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# Prodromal Symptoms and Early Detection of Schizophrenia

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## INTRODUCTION

Prodromal symptoms occurring before the first-ever onset or relapse of schizophrenia were observed a long time ago. In 1861 the pioneer of modern, scientifically oriented psychiatry, the Berlin-based psychiatrist Wilhelm Griesinger [1], described a melancholic prodromal stage that tends to precede psychosis. Kraepelin [2] described a series of “minor changes in mood, which may be recurrent or persist for weeks, months or even for years as the only premonitory signs of an imminent mental disorder”. The main symptoms of this “stage of the prodrome” were “increased irritability and moodiness, restlessness, unmotivated spells of high or frequently low spirits... Further prodromal signs that can be observed frequently are absent-mindedness, lack of interest or markedly increased activity”.

Bleuler [3] called this premonitory stage latent schizophrenia and described it as characterized by irritability, introversion and eccentric behaviour. He put forward the hypothesis, later revived by Häfner [4] and Maier *et al.* [5], that the underlying disease process may come to a halt at any stage of its early development. Such a process ending prematurely may bring forth mild, nonpsychotic symptoms such as schizoid or schizotypal personality disorders.

In the period during and following World War I research on the topic lacked in vigour, but was soon resumed by Sullivan [6] in a hope of finding reliable early prognostic indicators of psychosis as a basis for early treatment. Proceeding from a psychoanalytical–psychodynamic theory, Sullivan based his explicatory models on neurotic reaction patterns, such as hysteria, neurasthenia and obsessive–compulsive reactions. The sequence of these reaction patterns at the prodromal stage of psychosis

was seen by Sullivan as a hierarchical sequence of neurotic defence mechanisms adopted to fend off more severe psychopathology as the disorder progresses.

After Sullivan's unsuccessful endeavours to find reliable prognostic indicators of incipient psychosis, Cameron [7,8] set out to study the prodromal stage of schizophrenia in greater detail by clinical methods. Cameron [7] was also the first to assess the duration of untreated psychosis (DUP): 32.4% of the patients he studied had suffered from more or less rapidly accumulating psychotic symptoms for up to six months from their onset until first admission, 17.5% for six months to two years and 48.1% for more than two years. He found [8] that 83% of these patients first admitted because of schizophrenia had suffered a prepsychotic prodromal stage marked by deteriorating functioning, affective blunting, social withdrawal and bizarre thoughts and convictions. In most cases the prepsychotic prodromal stage showed a smooth transition to paranoid delusions and other positive symptoms of full-blown psychosis.

Cameron defined the DUP by two timepoints that can be determined fairly reliably, i.e. by onset of psychotic symptoms and first admission. For this reason his estimates can be compared with results based on similar definitions from more recent studies, as reflected in the similarity of the results [9,10] presented in Table 1.1.

## STAGE MODELS OF THE EARLY COURSE OF SCHIZOPHRENIA

### Conrad's Model

The first stage model of the early course of schizophrenia was proposed by the Marburg-based psychiatrist Conrad [21], who studied 107 German soldiers admitted to a military hospital because of a mostly acute schizophrenic psychosis during World War II. On the basis of the symptoms and complaints reported by the patients, Conrad developed four – and a rarer fifth – stages of evolving and two stages of remitting schizophrenia.

Stage 1, called *trema*, could last for several years. Conrad described it as characterized by uncertainty, depression, anxiety, suspiciousness, first signs of attenuated delusions and social withdrawal. He likened what patients at this stage feel to the anxiety that takes possession of actors before entering the stage.

The next stage, *apophany*, brings forth strange experiences that the patients cannot explain, fully elaborated psychotic symptoms – hallucinations,

TABLE 1.1 Duration of the prephase of schizophrenia from onset (first sign, first psychotic symptom) until first contact or first admission (modified from Häfner *et al.* [10])

Study	<i>n</i>	Duration from first sign (in years)	Duration from first psychotic symptom (in years)
Gross [11]	290	3.5	
Lindelius [12]	237		4.4
Huber <i>et al.</i> [13]	502	3.3	
Loebel <i>et al.</i> [14]	70	2.9	1.0
Beiser <i>et al.</i> [15]	70	2.1	1.0
McGorry <i>et al.</i> [16]	200	2.1	1.4
Lewine [17]	97		1.9
Häfner <i>et al.</i> [18]	232	4.8	1.1
Johannessen <i>et al.</i> [19]	43		2.2
Ho <i>et al.</i> [20]	156	2.7	1.4

delusions, thought disorders etc. – and derealization. Insight and reality control are lost.

The third stage was called by Conrad *anastrophae*. It is characterized by formal thought disorder and a delusional-projective attribution of inexplicable experiences to external causes, which Conrad interpreted as secondary delusions in the manner of Bleuler. The fourth stage that the previous stage of increasing psychotic symptoms may lead to was called by Conrad *apokalypse*. It is identical to full-blown, severe psychosis associated with disorganization, severe anxiety, restlessness and catatonic symptoms.

Sometimes a fifth stage, *catastrophae*, follows, which shows increasingly severe psychotic symptoms, agitation, disorganization and concomitant physical phenomena. According to Conrad, *catastrophae* results in *terminale*, which usually ends in death. This final stage corresponds to the so-called pernicious or febrile catatonia. In those days, when antipsychotic treatment was lacking, it occurred fairly frequently as a consequence of desiccation, electrolyte imbalance, increased body temperature and protein catabolism in the muscles due to sustained and severe psychotic tension.

### Docherty *et al.*'s Model

Another stage model designed with the aim of enabling early recognition was published by Docherty *et al.* in 1978 and has been entered especially in the Anglo-American canon of knowledge [22]. The introduction to this work reads like a statement from current research efforts to improve our understanding of the early course of schizophrenia:

There are many reasons for wanting to know more about the period of onset of schizophrenic psychosis. The dearest benefit is in the area of preventive psychiatry. The establishment of regular premonitory signs might permit a reliable early recognition of impending psychosis and also the staging of the degree of psychological and biological decompensation. That is an assessment of how close a patient is to a psychotic episode. Further this knowledge raises the possibility of developing a clearer rationale for stage-appropriate treatment.

We think that the available data strongly suggest that schizophrenic psychosis is one stage in a process of psychological and biological breakdown that has a specific structure and a characteristic unfolding. . . . The structure consists of the sequential appearance of hierarchical or distinguishable and recognizable psychological states.

Reflected in these sentences are a few theoretical premises. Docherty *et al.*'s model of the onset of schizophrenic psychosis consists of four – or six – stages. Stages 5 and 6, psychotic resolution and remission, are regarded as phases of remitting psychosis and increasing mental stability. The “empirical basis” of the model were three case histories and a survey of the extremely heterogeneous pertinent literature, including Conrad’s stage model.

Stage 1, which Docherty *et al.* called *overextension*, is characterized by experiences of passivity, overstimulation, irritability, persistent anxiety and first signs of cognitive impairment (distractability). This stage tends to show a lengthy, insidious course. Predominant at stage 2, called *restricted consciousness*, are such symptoms as apathy, social withdrawal, hopelessness and somatization, but also deterioration of personal appearance and – here the authors follow Sullivan – obsessional and phobic symptoms. The third stage, *disinhibition*, brings forth symptoms that give the impression of patients losing their inhibitory abilities: hypomania, elevation of mood and occasional ideas of reference. This stage, still part of the prepsychotic prodromal period, is followed by a fourth called *psychotic disorganization*, characterized by disorganization of cognition and perception, hallucinations, ideas of reference, disorders of self and sometimes by catatonic symptoms. In the stages that follow, i.e. psychotic resolution and remission, as stability of the mental state increases, affective and psychotic symptoms remit completely or in part.

### **Empirical Testing of Conrad’s and Docherty *et al.*’s Models**

We applied the structural equation modelling technique (SEM) to test the internal validity of Conrad’s and Docherty *et al.*’s stage models. As latent

variables we chose the symptoms and symptom patterns subsumed under the stages and the stages as such [23]. We also tested external validity, i.e. to what extent the two models tallied with each other and with empirical data on the early course of schizophrenia collected retrospectively using the Interview for the Retrospective Assessment of the Onset of Schizophrenia (IRAOS) [24–28] in a representative sample of first illness episodes of schizophrenia ( $n = 232$ ) from the Age, Beginning, Course (ABC) Schizophrenia Study. Our analysis is based on a subsample of 170 patients who had experienced a clear-cut prepsychotic prodromal stage (73% of 232).

Neither of the two models was significantly supported or even converged in the analysis of internal and external validity or in the comparisons with the empirical data. Conrad's model explained 74% (goodness of fit: 0.79, adjusted 0.74) and Docherty *et al.*'s model 71% (goodness of fit: 0.75, adjusted 0.71) of the empirical data, thus failing to attain the conventional level of goodness of fit of  $\geq 90\%$  [23].

This result is no surprise. The reasons lie not only in the construction weaknesses of these models, but also in the partly imprecise description of the symptoms and their occurrence at the stages.

Because of the difficulties posed by a comprehensive validation, we had earlier compared the sequence of symptom onset over time as an indicator of the sequence of stages in Conrad's model with a slightly different set of the IRAOS data from the ABC study [29]. The results confirmed Conrad's model only with respect to prepsychotic "trema" as the first stage of illness (this was the case in 76% of the first-admission sample, of whom 84% were first illness episodes and of these first-episode cases 73% had experienced a prepsychotic prodromal stage). But the comparison failed to provide any evidence for the sequence of the other stages. To conclude, Conrad's model provides a correct representation only of the distinction between a prepsychotic prodromal stage, which he called "trema", and the subsequent stage of psychosis.

## Foulds' Model

A third stage model, not limited to schizophrenia, of how mental disorders develop and remit, was proposed by Foulds [30]. The model proceeds from the premise that there is a natural sequence of stages from minor to increasingly severe psychopathology and a symmetrically reversed sequence in remitting illness. The stages of evolving illness consist of dysphoric symptoms, neurotic symptoms, psychotic symptoms, integrated delusions and disintegrated delusions combined with psychotic disorganization on top.

