of the signs and symptoms of schizophrenia should place a strong emphasis on both positive and negative symptoms (Andreasen and Flaum 1991; Carpenter and Strauss 1991; Strauss et al. 1974).

2. The assessment should be carried out with the same instruments at different times to allow the identification of change.

But, even if these conditions are fulfilled, unresolved problems remain. Cross-sectional assessments are time-consuming and job-extensive. Therefore, the decision how frequent and at what time the assessments are carried out is not made as a rule under content-related aspects, but follows practical necessities. However, those symptoms which determine a diagnosis of schizophrenia and, therefore, are also relevant for the description of course are frequently unstable over time. This reduces the probability of identifying a patient as 'in episode' exactly when the measurement is carried out. So it is often impossible to decide whether a proband is no longer suffering from schizophre-

nia and can, therefore, be considered as "recovered" (DSM-IV; American Psychiatric Association 1994), or as "in full remission" between two episodes.

The course of schizophrenia as reflected in treatment measures

From textbooks and from other sources we can learn that in the long run the clinical picture of schizophrenia will change. While during the first years positive symptoms, like delusions and hallucinations, will dominate, later in the course the symptomatology becomes more inconspicuous with negative and unspecific symptoms taking centre. Breier et al. (1991) formulated a process model of chronic schizophrenia in which the early stage of the illness is characterised by deterioration, the middle stage by relative stability and the final stage by gradual improvement.

This model is obviously confirmed by analyses of utilisation data of psychiatric hospitals: analysing case register data from Victoria/Australia, Denmark and Salford/England, Eaton and colleagues (1992a; 1992b) could demonstrate a decline in the rate of rehospitalisation over time
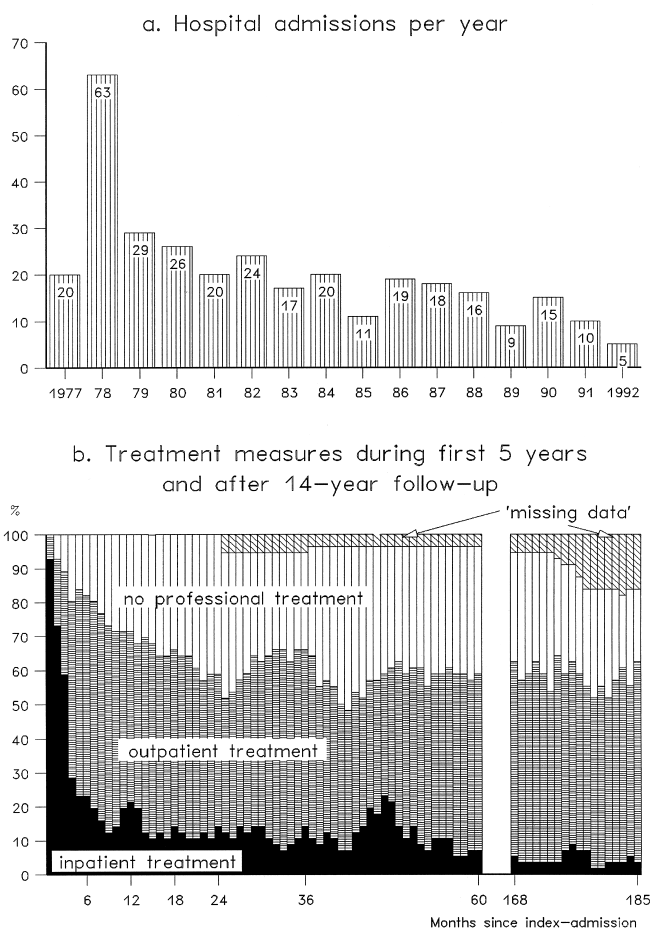
Fig. 5 Treatment measures

suggesting a progressive amelioration rather than deterioration in the course of schizophrenia.

In our Mannheim 'Disability' cohort we get a very similar pattern with regard to the use of inpatient services.

Figure 5a shows the number of readmissions in the Mannheim 'Disability' cohort per calendar year for the entire period between the beginning of the study in 1978 and year 1992. On average, 5.7 admissions are counted per patient, with a maximum of 19. For 9 out of 56 probands, the index admission is the only inpatient treatment episode during the whole period of observation. There is a significant decrease in the need for inpatient treatment (Cochran's Q-test; p < 0.001) over time.

The picture becomes more informative if one also considers out-patient care measures. In Fig. 5b, two periods are compared with respect to treatment modalities: (1) the first five years after first hospital admission and (2) the 18-month period after the 14-year follow-up. For every single month during these two periods we calculated the proportion of patients being in inpatient or outpatient treatment, both being without professional help. Again, one can see the decrease in the need for inpatient treatment, but at the same time there is an increase in the number of patients with outpatient contacts. In total, the proportion of patients in treatment – inpatient or outpatient – 14 years after index admission remains the same as compared with the share of patients in treatment 12 months after the beginning of the study. On average, some 60% of the patients are in in- *or* outpatient treatment every single month.

