Eur Arch Psychiatry Clin Neurosci (2004) 254 : 117–128 DOI 10.1007/s00406-004-0508-z

ORIGINAL PAPER

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Early detection and secondary prevention of psychosis: facts and visions*

Received: 5 March 2004 / Accepted: 16 March 2004

Abstract As effective and practical approaches to primary and universal prevention of psychosis are lacking, intervention efforts are targeted at the early stages of schizophrenia to prevent (by way of secondary prevention) or postpone psychosis onset, reduce severity of illness or at least ameliorate the social consequences involved. Early intervention requires early detection and early recognition (diagnosis) of persons at risk and early prediction of psychosis. Within the German Research Network on Schizophrenia (GRNS) awareness programmes are being carried out in several German cities, and these efforts are already improving utilisation of early-recognition and early-prediction services by at risk persons. The empirical basis of developing a two-step early-recognition inventory and strategies of application will be discussed. This instrument is supplemented by a set of cognitive tests, prospectively validated in the GRNS. Results from preliminary analysis of data covering a two-year period demonstrate that the inventory and the cognitive tests are readily accepted. When used for screening in non-specialist settings and at the next level, i. e. at early-recognition centres, they seem to permit identification of at-risk persons. Early intervention is being tested 1) in a randomised controlled multi-centre trial consisting of a specially developed cognitive-behavioural therapy in the early (prepsychotic) prodromal state and 2) on additional treatment with appropriate doses of amisulpride in the late prodromal (early psychotic) state. Preliminary data from Study 1 covering 16.3 months show significantly fewer transitions to psychosis and from Study 2 reduced positive and negative symptoms and improved global functioning compared with controls who had received normal clinical treatment. As a result, both the early-recognition inventory plus cognitive tests and the two therapy strategies are feasible. We hope that the favourable trend indicated by the preliminary data will be confirmed in the final analysis planned for 2005 and the objective of implementing effective and practical secondary prevention of psychosis and its consequences will be attained.

Key words schizophrenia · prodrome of schizophrenia · early intervention · early-recognition inventory · cognitive-behavioural intervention

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* This paper was written within the framework of the German Research Network on Schizophrenia and was funded by the German Federal Ministry for Education and Research BMBF (grant 01 GI 0236).

EAPCN 508

Introduction

Primary and secondary prevention of schizophrenia are topics not yet researched in all their aspects. The aim of primary prevention is to eliminate aetiological risk factors or to strengthen individual resilience to the morbid risk. The chances of identifying types of at-risk persons will increase as more and more risk genes are being localised and cloned and their pathophysiologically active products are being discovered. But prospects of primary prevention at the genetic level have not yet emerged.

To reduce damage of the developing brain during pregnancy, birth or in early infancy by improving maternal care (Warner 2001) is expensive because of the high frequency of such complications. However, such an approach would have beneficial effects on other CNS risks, too, such as epilepsy, ADHD, learning disability and mental retardation.

According to the results of a Finnish adoption study (Tienari et al. 2002) a favourable family atmosphere in childhood and adolescence is a protective factor improving individual resilience. Preventive interventions would have to be focused on high-risk children, but the prospects of bring about a necessary change in an unfavourable family atmosphere are limited.

Another way of strengthening individual resilience might be offered by oestrogens with their neuroprotective and functional effects on the genomic and the neurochemical level (Häfner et al. 1991; Häfner 2003; Fink 1995; Behl 2002; Kulkarni et al. 2002). But a substance sufficiently effective and without hormonal side-effects is still a rather distant vision.

As a result, current hopes rest on secondary-preventive early intervention, especially since the early illness course has been shown to be the most active period of illness, during which most of the consequences of the disorder occur (Häfner et al. 1999 a).

The aims of early intervention are to prevent or postpone psychosis onset, reduce severity of illness or at least ameliorate the social consequences involved.

The preconditions for practising economically and ethically justified early intervention – consisting of psychosocial methods at the prepsychotic prodromal stage and of 2nd-generation neuroleptic medication in the psychotic prephase – are an early detection and recognition (diagnosis) of persons at risk and a sufficient prognostic power of the instruments used. As these techniques are still undergoing validation, static risk factors, e. g. familial load, obstetric complications and progressive functional impairment (Yung et al. 1998; Phillips et al. 2000) were used as additional criteria for including probands in the intervention programmes whose results have already been published. The asset of this procedure is an acceptably low NNT (Number Needed to Treat, McGorry et al. 2002); its liability is an insufficient identification of at-risk persons in the population at large.