Construed as applicable to all types of mental illness, this model can hardly be expected to be of sufficient specificity in terms of diagnostic power. Because of that, it is no surprise that de Jong *et al.* [31], studying a sample of first-episode cases of schizophrenia assessed by the Present State Examination (PSE) in Groningen, and Biehl *et al.* [32], who studied a first-episode sample of 70 patients with schizophrenia from Mannheim, found a sufficient goodness of fit for the sequence of Foulds' stages in about 85% of their samples. This result means that Foulds' stage model is applicable to the early course of schizophrenia without any substantial benefit in terms of the information it provides, but probably also to many other illnesses with progressive types of courses culminating in psychosis.

## RECONSTRUCTING ILLNESS ONSET AND EARLY COURSE

### The ABC Schizophrenia Study

Using the IRAOS interview, the ABC Schizophrenia Study examined a population-based sample of 232 first illness episodes, representing 84% of 276 first treatment episodes, and a representative subsample of 130 subjects, who were compared with two age- and gender-matched control samples – one from the “healthy” population ( $n = 130$ ), the other first hospitalized with a diagnosis of depressive episode ( $n = 130$ ).

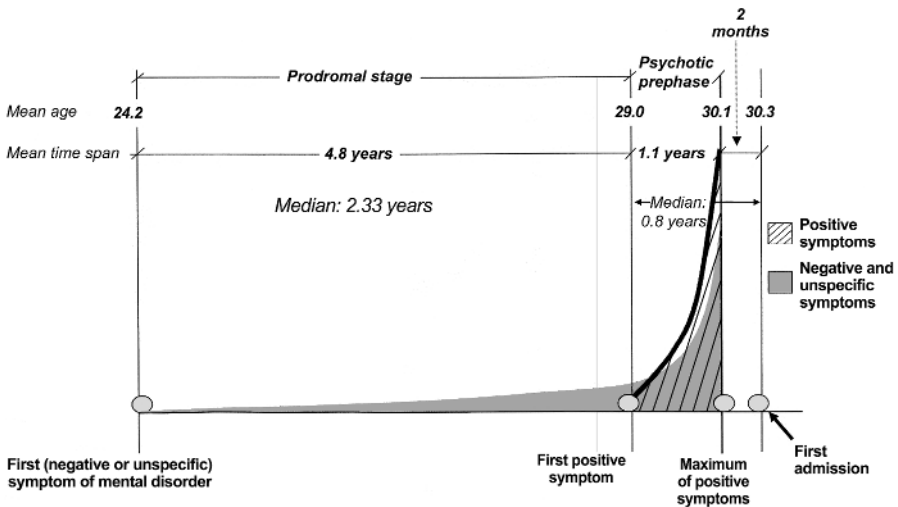
Survival analysis of the duration of early illness course from onset to first admission as target event revealed a distribution of durations of the early illness course that was markedly skewed to the left. One third (33%) of the broadly defined cases of schizophrenia took less than one year from prodromal onset to develop psychotic symptoms. Only 18% had an acute type of onset of four weeks or less, 15% a subacute type of 4 weeks to one year and 68% a chronic type of onset of one year or more. Only 6.5% started with positive symptoms; 20% presented both positive and negative symptoms within the same month. A prepsychotic prodromal stage with negative or nonspecific symptoms prior to the emergence of the first positive symptom was experienced by 73%.

Nonspecific and negative symptoms started to increase early, positive symptoms quite late, the first of them appearing one year and one month before the climax of the first episode and one year and three months before first admission. In the psychotic episode all three symptom categories accumulated rapidly and reached a maximum followed by almost parallel decreases.

## Defining and Operationalizing the Prodromal Stage and the Milestones of the Early Course of Schizophrenia

The “clinical” end of the early illness stage (first treatment contact or first admission) is easy to define. But this event is determined not only by the increase in serious symptoms and impairment, but also by patients’ help-seeking behaviour and the availability of adequate care. A suitable illness-related event to mark the end of the early illness stage is the climax of the first psychotic episode, operationalized as the maximum of positive symptoms [18]. Figure 1.1, based on data from the ABC Schizophrenia Study, depicts the mean durations (and medians) of the intervals between the milestones or stages of evolving schizophrenia.

In practice, but also in many epidemiological and clinical studies, the onset of schizophrenia and of many other disorders is defined by the first contact with mental health services. This fact, namely, that the prodromal and the psychotic phase preceding first contact may last a few years, has implications for the interpretation of research results based on first admission as the definition of illness onset. This holds, for example, for reports of a significant excess of first admissions for schizophrenia from the lowest social class and from poor disintegrated neighbourhoods of big cities [33,34] as well as their possible interpretation as social causation versus social selection [35,36]. The same is also true for studies that do not distinguish the prodromal stage from “premorbid” development



**Figure 1.1** The prephases of schizophrenia from first sign of mental disorder to first admission. Modified from Häfner *et al.* [10] by permission of Springer-Verlag

(adjustment): when poor global functioning represents an early consequence of the prodromal stage of the disorder, it is no wonder that “premorbid” functioning possesses such high prognostic power for the social course of the disorder [37]. Prognoses of this type merely tell us that fairly stable features of the disorder continue to persist in the further illness course.

Psychosis onset as the end of the prodromal stage can be determined fairly reliably by the timepoint at which the first psychotic symptom appears. Considering the fairly common occurrence of single psychotic symptoms in the nonpsychotic general population [38–40], with lifetime rates ranging from 5% to 15%, it is advisable to operationalize psychosis onset by persistence of psychotic symptoms for at least one week. By this criterion the fairly rare brief limited intermittent positive symptoms (BLIPS) [41], defined by persistence for up to one week, are subsumed under the prodromal stage or classified as not yet progressing risk indicators.

The onset of the prodromal stage is marked primarily by symptoms not specific to schizophrenia, and for this reason it is far more difficult to define. An operational definition must distinguish between stable, persistent single symptoms on the one hand and early or premonitory signs of other mental disorders on the other hand. An optimal solution to this problem has not yet been found either at the psychopathological or the biological level. For this reason in the ABC Study we used an operational definition based on the different specificities of the three symptom categories: nonspecific symptoms qualified as first signs of the disorder only if they persisted continuously until first admission, negative symptoms, if they were continuous or recurrent, and positive symptoms in any case, even if they had occurred only once for at least two weeks. But it might well be that in the future a neurobiological indicator will be found that marks the onset of the most active neurodegenerative phase in the course of schizophrenia.

## **DURATION OF UNTREATED ILLNESS AND UNTREATED PSYCHOSIS AS INDICATORS OF AN UNFAVOURABLE FURTHER ILLNESS COURSE**

In current clinical practice, the first treatment contact of persons falling ill with schizophrenia is preceded by incipient psychosis with a mean duration of about a year or more (DUP) and a prepsychotic prodromal phase with a mean of several years (duration of untreated illness, DUI = duration of the prodrome+DUP) (see Table 1.1).

DUP and, in rare studies, also DUI have been described as prognostic indicators of unfavourable aspects of course and outcome in schizophrenia. The following short-term effects of a lengthy untreated first psychotic episode have been reported: delayed and incomplete remission of the first episode versus better therapy response and more rapid remission [14,16,42–46], longer active illness or longer presence of psychotic and negative symptoms [47,48], reduced level of global functioning [49] and a longer duration of hospitalization and higher treatment costs [45,46,50].

The results on the association between DUP or DUI and medium- or long-term outcome are less clear-cut. McGorry *et al.* [16], in their investigation of 200 patients (about 50% with schizophrenia), demonstrated a positive association between DUP and positive and negative symptoms, global functioning and quality of life 12 months after first assessment. Johnstone *et al.* [42], Larsen *et al.* [51] and McGorry *et al.* [16] observed an increased frequency and severity of relapses. Helgason [52] found a higher risk of relapse and a longer duration of hospitalization and less compliance. A greater burden on the family and a higher expressed emotions level have also been reported [53,54]. Other effects observed are a less supportive social network [51], higher risk of depression and suicide [55–58], more stress in work- and education-related situations [59,60] and more substance abuse and delinquent behaviour [61]. In sum, almost all the characteristics that make up an unfavourable course of schizophrenia have been reported.

Analyses based on a representative follow-up sample of first illness episodes of schizophrenia in the ABC study [62] showed that DUP was a significant predictor only of psychotic and nonspecific symptoms at five-year follow-up. In contrast, DUI predicted negative and nonspecific symptoms and social outcome. Neither DUI nor DUP significantly predicted the frequency and duration of, and intervals between, psychotic relapses. This result sounds quite plausible because, apart from the nonspecific component, the powerful predictions were limited to the symptom categories prominent in these two phases. A prolonged DUI is characterized mainly by negative symptoms, a short DUP primarily by positive symptoms.

In contrast, three studies found no such association: Craig *et al.* [63] could not demonstrate any association between DUP, illness course and clinical outcome 24 months after first assessment, nor could Robinson *et al.* [64,65] or Ho *et al.* [66] in a well-designed and systematic study (Table 1.2).