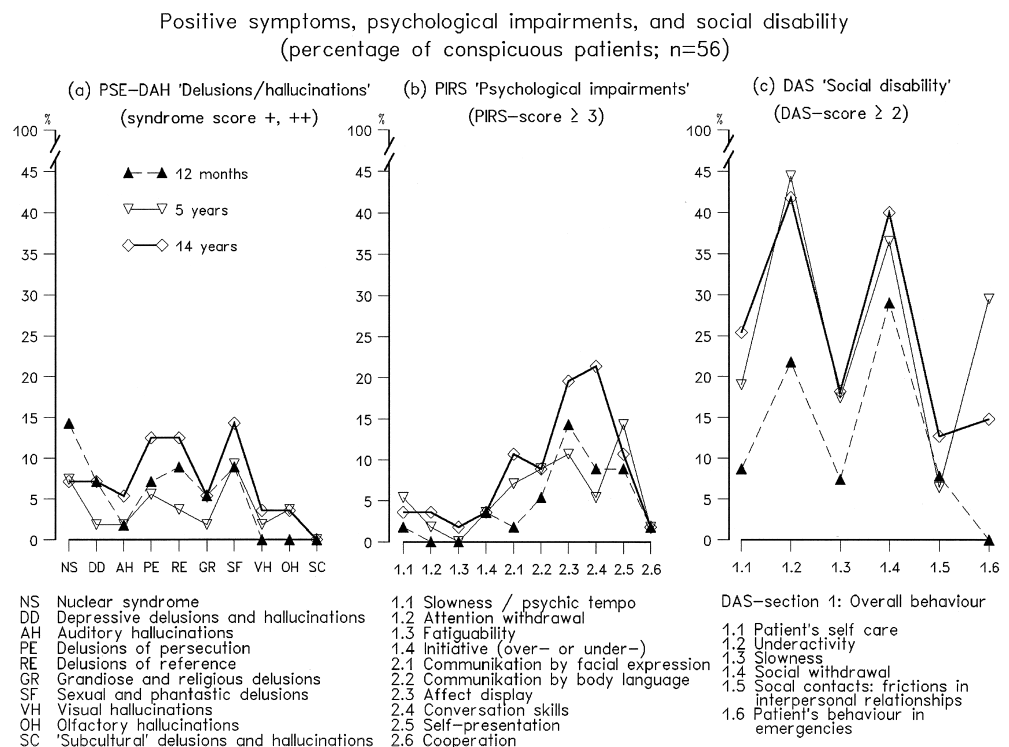The course of schizophrenia as reflected in signs and symptoms

A comparison of the treatment measures with the findings on psychopathology in the cohort makes clear that the decrease in the need for inpatient treatment does not go along with a drop in conspicuous psychopathology.

Figure 6 shows the share of patients from the Mannheim 'Disability' cohort with significant ratings in those syndromes constituting the PSE-subscore DAH 'delusional and hallucinatory syndromes' (Wing et al. 1974; ratings according to the 'syndrome check list'). The figure reflects the profiles at three cross-sectional assessments: 1 year, 5 years and 14 years after index admission. Independent of the time of measurement nuclear syndrome, delusions of persecution and reference and sexual/fantastic delusion are rated most often. It is striking that there is no decline in the number of conspicuous probands in the long run.

Concerning the course over time, the same is true for impairments, as measured by the PIRS (Biehl et al. 1989) and social disabilities (DAS-M; Jung et al. 1989). The only significant change is an increase in the proportion of disabled people but this already takes place during the first five years of observation.

Combining the results on treatment measures and symptomatology over time it becomes evident that data on hospital treatment and readmissions alone can no longer be seen as an indicator of the course of schizophrenia.

Fig. 6 Symptomatology, psychological impairments, and social disability 1, 5, and 14 years after first hospital admission

Positive symptoms, psychological impairments, and social disability
(percentage of conspicuous patients; n=56)

(a) PSE–DAH 'Delusions/hallucinations'
(syndrome score +, ++)

▲– –▲ 12 months
▽—▽ 5 years
◇—◇ 14 years

NS DD AH PE RE GR SF VH OH SC

NS Nuclear syndrome
DD Depressive delusions and hallucinations
AH Auditory hallucinations
PE Delusions of persecution
RE Delusions of reference
GR Grandiose and religious delusions
SF Sexual and phantastic delusions
VH Visual hallucinations
OH Olfactory hallucinations
SC 'Subcultural' delusions and hallucinations

(b) PIRS 'Psychological impairments'
(PIRS-score ≥ 3)

1.1 1.2 1.3 1.4 2.1 2.2 2.3 2.4 2.5 2.6

1.1 Slowness / psychic tempo
1.2 Attention withdrawal
1.3 Fatiguability
1.4 Initiative (over– or under–)
2.1 Communikation by facial expression
2.2 Communikation by body language
2.3 Affect display
2.4 Conversation skills
2.5 Self–presentation
2.6 Cooperation

(c) DAS 'Social disability'
(DAS–score ≥ 2)

1.1 1.2 1.3 1.4 1.5 1.6

DAS–section 1: Overall behaviour

1.1 Patient's self care
1.2 Underactivity
1.3 Slowness
1.4 Social withdrawal
1.5 Social contacts: frictions in interpersonal relationships
1.6 Patient's behaviour in emergencies

The outcome of schizophrenia

Summarising the opinion about the 'final' outcome of schizophrenia, one-third of all schizophrenic patients recover completely, one-third are characterised by repeated episodes of the illness at a low disability rate, and one-third become chronic. This rule of thumb is well known and has found its way into today's textbooks. However, a closer look at the pertinent literature for an empirical basis of this rule reveals that the findings are by no means as clear as the rule suggests (an der Heiden 1996). For example, in the *"Vermont Longitudinal Study"* Harding and colleagues (1987a; 1987b) reported that 60 % of the schizophrenic patients in their study (long-stay patients, "who had not improved sufficiently with chlorpromazine") had a "good" outcome, as operationalised by a Global Assessment Scale-Score (GAS; Endicott et al. 1976) above 61 after a course of 32 years on average, 68 % showed no signs or symptoms – neither positive nor negative – of a schizophrenic condition at follow-up. In contrast, only 3 % of the sample ("young, chronically ill") of the *"NIMH Longitudinal Study of Chronic Schizophrenia"* (Breier et al. 1991) showed comparable good values in GAS-scores, on average 13 years after illness onset. There was not a single patient who could be regarded as recovered or only slightly disabled.

While both studies had in common that they were dealing with chronic patients and had administered at least one identical measure, outcome assessment of schizophrenic conditions in general is characterised by a heterogeneity of concepts (an der Heiden 1996; Hegarty et al. 1994).

The determination of outcome in schizophrenia: conceptual thoughts

An attempt to determine the outcome of schizophrenia cross-sectionally by assessing patients at a time randomly chosen some 10, 15 or 20 years after a first hospital admission, can only give reasonable and valid results in those cases where from some point on the illness no longer undergoes any greater change. In all other cases, where this assumption does not apply, every result on outcome would be random. So, as a working hypothesis, we consider outcome in most cases as part of the course, showing – apart from short-run variations – some stability over time. It has to be emphasised that this does *not* exclude unstable or 'chaotic' courses. However, as in such cases – by definition – the status undergoes unsystematic modifications over time the determination of outcome is questionable within the described strategy of outcome determination.

As a first consequence, what has been said with respect to measures is of course also true for the assessment of outcome. Outcome should be defined by means of those symptoms which are characteristic of the course of schizophrenia. A second consequence says that differences between groups with respect to outcome should also be discernible at different points in time.

Deciding to use the positive and negative syndrome for outcome assessment, one has to bear in mind that a neuroleptic treatment aims in particular at eliminating positive symptoms (e. g. delusions and hallucinations). So it is possible that in the individual case the patient seems inconspicuous only because the symptoms have been suppressed successfully. This suggests considering treatment criteria for outcome assessment as well. Finally, since outcome indicators from the area of psychopathology are mostly indicators fluctuating over time, cross-sectional assessments should be replaced by some longitudinally designed evaluation to allow a valid reflection of phenomenology.

The outcome of schizophrenia: results

Considering positive and negative symptoms and treatment measures with neuroleptics during a 9-month period 14 years after index admission, we were able to separate three different groups in our 'Disability' cohort:
– The largest group with some 60 % consists of patients clearly showing positive and/or negative symptoms during a 9-month period after the 14-year follow-up.
– There is a small group (15 %) consisting of patients who do not show any kind of symptomatology but who are treated with neuroleptics.
– There is a third group with some 25 % who neither present clinical characteristics nor undergo neuroleptic treatment.

What does this mean with respect to the long-term course of schizophrenia? So far, talking about onset and middle course of schizophrenia we ignored the fact that schizophrenia comprises a heterogeneous group of syndromes. But, if we now consider the possibility of different outcome groups showing some stability in outcome according to our working hypothesis the results should become more differentiated (Fig. 7, cf. Fig. 5).