The inconsistency of the results from the studies on the topic is very likely explained by great differences in the study samples. It is reasonable to presume that a prolonged prodromal stage – whatever its underlying cause may be – involving a great number and severity of negative symptoms and presumably also associated with a lengthy psychotic stage is an unfavourable prognostic indicator of the further illness course. Edwards and

**TABLE 1.2** Selected studies on short- and long-term prediction of course and outcome by duration of untreated psychosis (DUP) or duration of untreated illness (DUI)

Study	Subjects	Observation period	Shorter DUP or DUI predicts better outcome or shorter first episode	Longer-perspective course and outcome
Altamura <i>et al.</i> [67]	67 DSM-III-R schizophrenia spectrum	4 years	Yes	Short DUP → less psychotic relapses
Malla <i>et al.</i> [68]	106 non-affective psychoses	1 year	Yes	Short DUP → positive outcome; long DUI → higher negative and disorganization factor scores
Malla <i>et al.</i> [68]	53 non-affective psychoses	13 months	Yes	Little evidence of any association between DUP or DUI and course of schizophrenia; long DUI more likely unemployed, alone or homeless
Ho <i>et al.</i> [20]	156 DSM-IV schizophrenia spectrum disorder	First episode and retrospective until onset	No	No significant correlations between DUP and neurocognitive functioning
Joyce <i>et al.</i> [69]	136 schizophrenia, 81 controls	1 year	Yes	Long DUP → neuropsychological deficits and clinical deterioration
McGorry <i>et al.</i> [70]	203 schizophrenia	1 year	Yes	Long DUP → strong and consistent prediction of severity of symptoms and functional outcome
Hoff <i>et al.</i> [71]	50 schizophrenia	1 year	Yes	Long DUP → no association after recovery from first episode
Craig <i>et al.</i> [63]	155 schizophrenia, 115 bipolar disorder, 75 unipolar depression	2 years	No	No association
Barnes <i>et al.</i> [72]	53 schizophrenia (first episode)	First episode and retrospective until onset	No	No association
Harrigan <i>et al.</i> [73]	354 schizophrenia	1 year	Yes	Long DUP → deterioration of functioning
Häfner <i>et al.</i> [62]	115 schizophrenia (first episode)	5 years	Yes	Long DUP → more psychotic and unspecific symptoms; long DUI → more negative symptoms and poorer social outcome

McGorry [74] have published a fairly comprehensive, but unsystematic list of the potential risks of delayed treatment:

1. slower and less complete recovery;
2. poorer prognosis (subsumed under this heading are numerous results or hypotheses on the further course of the disorder, measures of symptoms and impairment, relapse rates and duration of symptom-free intervals in particular);
3. increased risk of depression and suicide;
4. interference with psychological and social development;
5. strain on relationships;
6. loss of family and social support;
7. disruption of patient's parenting skills (for those with children);
8. distress and increased psychological problems within the patient's family;
9. disruption of study and employment;
10. substance misuse;
11. violence/criminal activity;
12. unnecessary hospitalization;
13. loss of self-esteem and self-confidence;
14. increased costs of management.

### **The Hypothesis of the Neurotoxicity of Psychotic Episodes**

In his early writings, Kraepelin [2] had presumed that the "florid bouts of illness" – psychotic episodes – lead to a certain amount of irreversible consequences he called "defects". This model, implying that schizophrenia shows a deteriorating course in the form of steps, as depicted in the trajectory proposed by Breier *et al.* [75], has been revived by Wyatt [76,77], Loebel *et al.* [14] and Lieberman *et al.* [78,79]: "The illness gets gradually worse during that period indicating that untreated psychosis may constitute an active morbid process, 'toxic' to the brain. If this disease process is not treated and suppressed early enough, it may become chronic" [14,76,79]. McGlashan and Johannessen [80] presume that the plasticity of the brain can be preserved and prevented from deteriorating if the persons affected receive both antipsychotic medication and simultaneously social stimulation at a sensitive stage of the illness.

The neurodegenerative effect of the first psychotic episode – if it really exists – should become visible as pronounced deterioration following the psychotic "bout" in first-episode cohorts. But this does not seem to be the case when judged by mean symptom scores and measures of social impairment in methodologically sound, prospective first-episode studies.

Nor can the effect be demonstrated on mean scores from neuropsychological tests in the majority of studies [81]. In fact, global impairment and its social consequences emerge as early as the prodromal stage without clear signs of gaining momentum in the psychotic episode.

If the duration or severity of psychotic episodes were causally associated with indicators of a poor further illness course, evidence for such an association would be provided by findings that psychotic symptoms predict subsequent negative symptoms. For this purpose we operationalized the symptom dimensions of schizophrenia on the basis of Liddle's three-factor model [82–84] to obtain comparable measurements [85]. We prospectively assessed the representative ABC follow-up sample of 115 first-illness episodes at six cross-sections over five years after first admission. The negative factor remained independent of the two other factors, throughout the cross-sections, but highly significantly correlated with itself from cross-section to cross-section. In conformity with results from numerous follow-up studies, the negative factor turned out to be the most stable component independent of the course of the psychotic symptom dimensions in schizophrenia. The two other factors (reality distortion and disintegration) showed a few autocorrelations and significant intercorrelations at several cross-sections as well as courses independent of the negative factor. Similar results have been reported by Arndt *et al.* [86], who showed that Liddle's three factors varied independently over two years, and Salokangas [87], who showed the same over five years.

The analysis discussed above of how DUP and DUI influence five-year outcome can also be regarded as a test of the hypothesis about the neurotoxicity of psychosis. The result that significant effects could be shown to exist only at the level of the quantitatively predominant symptoms corresponds to the results on the stability of the factors.

To test the neurotoxicity hypothesis, Ho *et al.* [20] recently conducted a cross-sectional study of 156 first episodes of schizophrenia at the levels of symptoms, neuropsychological test results and brain morphology. The authors were unable to find significant correlations of DUP either with changes in grey matter volumes, symptoms or neuropsychological test results.

The reasons for the inconclusiveness of the findings concerning the effects of DUP and DUI probably lie in the great methodological differences of these studies (Table 1.2). Exact comparisons of the two periods concerned, DUP and DUI, are hardly possible due to differences in the definitions used and/or non-use of appropriate assessment instruments. With a few exceptions, the samples studied were not representative. Because of the extremely heterogeneous course of schizophrenia, the proportions of unfavourable courses in the study samples probably varied a great deal. The difficulties encountered in studying associations between

DUP and illness course are by no means minor in studies based on magnetic resonance imaging (MRI) and computed tomography (CT) scans. Some studies have shown that morphological brain changes occur early in the illness, before the psychotic stage. Other studies have demonstrated that compared with age-matched controls brain volume reduction increases over time (five years) in some cases [88]. However, it is not yet possible to tell the exact proportion of these cases in the total of people with schizophrenia (Table 1.3).

### **Does a Shortened DUP Lead to a More Favourable Illness Course and Better Outcome?**

This important question stems from a hope of reducing the adverse consequences of the disorder by shortening the untreated early illness period. But objections have been raised against the implied causal association: “is the link due to a common underlying factor, such as a more severe form of the illness with functional impairment after an insidious onset, more negative symptoms, more paranoid ideation?” [74]. At any rate, it has been known since Kraepelin’s days that an insidious onset with a long prodromal phase featuring negative symptoms and impairments is a clinical indicator of a poor illness course. In contrast, a highly acute onset without a prodromal stage seems to be associated with a favourable illness course as an intrinsic factor of the disease process. Verdoux *et al.* [95] have shown that demographic and clinical factors that predict a poor prognosis may also be associated with delayed presentation to psychiatric services.

Evidence for the assumption that shortening the early illness stages (DUP, DUI) ameliorates the further illness course could only be obtained in randomized controlled intervention studies among patients at early stages of their illness. Because of the unresolved problems posed by early recognition and reliably predicting psychosis risk, the studies were based on conventional definitions of high psychosis risk. The study conducted by McGorry *et al.* [70], which was based on 59 ultra-high-risk (UHR) probands, showed that, after one year of targeted cognitive behavioural therapy and low doses (on average 1.3 mg pro die) of risperidone, 7.1% of the fully compliant patients transited to psychosis, compared with 29.4% of the not fully compliant index cases and 35.7% of the controls, who had received unspecific therapy. Lewis *et al.* [96], in a study in which high-risk probands at the prodromal stage received cognitive behavioural therapy and social support, also found significant differences in outcome between the index cases and controls.

**TABLE 1.3** Changes in brain morphology at the prodromal stage of schizophrenia according to selected studies

Study	Subjects	Brain imaging	Before or at first psychotic episode	At follow-up
Johnstone <i>et al.</i> [89] Lawrie <i>et al.</i> [90]	162 psychotic risk; 18.1% psychotic (11.6% schizophrenia), 33% partly psychotic Risk period: 6 years	MRI	High-risk subjects: reduced hippocampal and thalamic volumes, changes occur before psychosis	High-risk subjects show reductions in temporal lobe volumes; with approaching psychosis anomalies increase
Hoff <i>et al.</i> [71]	50 first episode schizophrenics 25 controls	MRI volumetry	First episode: structural anomalies	No significant correlation of DUP with severity of either cognitive or structural brain deficits
Fannon <i>et al.</i> [91]	37 first-episode schizophrenics Risk period: 1 year	MRI	First episode: smaller brain volumes and cortical grey matter volumes and larger lateral and third ventricle	No association between DUP and any changes
Ho <i>et al.</i> [20]	156 DSM-IV schizophrenia Risk period: 2 years (1 episode)	MRI grey and white volumetric and surface anatomy measurement	First episode: no association between DUP and volumetric measures of the brain	No association between DUP and MRI anomalies
Pantelis <i>et al.</i> [92]	75 ultra-high-risk (UHR) cases; 31% psychotic Risk period: 1 year	MRI volumetry	High-risk cases: brain changes appear before psychosis and further changes occur	Psychotic cases: reduction in grey matter volume and left caudate and hippocampus
Copolov <i>et al.</i> [93]	32 first episodes with schizophrenia; 39 UHR cases Risk period: 1 year	MRI volumetry hippocampus	High-risk subjects: hippocampus ~10% volume reduction	15 of 39 psychotic: no progression of hippocampus reduction
Malla <i>et al.</i> [94]	114 first episodes (schizophrenia or schizophreniform)	CT	First episode: modest enlargement of sylvian fissure and ventricle; no association with DUP	Chronic cases: sylvian fissure significantly larger

CT, computed tomography; DUP, duration of untreated psychosis; UHR, ultra high risk.

Hence, appropriate early intervention administered to high-risk individuals from the late prepsychotic stage onwards can succeed in delaying the onset of a psychotic episode. This effect is analogous to that in relapse prevention in schizophrenia. But will early intervention also help to reduce negative symptoms and functional impairment enduringly?