In those patients who belong to the 'recovered' group at the time of the long-term follow-up, we can see that after
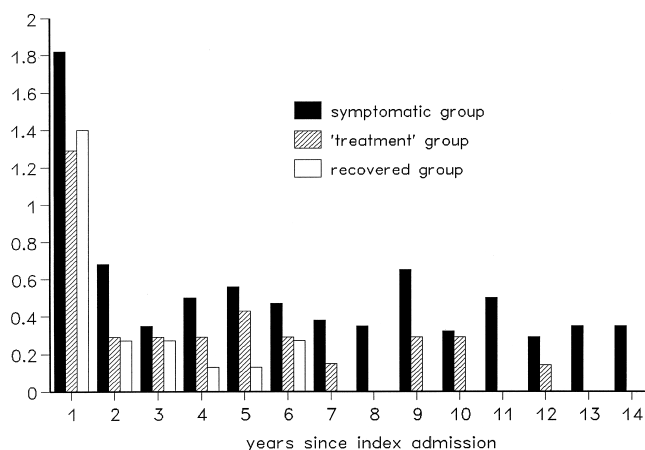

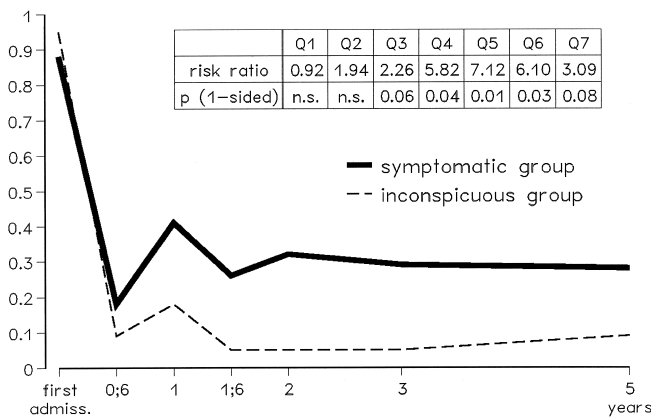**Fig. 7** (Re)admissions per patient during the course of 14 years by outcome group

Fig. 8 Risk for positive symptoms during five years after index admission, by outcome groups

six years there is not a single readmission to register. In contrast, in the 'symptomatic' group, there is hardly any change in the number of readmissions over time. The differences between the three groups are highly significant.

What about the change in the clinical syndromes over time? By separating the total group in different outcome groups the picture becomes very similar to that shown for rehospitalisation data. While in the recovered group by definition positive symptoms have dropped to zero until long-term follow-up, in the 'symptomatic' group in the long run there is no visible decrease in the average number of hallucinations and delusions, even more than 14 years after index-admission.

Already one year after index admission the groups can be clearly separated. For those patients who belong to the symptomatic group some 14 years later the probability of showing positive symptoms is between two and seven times higher at each cross-sectional assessment during the first five years of observation than in the other two groups (Fig. 8).

Conclusions

In three-quarters of the cases the onset of the first psychotic episode in schizophrenia is preceded by a prodromal phase with a mean length of about five years. The earliest signs of the disorder are depressive and negative symptoms. Early depressive symptoms at a cumulative prevalence of over 80 % until first admission predict higher overall symptom scores in the first illness episode and lower scores for affective flattening in the medium-term course.

Applying the same measures at different cross-sectional assessments, there is a close correspondence between the profiles of psychopathological syndromes and impairments over time. In contrast to what one would have expected according to current models of the schizophrenic course, there is no decrease in the number of patients with acute symptomatology until 14-year follow-up. Rather, there is a tendency of an increase without however achiev-

ing statistical significance. The same is valid for psychological impairments.

The result for social disability is somewhat different. Here we find a significant increase of disability over time. But the change already takes place within the first five years.

With respect to long-term course approx. 60 % of those falling ill with schizophrenia become chronic and approx. 25 % will recover during the first five to six years. In the subgroup with a chronic state 14 years after index admission on average there is neither a decline in positive symptoms (delusions, hallucinations) nor a reduction in the need for hospital treatment, the latter result standing in clear contrast to the observations in the total group.

Our analyses revealed that operationalising the long-term course of schizophrenia by means of inpatient treatment data only (Eaton et al. 1992a; 1992b; Engelhardt et al. 1982) does not seem to be sufficient. As can be deduced from our juxtaposition of treatment data and illness indicators at different times, it seems that with increasing illness duration more and more also psychotic symptoms and exacerbations may be treated by outpatient measures. The approximate agreement of the number of illness episodes with the number of the hospital admission found by Marneros and colleagues (1991) cannot be confirmed by our prospective data.

In January 1999 we started work on a 12-year follow-up in our ABC first-episode sample. One of the main research topics in this study will focus on the prognostic relevance of signs and symptoms from the prodromal phase for long-term course, for example, with respect to remissions and relapses. So, for the very first time, it will be possible to combine data about the very beginning of schizophrenia, collected in a controlled large scale epidemiological study on first-episode patients with equal starting points concerning illness stage with data prospectively collected over a period of 12 years.

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