In view of the independent courses of the negative-impairment dimension and the positive-symptom dimension over time, shortening the prodromal stage characterized by negative symptoms or DUI as a whole seems more promising than reducing the purely positive symptoms. In this context it should be kept in mind, as mentioned above, that in the first psychotic episode unspecific and negative symptoms also increase simultaneously with positive symptoms [18]. The aim of early intervention is not only to reduce the most enduring component of the illness, but also to try to reduce or even prevent the early social consequences, which decisively co-determine the social course of the disorder and the kind of life patients will be able to lead. This is why diagnostic recognition and prediction of schizophrenia as early as the prodromal stage are so important.

## **ASSESSING PRODROMAL SYMPTOMS AND IMPAIRMENT IN THE EARLY COURSE OF SCHIZOPHRENIA**

### **Residual Symptoms as Prodromal Signs**

Because of the great difficulty in obtaining information on the onset and early course of schizophrenia prospectively, due to the low incidence rate and a frequent onset with uncharacteristic symptoms, prodromal signs usually go unheeded when they appear. In traditional clinical settings, first contact with mental health services in most cases takes place during the first psychotic episode. Help-seeking is usually precipitated by a loss of working ability and the distress caused by psychosis to the sick person and his/her environment. In the ABC Schizophrenia Study the time span between onset of the first psychotic episode and first contact varied around a mean of 1.3 years (median 0.8 years).

Due to their obscurity, the prodromal symptoms of the first episode were also lacking or listed incompletely in the international classification systems and at first reconstructed on the basis of symptoms occurring in the further illness course [97].

Different attempts have been made to assess prepsychotic prodromal symptoms that do not usually come to clinical observation. Janzarik [98] and Gross [11], proceeding from clinical observation of residual symptoms

in the psychosis-free interval in patients with long histories of illness, found above all negative symptoms and signs of functional impairment, at that time called a "defect". Presuming that prodromal and residual symptoms are identical, Janzarik concluded that there must be an "antecedent defect state" observable before the first psychotic episode, whereas Gross [11] and Huber *et al.* [13] spoke of "basic symptoms" which, unlike psychotic symptoms, are direct expressions of degenerative brain changes. Such prodromal symptoms also to be found among the residual symptoms include, for example, affective flattening, avolition, and difficulties of thinking and concentration [13].

This approach is in part well founded, because negative symptoms and functional impairment constitute the most stable symptom dimension in schizophrenia. As retrospective analyses have shown [18], they tend to emerge long before psychosis onset (see Table 1.1). Negative symptoms manifest themselves before and simultaneously with positive symptoms and reach a maximum at the climax of the psychotic episode. As the psychosis remits, they too remit fully or in part [18]. In the further illness course, their prevalence shows a plateau [99]. But prodromal symptoms are not limited to the negative symptoms and functional impairment observable at the residual stage. Affective, especially depressive, dysphoric and other "unspecific" symptoms and behavioural anomalies play an important role at the prepsychotic stage.

### **Assessing Prodromal Symptoms Before Psychotic Relapses**

The first attempts at systematically assessing prodromal signs retrospectively were made in the context of targeted antipsychotic therapy of relapses. The advantages of this procedure are that the prodromal symptoms of relapses are not as remote in time as those of the first episode and that their prognostic efficiency can be prospectively validated [100–105]. The results obtained were valuable, but of insufficient predictive power, presumably due to differences in the type of prodromal signs included in the assessments and insufficient monitoring of their development over time.

In addition it is unclear whether the first psychotic episode is preceded by an interindividually identical pattern of prodromal symptoms and whether the prodromal symptoms in each individual case undergo changes in type and sequence. Meanwhile, intraindividual stability is presumed in clinical practice, and on that basis educational interventions are being offered particularly in relapse-oriented, targeted and crisis-intervention therapy [74,106–109].

**TABLE 1.4** The ten most frequent earliest signs of schizophrenia (independent of the course) reported by the patients

	Total ( <i>n</i> = 232) %	Men ( <i>n</i> = 108) %	Women ( <i>n</i> = 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

All items were tested for gender differences. Only "worrying" showed a significant difference ( $p < 0.05$ ).

Source: modified from Häfner *et al.* [10] by permission of Springer-Verlag.

Various items from scales for the identification of early signs and symptoms of psychotic relapses [102,110] have been integrated in subsequently generated instruments for the assessment of onset and early course in schizophrenia [24–26,111,112].

Systematic studies of the onset and prodromal symptoms of schizophrenia have relied on retrospective assessments of representative samples of first-episode cases of schizophrenia. Table 1.4, taken from the ABC Schizophrenia Study, shows the ten most frequent initial symptoms. These symptoms are equally frequent in men and women, except worrying, an item which is also more frequent in women in population studies. The majority of these items belong to two symptom dimensions, the affective–depressive and the negative one. The early occurrence of indicators of functional impairment, such as trouble with thinking and concentration or loss of energy, pointed to a risk of early consequences of the disorder in terms of global dysfunction and social decline.

## The Earliest Psychotic Symptoms

In the ABC Schizophrenia Study [18], the earliest positive symptom, delusions, appeared on average 14.3 months, the first hallucination 8.7 months and the first formal thought disorder 8.2 months before first admission. This result provides no evidence for the hypothesis that delusions are an expression of cognitive coping with the distressing

experience of hallucinations. The cumulative prevalence of delusions in the early course was 96%, that of auditory hallucinations 69% and that of thought disorder 62%. The fact that their prevalence approaches 100% reflects the role of positive symptoms as the leading diagnostic criteria for schizophrenia and, hence, also the type of patients included in or excluded from study samples of schizophrenia.

### **The Sequence of First-ever Onset of Symptoms**

Arranging the early symptoms by their time of emergence in a time matrix of up to 60 months before first admission, we found that four depressive symptoms (depressed mood, suicide attempt, loss of self-confidence and feelings of guilt) tended to occur five to three years before first admission. In the second time window, four to two years before first admission, with a clear overlap with the depressive syndrome, all the negative symptoms appeared. After a short interval characterized by the emergence of dysphoric symptoms, positive symptoms appeared in the last year before first admission. This sequential pattern of emergence of various types of symptoms gives the impression of a regular sequence of stages reminiscent of Conrad's [21] and Docherty *et al.*'s [22] models. However, these stages of the early course of schizophrenia reconstructed on the basis of group means do not necessarily apply to individual cases.

### **Depressive Symptoms as Prodromal Signs of Schizophrenia**

Several first-episode studies have consistently reported an extremely high frequency of depressive symptoms in the first psychotic episode: depressive mood or at least two depressive symptoms were found in 70–75% of cases [56,57,113–115].

As shown above, depressive symptoms frequently appear long before the first positive symptom [16,114,116]. In the ABC study cohort, the lifetime prevalence of depressive mood of a duration of two or more weeks – assessed until first admission – was 81%. In 39% of cases the symptom was continuously present, in 34% recurrent, and in 8% it occurred only once. Only 19% of the first-episode cases of schizophrenia reported not to have suffered from an episode of depressed mood [114].

A comparison of 57 first-episode patients with schizophrenia with 57 population controls matched by age, sex and place of residence showed that three out of four depressive symptoms were significantly more frequent in patients than in controls [114]. For depressive mood, the lifetime prevalence

at first admission was 70.2% in patients versus 19.3% in controls, for feelings of guilt 33.3% versus 10.5%, and for poor self-confidence 59.4% versus 12.3%. The relative risks of these symptoms ranged from 3 to 5. The frequency of attempted suicide at the early illness stage showed a nonsignificant excess of some 40%. This result will probably attain significance in larger samples, thus indicating that early clinical intervention is needed here.

The depressive syndrome emerging at the early prodromal stage of schizophrenia is presumably for the most part a pattern of response of the brain to fairly mild degrees of dysfunction. It seems to be produced by the same neurobiological processes that bring forth psychotic symptoms at a later stage. In contrast, at the beginning of the prodromal stage, the distressing factors associated with the disorder – e.g. traumatic experiences of the psychosis, hallucinations in particular, and social consequences of schizophrenia – do not yet play a role.

### **Comparison of Prodromal Symptoms in Schizophrenia and Depression**

We compared a representative subsample of 130 first admissions for schizophrenia from the ABC study with 130 age- and sex-matched “healthy” controls from the general population and 130 first admissions because of a depressive episode. Of the latter group, 70% suffered from a severe depressive episode. All these samples went through IRAOS interviews. Preliminary results show that DUI was significantly longer in depression (7.2 years) than in schizophrenia (5.3 years) ( $p < 0.05$ ). Equal proportions of both samples had received psychotropic medication before first admission: 19% of the patients with schizophrenia and 20% of the depressed patients.

As shown in Table 1.5, the two disorders share eight of their ten most frequent initial symptoms. These shared symptoms are primarily core depressive symptoms and indicators of functional impairment. In the further course of the prodromal stage, cognitive and social functioning deteriorate in depressive illness, too, but less markedly than in schizophrenia. This result is also reflected in a comparison of the cumulative prevalence rates of the ten most frequent symptoms in the early course of schizophrenia and depression (Table 1.6). Towards the end of the prodromal stage, the two disorders become clearly distinguishable, as psychotic symptoms appear and functional impairment clearly increases in schizophrenia and the depressive symptom dimension becomes predominant in depression.

TABLE 1.5 The ten most frequent initial symptoms (IRAOS items) in schizophrenia and in depression

Symptom	Schizophrenic patients		Depressive patients		<i>p</i>
	%	Rank	%	Rank	
Worrying	19.2	4	14.1	5	n.s.
Headaches, other aches and pains	10.3	–	13.2	8	n.s.
Nervousness, restlessness	21.9	2	6.2	–	<0.001
Anxiety	23.2	1	15.4	4	n.s.
Difficulties of thinking, concentration	17.1	5	16.5	3	n.s.
Depressed mood	20.6	3	34.9	1	<0.05
Loss of self-confidence	11.9	8	14.0	6	n.s.
Social withdrawal	11.6	9	13.3	7	n.s.
Disturbed sleep and/or appetite	15.0	6	21.9	2	n.s.
Loss of energy, slowness	13.5	7	8.5	10	n.s.
Loss of libido	4.1	–	8.5	10	n.s.
Oversensitivity	3.3	–	9.3	9	n.s.
Other changes in affect (blunted etc.)	11.1	10	0.8	–	<0.001

TABLE 1.6 The ten most frequent symptoms (IRAOS items) in the early course of schizophrenia and depression (period prevalence)

Symptom	Period prevalence from symptom onset until first hospital admission				
	Schizophrenic patients		Depressive patients		<i>p</i>
	%	Rank	%	Rank	
Worrying	74.6	9	94.6	4	<0.001
Nervousness, restlessness	88.3	3	81.5	10	n.s.
Anxiety	88.1	4	81.5	10	n.s.
Difficulties of thinking, concentration	93.8	1	96.9	3	n.s.
Depressed mood	84.9	5	100.0	1	<0.001
Loss of self-confidence	68.3	10	89.2	7	<0.001
Social withdrawal	79.8	8	90.8	6	<0.05
Disturbed sleep and/or appetite	93.8	1	98.5	2	n.s.
Loss of energy, slowness	82.5	6	93.8	5	<0.05
Delusional mood	68.3	10	4.6	–	<0.001
Delusional misinterpretations; delusions of reference	80.3	7	6.2	–	<0.001
Reduced spare time activities	63.5	–	89.1	8	<0.001
Reduced interests, citizen role	33.9	–	87.7	9	<0.001

## Depression in the Early Illness Course as a Prognostic Indicator of the Later Course

We studied the further illness course and the predictive efficiency of prodromal symptoms in 115 first illness episodes from the representative subsample of 130 first admissions at six cross-sections over five years after first admission [114]. Patients with schizophrenia who suffered from depressive mood ( $\geq 14$  days) in the early illness course were compared with age- and gender-matched patients without depressive episodes. The group with depression in the early course of schizophrenia showed significantly higher scores of depressive, but also of positive, negative and nonspecific symptoms in the first episode than did nondepressed patients. With remission of the episode, the mean score for depressive symptoms fell with psychotic symptoms without any indication of a "wave" of postpsychotic depression and remained more or less stable until five years after first admission. The presence of depressive symptoms in the early illness course predicted the occurrence of neither positive nor depressive or nonspecific symptoms after remission of the psychotic episode. In contrast, the absence of depressive symptoms in the early course was significantly correlated with affective flattening in the five years following first admission. The implication of this finding is that prodromal depression predicts a severe first psychotic episode, whereas a low score of prodromal depressive symptoms predicts more affective flattening after the remission of the episode.

## Early Functional Impairment and Social Consequences

Because of the early emergence of negative symptoms and functional impairment, most patients with schizophrenia started to suffer from social disability (Disability Assessment Schedule, DAS score  $\geq 2$ ) 51 to 24 months before first admission, long before they received appropriate treatment. Two years before first admission, 57% of the patients were considerably impaired, when judged by the overall DAS score ( $\geq 2$ ), in the domains of work performance, household activities, communication and leisure activities. This result raises the question at which point do the social consequences actually emerge.

The effect of early social disability on the further illness course can only be judged against a baseline, i.e. the social status or level of social development at illness onset. In the ABC first-episode sample, no significant differences were observable in the fulfilment of six main social roles between patients and controls at the age of illness onset. By the time

of first admission, patients with schizophrenia had fallen significantly behind the controls in several roles, most markedly in marriage or stable partnership. In sum, before illness onset, patients with schizophrenia were probably slightly, but not yet markedly and significantly, socially disadvantaged [62].

### **Age and Gender as Risk Factors**

Age and level of social development are highly significantly correlated. Men fall ill with schizophrenia 3 to 4 years earlier and, in our population of origin, married 2.5 years later than women. Their level of social development at illness onset, in the social role of marriage in particular, was therefore considerably lower than that of women. In addition, young men with schizophrenia showed a significant excess of socially adverse behaviour at first admission, e.g. self-neglect, lack of interest in finding a job, deficits in hygiene, aggressive behaviour and an elevated lifetime prevalence of alcohol and drug abuse until first admission. Female patients in contrast showed a significant excess of "social conformity", which presumably reflects a different type of adaptive behaviour. The socially adverse behaviour of young males has been confirmed in many population studies by elevated rates of conduct disorders, aggressiveness, antisocial personality, and alcohol and drug abuse [117,118]. In schizophrenia it must therefore be classified as gender-specific illness behaviour and not as a direct expression of the disorder [18].

The more favourable social course of the disorder observed in premenopausal women has to do with their higher level of social development in our culture as a result of a later illness onset and socially more adaptive illness behaviour. It does not appear to be related to women having a milder form of the disorder.

In a stepwise logistic regression [119], the level of social development at the first psychotic symptom and the socially adverse behaviour at the end of the prephase turned out to be the only factors significantly predicting five-year social outcome. The traditional prognostic indicators – age, gender, symptomatology and type of illness onset – merely had indirect effects via the level of social development at illness onset and illness behaviour. The symptom-related illness course showed no sex difference. It seems that the social course of schizophrenia is largely determined by social status or development at illness onset as well as the functional impairment and social disability that emerge in the early illness course. In early-onset illness, the consequence is social stagnation at a low level of social development; in late-onset illness, when a comparatively high level of social development has been attained, the consequence is social decline [62].

The earlier onset of schizophrenia in men has been widely reported (for review, see 120–122). The difference is not an artefact due to gender differences in diagnostic definitions and procedures, help-seeking behaviour or in the length of the early illness course [123–126]. An analysis of pooled data from 10 centres of the World Health Organization (WHO) Determinants of Outcome of Severe Mental Disorders (DOSMED) study [127] showed a mean difference of 3.4 years and some consistency across countries and cultures.

No such gender difference in age at onset is shown by siblings and twins [128,129], and this is almost exclusively because of women's reduced age of onset. Studying the ABC first-episode sample, Könnecke *et al.* [130] found that two risk factors for schizophrenia (at least one first-degree relative with schizophrenia and pre- and perinatal complications) significantly reduced the gender difference in age at onset by significantly lowering the age of onset in women, but not in men. When neither risk factor was present, the mean age of onset in women was 4.9 years later than in men. Underlying the protective effect of oestrogen that delays illness onset, there seems to be an antagonistic balance between the sex hormone and strength of predisposition to illness. The delaying effect of oestrogen on illness onset is the strongest in cases who have the weakest predisposition to illness or lack the two risk factors.

The duration of the prodromal stage does not differ significantly between the sexes or in five-year age groups over an age range of 12 to 59 years, apart from a slightly shorter duration in early-onset illness. Male onsets peak at 15 to 24 years, female onsets at age 15 to 29 years. Because of decreasing oestrogen secretion with age, women aged 45 to 50 years show a second peak of onsets lower than the first one. The second peak has also been demonstrated on pooled data from the WHO DOSMED study [127] and in the Camberwell case-register population [126]. The explanation of these sex differences by a protective effect of oestrogen [125,131] was supported in animal experiments by the attenuating effect that a four-week oestrogen treatment had on apomorphine-stimulated dopaminergic behaviour as a result of sensitivity reduction in central D2 receptors [132,133].

### Further Syndromes of the Prodromal Phase

Less frequent than depressive symptoms in the early course of schizophrenia are manic and hypomanic symptoms. In studies their frequencies range from 3% to 10% of cases depending on the symptoms defined. They are in part associated with other bipolar symptoms and primarily have episodic or intermittent courses [99].

The catatonic syndrome, which was fairly frequent before the advent of neuroleptics and still is in some developing countries, has become rare in Western Europe and the USA. Only recently have catatonic features started to attract renewed interest [134]. They seem to be most prevalent at a young age. But these fairly rare catatonic subtypes do not seem to be very stable over time [135].

### **Lists of Prodromal Features of Schizophrenia**

Yung and McGorry [41] and Edwards and McGorry [74] have listed the prodromal features in first-episode psychosis most commonly described in the literature. All these symptoms have also been included in the IRAOS and were assessed in the ABC Schizophrenia Study:

1. reduced concentration and attention;
2. reduced drive and motivation, anergia;
3. depressed mood;
4. sleep disturbances;
5. anxiety;
6. social withdrawal;
7. suspiciousness;
8. deterioration in role-functioning;
9. irritability.

Edwards and McGorry [74] also list the four symptom categories experienced prior to a first or current psychotic episode. They, too, are based on the literature and the authors' own data:

1. Changes in affect: suspiciousness, depression, anxiety, mood swings, feelings of tension, irritability, anger.
2. Changes in cognition: odd ideas, vagueness, difficulties with concentration or recall.
3. Changes in perception of self, of other people, of the world at large.
4. Physical and perceptual changes: sleep disturbances, appetite change, somatic complaints, loss of energy or motivation, perceptual disturbances.

These indicators of the prodromal stage can be informative but, as they are described in a quasi-cross-sectional manner and no information is provided on their frequencies or sequence of emergence, they are not helpful in reconstructing the early illness course.

It was also the McGorry group which brought to our attention the existence of two further types of symptoms in incipient psychosis, i.e. attenuated psychotic symptoms and the rarer BLIPS [41].

### **Can Substance Misuse Trigger a Premature Onset of the Prepsychotic Prodromal Stage?**

In the ABC Schizophrenia Study, the lifetime prevalence of alcohol abuse until age at first admission was 24% for the first-episode sample and 12% for matched controls from the same population [119,136,137], and that of drug abuse 14% for patients and 7% for controls. Studies on the topic almost invariably show a preponderance of men in substance abuse. We found a cumulative prevalence (until first admission) of any type of substance abuse of 39% for men and 22% for women. Cannabis was the most frequently abused substance (88%), followed by alcohol (58%).

In this study, 35% of the patients with drug abuse and 18% of those with alcohol abuse started with the abuse behaviour in the same month as the onset of schizophrenia occurred. In this small group, precipitation of illness onset by substance abuse cannot be excluded, especially since these patients were significantly younger (8 years) at illness onset than non-abusing patients. In contrast, we could not support in our study the dopamine-receptor hypothesis of a drug-related precipitation of the psychotic episode. However, presence of alcohol and drug abuse in the early illness course predicted an elevated score for positive symptoms in both the psychotic episode and at five cross-sections over five years following first admission. In contrast, substance abuse significantly reduced affective flattening with a latency of several years, probably in the context of a dysfunctional self-therapy of apathy. At the same time, substance and drug abuse may have contributed to poorer compliance with antipsychotic therapy, which again could have contributed to an increased level of positive symptoms [137].

### **Premorbid Personality Traits**

Indicators more closely related with the disorder that have been reported from the recent prospective epidemiological cohort studies seem to offer prospects of identifying at-risk persons. The Swedish conscript study [138] of 50 084 young men aged 18 to 20 years showed that four items (having fewer than two friends, preference for socializing in small groups, feeling

more sensitive than others, and not having a steady girlfriend) were associated with a high relative risk (odds ratio: 30.7) of being admitted to inpatient treatment with a diagnosis of schizophrenia in a period of risk of 13 years. But in the total sample a positive response to all four items predicted psychosis only in 3%, because of the high prevalence of these features in the conscript population.

Davidson *et al.* [139] and Rabinowitz *et al.* [37] studied 16- to 17-year-old Israeli male conscripts. The authors identified 692 individuals who had been hospitalized with a diagnosis of schizophrenia for the first time in a mean period of nine years following initial testing. When these individuals were compared with the entire conscript population and with matched controls, the results pointed in the same direction as in the Swedish study. The main indicator of risk was poor social functioning, with an effect size difference of 1.25. With effect sizes ranging from 0.44 to 0.58, the young males later hospitalized with a diagnosis of schizophrenia also fared worse than controls in all tests of cognitive functioning.

As poor communicability and lack of social drive have also been found in population cohort studies of persons later falling ill with schizophrenia, this stable behavioural dimension probably represents the most pronounced psychological indicator of vulnerability to schizophrenia.

In prospective assessments of schizophrenia onset the distinction must be drawn between prodromal symptoms and premorbid antecedents or indicators of other causes. Since schizophrenia onset is marked by unspecific symptoms in 73% of cases, it is a very difficult event to recognize in prospective studies of whatever design. The same is true for the diagnostic classification of the first unspecific symptoms. For this reason, as long as sufficiently powerful discriminatory and predictive early indicators of schizophrenia are lacking, schizophrenia onset and prodromal stage can only be assessed retrospectively in cases clearly diagnosable as schizophrenia, ideally in recent-onset, representative first-episode samples.

Three aspects of transition from a premorbid risk status to a prodromal stage of the disorder can be distinguished: (a) new symptoms appear and those already persisting deteriorate, frequently involving increased subjective distress; (b) symptoms accumulate, probably following a typical pattern (stage model); and (c) progressive deterioration occurs in social and cognitive functioning or in deficits measured by neuropsychological tests. A characteristic of the prodromal stage of key importance is the gradient of change or deterioration.

The early illness stage usually involves increasing communicative and social impairment and behavioural changes detrimental to the person's functioning in the social, school, work and family environment.

## INSTRUMENTS FOR ASSESSING THE ONSET AND EARLY COURSE OF SCHIZOPHRENIA

The success of early intervention programmes depends on the degree to which help-seeking can be mobilized among at-risk persons in the population, for example by carrying out awareness programmes that provide basic information on schizophrenia and its treatment [74,140]. Antistigma and information campaigns play an important role, as successfully demonstrated by the WPA Global Programme Against Stigma and Discrimination Because of Schizophrenia [141]. Another precondition is a well-functioning network of low-threshold pathways to care [142], that is, easily accessible and as far as possible stigma-free early intervention centres or other suitable mental health services [16,143].

### Indicators of Prognostic Accuracy

Early recognition inventories should allow a correct identification of "at-risk mental states". This objective is attained when as large a proportion of at-risk persons as possible is classified as such (i.e. the test for diagnostic ascertainment is highly sensitive) and at the same time as large a proportion of risk-free persons as possible is identified as not being at risk (specificity). But there is no single symptom or single risk factor of sufficient diagnostic efficiency that early recognition could be based on. Usually a selection of several prodromal symptoms is used as a basis for a total score that indicates psychosis risk. Besides symptom scales, other risk factors can be taken into account, e.g. biological indicators such as smooth pursuit eye movement or MRI parameters, in order to create the best possible criteria. A technique for generating combinations of indicators is the Receiver Operating Characteristic Analysis (ROC Analysis), which helps to find out an optimum cut-off based on a combination of single items [112]. Further indicators of the predictive power of early recognition inventories are the positive and the negative predictive power (PPP and NPP). These measures are suited to assessing individual psychosis risk in actual test situations when the persons examined present or do not present a particular symptom (more generally: receive a positive or a negative test result, which usually represents a cut-off based on a selection of several features).

Contemporary early recognition instruments of high sensitivity for identifying large proportions of at-risk persons in the general population all have insufficient specificities. But even if sensitivity and specificity were satisfactory (e.g. 0.95), the number of false positive cases would be rather high, because of the low base rate of schizophrenia in the general

population. Let us presume that 1% of the population at large is at risk for schizophrenia. By screening 1000 individuals only 10 at-risk persons would be identified. The problem is the high number of 50 false positives among the 990 persons not being at risk.

### **Strategies to Improve the Predictive Accuracy of Diagnostic Tests**

An attempt to solve this problem is a multi-level procedure of case identification (sequential screening) [144]. If case identification is based, instead of on the general population, on a group of people who have already contacted a general practitioner, psychologist or a counselling service because of mental problems, the rates for false positive cases will drop considerably.

The Early Recognition Inventory (ERiraos), which we developed in the German Research Network on Schizophrenia, pursues a two-step strategy for the identification of at-risk persons. In the first step a screening procedure of a high sensitivity and slightly increased risk threshold is applied in general practices, counselling services or schools. In these populations at an increased risk, the ratio of risk persons to non-risk persons is far better in balance and the number of false positives much lower. The risk persons thus identified are referred to a specialist service or an early intervention centre where they will be examined by more differentiated instruments of the highest possible diagnostic and predictive power. In the efforts to validate such early recognition inventories, which have to be practical and economic to use and produce favourable results, biological tests may follow at a third level of risk identification. Designs of that type are being pursued in the Edinburgh high-risk study [89] and in a multicentre study in Germany [145].

An early recognition inventory successfully validated and fulfilling all the requirements mentioned is not yet available. To achieve an acceptable number needed to treat (NNT) and, hence, to meet the main economic and ethical requirements, risk predictions in early recognition instruments (state criteria) will be supplemented by "longstanding biobehavioural markers" [146]. The ones most frequently used are age of risk (e.g. up to 30 years), family history (at least one first-degree relative with schizophrenia), schizotypal personality and history of obstetric complications. An example of a set of risk criteria, which has been prospectively validated, was developed by Yung *et al.* [147,148] and Edwards and McGorry [74] with their operationalized concept of ultra-high risk (UHR) for psychosis. Included are the following trait factors [147]: age of risk 16 to 30 years,

schizotypal personality or a first-degree relative with a history of psychotic disorder. As state indicators they chose attenuated psychotic symptoms or BLIPS and a change in mental state and functioning which results in a loss of 30 points or more in the Global Assessment of Functioning (GAF) scale for at least one month. Such a definition of an increased risk has considerable advantages in terms of diagnostic and prognostic power. Its weaknesses are the selective nature of risk assessment and that it does not include a rule for quantitative risk estimation.

### The Chapman Scales

Chapman and colleagues [149–154] produced a list of early symptoms by studying first-episode cases of schizophrenia retrospectively. They focused on the cognitive character of the changes preceding the psychotic symptom pattern – disturbances of attention, perception and memory – supplemented by indicators of psychomotor functioning. They were the first to develop experimental procedures for assessing disordered perception on this observational basis. Proceeding from the construct of “psychosis proneness”, they developed several scales for the assessment of psychotic and psychotic-like experiences [153]: the 35-item Perceptual Aberration Scale, the 30-item Magical Ideation Scale, the Impulsive Nonconformity Scale (51 items) and the Social Anhedonia Scale (40 items). The scales were tested for internal consistency and retest reliability. The authors concluded that their scales are suited to identifying persons with schizophrenia proneness, but not to reliably predicting schizophrenia risk, nor do the scales permit one to distinguish between risk for schizophrenia and other types of psychotic disorder or affective illness with psychotic symptoms. If we enter the numbers of psychotic transitions as based on psychosis proneness in the four-cell matrix for calculating the usual indices of diagnostic efficiency, the probands identified by the two subscales tested as valid and the control group yield a high sensitivity of 0.92, an extremely low rate of false negatives (0.003%) and a negative predictive power of 99%. In contrast, the values for specificity (0.43), false positives (55%) and positive prognostic power (5.6%) are less favourable. The conclusion that the number of people with psychosis proneness by far exceeds the number of persons ever falling ill with schizophrenia may be correct, but it also means that the concept is hardly suitable for identifying persons at risk for psychosis if the aim is to refer them to treatment. Nevertheless the concept can be used for screening purposes, because it is fairly easy to use and helps to identify all at-risk persons at an early stage (10 to 15 years before the onset of psychotic symptoms).

### The Bonn Scale (BSABS)

On the basis of the results of a follow-up study of 502 first admissions to the University Hospital in Bonn [11,13], Gross and colleagues constructed the Bonn Scale for the Assessment of Basic Symptoms (BSABS) [155], which includes subscales on “dynamic deficiency”, cognitive disturbances of thought, perception and motor action, “coenaesthesias” and disturbances of the central autonomic nervous system and sleep disturbances. Each single item is rated by its closeness to positive symptoms in three degrees: (1) characteristic, which means the phenomenon observed is sufficiently similar to certain full-blown psychotic symptoms, (2) accompanied by a sense of strangeness, splitting or restlessness, and (3) associated with a delusional explanation. The instrument does not include a time matrix that would help to determine the gradient of change or timepoint and/or order of appearance, persistence and remission of symptoms.

The prodromal symptoms listed in the BSABS have attained the highest predictive power so far in predicting transition to psychosis, without taking the three degrees of intensity into account. Klosterkötter *et al.* [156] demonstrated transition from attenuated positive symptoms to full-blown psychosis in a descriptive design and predicted onset of schizophrenia in a prospective study over a mean follow-up period of 9.6 years [157]. Of a total of 338 patients who had been referred to any of the five German university hospitals participating in the study under various diagnoses because of suspected incipient schizophrenia, 160 patients who did not present psychotic symptoms at the initial assessment according to clinical records were followed up over a mean period of 9.6 years after first assessment. By the time of follow-up, 79 of these patients had fallen ill with DSM-IV schizophrenia – women on average after 4.3 years, men after 6.7 years [112]. Only two of these cases had not shown any basic symptoms at initial assessment, which yields a high sensitivity of 0.98 and a very low rate of false negatives of only 1.3%. Of the 81 patients who did not develop a DSM-IV schizophrenia during the study period, 33 had presented at least one basic symptom and 48 no basic symptoms. This corresponds to a rather high proportion of false negatives (20.6%) and a clearly lower specificity of 0.59. On the whole, however, a remarkably high proportion of the predicted outcomes were classified correctly (78%).

Klosterkötter *et al.* [112] also analysed the prognostic accuracy of the BSABS subsyndromes and found that “information processing disturbances” yielded the best result (PPP = positive predictive power: 0.77).

Information on the probands’ diagnoses and other characteristics of this highly selected group at entry into the study is lacking. Therefore, it is unclear to what type of at-risk population the results are applicable. Nevertheless, several of the basic symptoms have been included in other

early recognition instruments and are being subjected to further tests of validity.

### **Instruments Developed by the McGorry Group**

McGorry and colleagues in Melbourne started their analyses with the Royal Park Multidiagnostic Instrument for Psychosis (RP-MIP) [158,159]. This covers a large number of symptoms and diagnostic categories, using repeated interviews and multiple information sources. It is designed for the assessment of patients during the initial period of a psychotic episode and based on established international diagnostic instruments and classifications.

The Comprehensive Assessment of At-Risk Mental States (CAARMS), developed by the McGorry group [160], is an instrument designed for the prospective assessment of sub-threshold psychotic symptoms in high-risk groups. It consists of eight subsections (TC = disorders of thought content; PA = perceptual abnormalities; CD = conceptual disorganization; MD = motor disturbances; CA = disorders of concentration, attention, and memory; EA = disorders of emotion and affect; E = impaired energy and S = impaired tolerance to normal stress). Included in the TC scale, which measures attenuated and sub-threshold delusions, are five dimensions: content, conviction, action, frequency and duration. In the other domains three main aspects are distinguished and assessed for each symptom: intensity, frequency and duration, and degree of severity is determined by a combination of these aspects. A further subsection includes eight of Huber's basic symptoms, the last section three dissociative symptoms (amnesia, depersonalization, derealization). The interview is semistructured, sample questions (probes) are given for each symptom, and each section closes with additional questions on duration, frequency and pattern of symptoms.

### **Instruments Developed by the McGlashan Group**

Researchers at the Prevention through Risk Identification, Management, and Education (PRIME) Research Clinic of Yale University developed the Structured Interview for Prodromal Syndromes (SIPS) [161] and, to assess the severity of prodromal symptoms, the Scale of Prodromal Symptoms (SOPS) [162]. The SIPS is a diagnostic interview, the SOPS an associated severity scale. The aim of these instruments is to help to exclude current or previous psychosis, to diagnose one of three types of prodromal states and to assess the severity of prodromal symptoms. The following three

prodromal states are distinguished: (a) recent psychotic symptoms of short duration (in particular BLIPS), (b) attenuated psychotic symptoms and (c) a combination of genetic risk and recent deterioration of functioning. The symptoms are rated on a six-point severity scale. The five psychotic symptoms (unusual thought content/delusional ideas; suspiciousness/persecutory ideas; grandiosity; perceptual abnormalities/hallucinations; conceptual disorganization) denote a clear-cut psychotic state only at the highest severity, and stages 1 to 5 denote different degrees of prepsychotic severity. The six negative symptoms (social isolation or withdrawal; avolition; decreased expression of emotion; decreased experience of emotions and self; decreased ideational richness; deterioration in role functioning) as well as the four disorganization symptoms (odd behaviour or appearance; bizarre thinking; trouble with focus and attention; impairment in personal hygiene/social attentiveness) and the four general symptoms (sleep disturbance; dysphoric mood; motor disturbances; impaired tolerance to normal stress) are also rated on a six-point scale.

Results from a reliability and validity study are presented by Miller *et al.* [163]: inter-rater reliability as based on 18 patients (prodromal versus non-prodromal) was 93% (kappa: 0.81). As evidence for the prognostic power of the instruments the authors found that 6 out of 13 prodromal patients transitioned to psychosis within 6 months (46.2%) and seven (53.8%) within a year.

## **Instruments Developed by the Häfner Group**

### *The Interview for the Retrospective Assessment of the Onset of Schizophrenia (IRAOS)*

The IRAOS [24–26] is the most differentiated of the currently available retrospective early-recognition instruments. It is now available in an enlarged version [27], applicable to all types of psychotic illness and fully compatible with the first version [24–26]. It comprises the assessment of individual biography and social development in the most important social roles, of premorbid adjustment, emergence and accumulation of prodromal signs, of symptoms, abnormal behaviour, functional impairment and social disability. On the basis of IRAOS data it is possible to assess symptom onset, prodromal and psychotic onset, accumulation of symptoms and impairments, and social course. The IRAOS is used by psychiatrists or psychologists.

The development of the IRAOS started with the compilation of a list of prodromal signs and symptoms on an empirical basis. First the

literature was skimmed through for symptoms of incipient schizophrenia. A total of 240 symptoms were identified and were included in a questionnaire submitted to experts. Psychiatrists with at least two years work experience at four psychiatric hospitals were asked to rate the relevance of the prodromal and psychotic symptoms listed in incipient schizophrenia.

The list of symptoms generated in this way was integrated in the IRAOS in the form of closed questions and supplemented by open questions that the patient or his/her key informant are asked on the symptoms marking the onset of the disorder and on the timepoint of their emergence. During the revision of the IRAOS the symptom list was expanded to include 128 items, in order to be able to determine at which point in time the person assessed first fulfilled the criteria for an ICD-10 diagnosis of schizophrenia, affective disorder or other psychosis.

Biographical data on social development and illness course are collected on the basis of six roles relevant in the professional and family context and to the individual's objective social status. In this way individual social development, baseline at illness onset and possible interruptions or delays in social ascent can be determined. Besides the general sociodemographic data the IRAOS provides information on the patient's physical health, family situation and history of mental illness. Major life events are assessed on the basis of a layered time matrix divided into units which increase in length with growing distance to the interview (weeks, months, years). Individual anchor events, such as birthdays, holidays and family celebrations are recorded, which help the interviewee to remember the time of symptom emergence in relation to these events. Symptom emergence and remission are recorded in a calendar of episodes.

In a test-retest design two independent interviewers evaluated the IRAOS symptoms in a period varying from 7 to 15 months (mean: 10.4 months). As kappa values were low due to skewed symptom distributions, we report pairwise agreement rates (PAR): for 47% of the IRAOS symptoms PAR was between 0.60 and 0.79, and for another 27.3% it was between 0.80 and 1.00. Only in 4.5% of the symptoms was PAR below 0.40.

To control for recall deficits or memory biases, data were collected from three sources: patient, his/her closest relative and documents (e.g. medical records). The comparison of prodromal signs and symptoms as perceived by the patients and their significant others and registered by a family doctor, in school records etc. offered an important chance for testing the reliability of the information given by the patients. Hambrecht and Häfner [164] compared individual IRAOS data obtained from the patients in the ABC first-episode sample with the data provided by their family members who were in sufficiently close contact with the patients during the period of onset and early illness. Self-perceived symptoms such as subjective

thought disorders, which usually cannot be observed by others, had relatively low kappa and percentual agreement rates. High agreement rates of 0.8 and 0.9 were achieved on observable behaviour such as attempted suicide or disturbances of concentration and thinking. Concerning the time of symptom emergence, single psychotic phenomena such as delusions and hallucinations were frequently observed by the relatives with an average of only one month's delay. Nonspecific and negative symptoms, such as mild depression or loss of energy, were frequently noticed by the family members with a mean delay of six months. Still somewhat later (up to 12 months), these symptoms were noted in the documents such as medical case records etc., demonstrating that the patients communicated the onset of their first symptoms with a shorter delay to their relatives than to their doctors. The authors found a surprisingly high degree of agreement in overall estimates of the time of illness onset and of the milestones of the early course between the patients and their family members. As a result, the retrospectively collected IRAOS data yields a valid representation of the early course of schizophrenia at least as far as mean values are concerned.

Meanwhile, the IRAOS has been applied not only in the ABC study, but also by a great number of research teams working on the early and later course of psychosis in many countries (e.g. 165,166).

### *The Early Recognition Inventory (ERiraos)*

The ERiraos is a two-step procedure. First, potential at-risk persons are identified using a checklist. Then the persons thus identified are examined at an early intervention centre using the complete symptom list of the inventory as well as the modules and associated instruments designed for the assessment of risk factors.

The 17-item screening instrument of the ERiraos, the checklist, is designed to make persons at an increased risk of psychosis aware of this risk in order to enable them to get in touch with an early intervention centre. The checklist should sharpen the awareness of general practitioners, counselling services, psychologists, teachers etc. and facilitate the recognition of psychosis risk as early as the prodromal phase. If a defined cut-off is reached, the person in question should be referred to an early intervention centre for a more detailed risk assessment. The checklist is designed to avoid a hastened exclusion of at-risk persons (so-called false negatives) thus providing a low threshold in order to make sure that as few false decisions as possible are made at this stage of diagnosis.

The checklist is available as an interview and as a questionnaire. The checklist interview is administered by a general practitioner or some other

professional contact person, whereas the questionnaire version is done by the respondent without assistance.

The core element of the ERiraos is the symptom list, which includes 110 symptoms of beginning schizophrenia. It mainly contains prodromal symptoms of schizophrenia (unspecific symptoms, depressive symptoms, basic symptoms), but in addition it also includes psychotic symptoms, because in some at-risk persons obvious psychotic symptoms of short duration are already present in the prodromal phase. The inclusion of psychotic symptoms makes it possible to identify transition to psychosis, a prerequisite for recognizing psychotic episodes earlier than under the current conditions of treatment. It also allows one to study the course of schizophrenia from onset to full blown psychosis and the long-term course of the disorder.

The ERiraos symptom list is divided into 12 sections:

- S01 Introductory questions
- S02 Changes in mood, interest and drive
- S03 Disturbance of sleep and appetite
- S04 Changes in personality
- S05 Dysfunctional behaviour
- S06 Anxiety and obsessive-compulsive symptoms
- S07 Thought disorder
- S08 Disorders of self and delusions
- S09 Impaired bodily sensations (coenaesthesia)
- S10 Abnormal perceptions
- S11 Motor disorder
- S12 Observed behaviour

For risk persons, both the present state and previous course of illness before the first interview are recorded. To monitor the success of intervention, the ERiraos symptom list is carried out prospectively at different timepoints. The months in between the follow-ups are rated retrospectively. Of main interest at the first interview are the questions of how far the illness, e.g. the prodromal phase, has already progressed, and the sequence of symptom occurrence. Included in the ERiraos are roughly two thirds of the IRAOS symptoms, but its aim is to assess not only symptom onset, but also the increase in symptom severity (distress) and functional impairment. The symptom list of the ERiraos should help us to decide whether the persons assessed require intervention or not because of a risk for schizophrenia.

In order to improve predictions of illness risk by considering further risk factors, four modules were additionally integrated in the ERiraos and supplemented by two associated instruments. These are family (genetic)

risk, complications during pregnancy and childbirth, developmental retardation during infancy, comorbidity (especially if linked to alcohol and drugs), delinquency and schizotypal personality. The diagnostic criteria for schizotypy can be evaluated on the basis of the symptom list. A fourth module is presented as a questionnaire and given after the interview to assess ordinary life situations, serving as a further assessment of schizotypal features. The module on medication includes questions on the type and dosage of already prescribed medications, either current or earlier [172].

To determine the reliability of the ERIRAOS symptom list, videotaped interviews were presented to 9 or 10 interviewers at three rating sessions. The symptom ratings of the interviewers were compared with the standard ratings of the trainer team. Kappas for "symptom present in the year before interview" range between 0.56 and 0.77; for the rating of "subjective stress associated with the symptom" between 0.54 and 0.77. The reliabilities increased from the first to the third assessment.

An analysis based on 83 checklist interviews was also carried out. Prodromal symptoms assessed by the checklist have been present at least in 24.1% (ideas of reference) at-risk persons and in a maximum of 84.3% (tension, nervousness, restlessness). Checklist symptoms are more frequent in the late prodrome compared to the early prodrome ( $p < 0.05$  for ten symptoms). The most frequent prodromal symptoms are nonspecific (negative symptoms: loss of energy, loss of concentration, social withdrawal; depressive symptoms: depressive mood, loss of self-confidence, increased fatigability).

ERIRAOS data of 75 patients, interviewed at the early intervention centres in Bonn, Cologne, Dusseldorf and Munich, have been collected. Symptom onset dates back between 4.7 and 9.1 years. The earliest symptom is "preoccupation with mysterious things", but this item probably indicates a persistent schizotypal personality trait. The most frequent early symptoms are nonspecific (worries about mental functions, depressed mood, tension and restlessness) and are negative symptoms/social disabilities and depressive symptoms. In all, 73% of the patients fulfilled the checklist criteria already one year before inclusion in the early intervention programme.

In addition to the prodromal symptoms, 85% of the sample report further risk factors: 60% report difficulties in everyday situations, indicating schizotypal personality traits, 58% report alcohol or drug use, 21% obstetric or birth complications, 21% delinquency and 11% familial load with psychosis. In the subgroup with additional risk factors, the percentage of patients fulfilling the checklist criteria one year before inclusion in the early intervention study is increased from 73% to 87%.

## EVALUATING (VALIDATING) PRODROMAL SIGNS AND CRITERIA

### Validating the DSM-III-R Prodromal Symptoms

Listed in the DSM-III-R were nine prodromal symptoms of schizophrenia, generated by consensus and not empirically [167]: social isolation or withdrawal; marked impairment in role functioning; markedly peculiar behaviour; marked impairment in personal hygiene; blunted, flat or inappropriate affect; dissociative or metaphoric speech; odd or bizarre ideation; unusual perceptual experiences; marked lack of initiative, interests or energy.

The first attempt at cross-sectionally validating these prodromal signs was made by Jackson *et al.* [168] in a sample of 313 first episodes of various functional psychoses. Where the standard DSM-III-R assessment is utilized, inter-rater reliability is poor, as is test-retest reliability [97]. Analysing the comparative frequencies and diagnostic efficiencies of the prodromal signs in a retrospective design, the authors found relatively poor distinguishing efficacies between diagnoses. In a second study, McGorry *et al.* [169] followed up the prevalence of these nine prodromal symptoms prospectively in a large representative sample ( $n=2525$ ) of Australian school children at mean ages of 12, 14 and 16 years. The result supported the low discriminatory efficacy of these prodromal symptoms found in comparisons of diagnosed functional mental disorders: the prevalences ranged from 8% to 51% indicating a high frequency in the healthy population and a low specificity for schizophrenia.

A third study to improve the diagnostic efficiency and predictive power of these prodromal symptoms was conducted by McGorry *et al.* [170]. Of 200 individuals experiencing a first-onset psychosis and aged 14 to 46 years (mean: 25.23), 61 (30.5%) suffered from schizophrenia, 49 (24.5%) from schizophreniform disorder. Two sources were interviewed, patients and relatives, to obtain detailed information on the prodromal period. This information was registered in the RP-MIP. The result was that three items and more had a higher predictive power than single items. When the duration of the prodromal phase and especially prepsychotic deterioration in functioning were taken into account, the predictive power rose considerably. This means that the gradient of change – in clinical terms the observed deterioration – plays an important role in prognosis. Hence, the key finding was that prodromal deterioration which is relatively prolonged – a feature of course in combination with a symptom cluster – predicts schizophrenia within a first episode of psychosis sample as quite likely, but not with sufficient certainty. Meanwhile, the prodromal symptoms of schizophrenia listed in the DSM-III-R were dropped from the DSM-IV.

## First Results from Prospective Validation Studies of Early Recognition Inventories and Risk Criteria

Meanwhile, first studies on the risk of transition to psychosis in UHR individuals have been published. Yung *et al.* [147] identified 20 UHR individuals aged 16 to 30, referred for treatment and followed up at monthly intervals over 6 months. Eight (40%) of these patients developed a frank psychosis. Five of the patients became psychotic as early as the first month. Later studies conducted in larger samples have yielded very similar results for risk periods of one to two years, with the proportion of patients transiting to psychosis ranging from 25% to 41% [74]. A further independent validation of the UHR criteria was done in a control group of UHR cases in a randomized early-intervention study [70]. At one year of follow-up, the rate of transition to psychosis was 35.7% for the controls.

## CONCLUSIONS

On all dimensions of the disorder we call schizophrenia – symptoms, neuropsychological changes and functional impairment – the prodromal stage and the early psychotic stage preceding the climax of the first episode constitute the most active, most rapidly progressing and hence the most decisive period in terms of the social consequences of the disorder. It may even be of far greater importance for further illness course and social outcome than any of the later stages of illness. The prodromal period usually interferes with educational and occupational career at a stage most vulnerable to influence. In accordance with results from the ABC Schizophrenia Study, Eaton and Harrison [171] describe the onset of schizophrenia as follows: “The type of symptoms that show up first are affective, negative and cognitive and social dysfunction: depressed mood, trouble with concentration, poor work performance, subtle social deficits”.

The durations of the prodromal stages and of the psychotic episode until the climax of psychosis vary a great deal. According to studies on the topic, the mean duration of the prepsychotic prodromal stage ranges from two to five years (ABC Study: 4.8 years), and the psychotic stage until first admission currently still lasts slightly more than a year. In two thirds of cases more than a year elapses from illness onset until first admission, whereas only some 15% experience an acute type of onset of four weeks or less. Especially in patients with a chronic early course, early intervention appears promising and, since first successful results have appeared, also meaningful. The precondition is that individuals at incipient risk seek help, diagnosis can be given early and the time of onset of the psychotic episode

and the future illness course are predicted with sufficient accuracy. Three quarters of all cases of schizophrenia experience a prodromal stage without specific psychotic symptoms. We must find ways of detecting and recognizing the illness and of predicting its further course earlier than is currently the case, by using appropriate instruments and designs at early-intervention centres and by increasing awareness and knowledge in the population at risk.

When prodromal signs have appeared and symptoms and/or functional impairments increase (a positive gradient), it is very likely that it will come to a full-blown psychosis. When psychotic symptoms have emerged and persisted for at least one week, a schizophrenia spectrum disorder can be diagnosed and antipsychotic therapy initiated. The validation of early recognition inventories as a basis for early intervention will be a focal point of future research.

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