In an article recently published in this journal Wölwer et al. (2003) describe the German Research Network on Schizophrenia (GRNS), its objectives in research and care, and outline its organization. With reference to the information provided in that article on the overall GRNS research programme the present paper deals with a subsection of this effort: the multicentre projects subsumed for reasons of research logic in GRNS Project Network I. These projects jointly pursue the goal of early recognition and early intervention (Wölwer et al. 2003). The short-term objective of this project network is to develop practical and sufficiently valid screening instruments for use at the non-specialist, primary care level (GPs, counselling centres etc.). These instruments should help to identify persons at slightly increased risk for developing schizophrenia and to catch persons with untreated prolonged illness. In addition, early-recognition instruments and, if necessary, supplementary biological techniques of risk identification, which must be of sufficient diagnostic and prognostic power, are being tested for use at the secondary care level in specialist services (early-recognition centres and at a later stage psychiatrists). The aim is to create the preconditions for implementing and practising promising early intervention at an acceptable NNT.

In the intervention projects the efficacies and risks of two appropriate therapy regimens administered at the prepsychotic prodromal stage – in the project this stage is called "early prodromal state"- and at the early psychotic stage – in the project called "late prodromal state" – are being tested. Provided they turn out to be practical and effective – preliminary results already indicate that they will –, the therapies will be prepared for broad use in practice. After completion of data evaluation in the ongoing intervention projects appropriate therapy manuals and guidelines for practice will be worked out. As mentioned, these objectives reflect the increasingly well founded hope that it will be possible to reduce the severity of schizophrenia, a disorder with grave consequences – if it cannot be prevented completely –, postpose psychosis onset and reduce social consequences by implementing on a large scale early-recognition and early-intervention measures taken at the early illness stage. For the persons affected, their families and the national economy the gain would be substantial. To supplement this overview, written with theoretical and structural aspects in mind, preliminary results from studies into the main issues will be reported, in order to give at least a tentative assessment of the chances of success of the efforts.

The early detection of an imminent psychosis risk naturally requires that at-risk persons are aware of relevant premonitory signs and symptoms and seek help. The preconditions, however, are not optimal, as shown by the population surveys conducted by Angermeyer and group in eastern and western Germany (Angermeyer and Matschinger 1995, 1996 a, b, 1997). What is needed is:

- more knowledge of mental disorders, their precursor symptoms and early treatment among persons at risk.

- combating social stigma that hinders uncomplicated help-seeking at psychiatric services.
- an open, easy-access network of appropriate mental health services (at present early-intervention centres, later every psychiatrist trained on results from the CRNS projects (e. g. compiled in a test inventory or a manual).

The need for and approaches to improving awareness and early recognition were studied by Köhn et al. (2003) in a careful Cologne-based investigation of demographic data and symptom development in 82 first episodes of schizophrenia showing a mean duration of illness (DUI) of 5.9 years. When the total sample was divided into a group with a long DUI and one with a short DUI on the basis of the median, neither the demographic variables nor the core symptoms of psychosis showed significant differences. In contrast, the "chronic" prodromal symptoms depressive mood, anxiety and compulsive symptoms were significantly different. This result illustrates how important it is not to focus on psychotic symptoms only in early detection and early recognition of psychosis risk.

To attain the goal of early detection,

- several centres are cooperating in an effort coordinated by W. Gaebel to implement in Germany and adjust to local conditions the WPA Educational Programme "Fighting against Stigma and Discrimination because of Schizophrenia". The campaign has been started successfully and will be continued (Gaebel and Baumann 2003).
- A large-scale mental-health awareness and information campaign ("Awareness Programme") is being carried out in Cologne and Bonn under the supervision of J. Klosterkötter and W. Maier with the help of the media and lectures held to audiences comprising physicians, counselling workers and the general public. The campaign has been modelled on similar efforts carried out at the early-recognition centres in Melbourne (McGorry et al. 1996) and Stavanger (Larsen et al. 1998). Increasing numbers of at-risk persons utilising the early-recognition services offered are a first sign of success.

Before entering the issue of early recognition, we will briefly describe what is currently known of the early course of schizophrenia.

Huber (1966, Huber et al. 1979) and Janzarik (1968) early demonstrated that prodromal symptoms frequently occur in schizophrenia (Kraepelin 1893; Bleuler 1911) and prodromal "basic disturbances" transit to psychosis.

The most comprehensive, methodologically careful – retrospective – analysis of the early course of schizophrenia was done in the ABC Schizophrenia Study using the semi-structured IRAOS interview specially developed for that purpose (Häfner et al. 1992, 1999 b, 2003 a). Included in the IRAOS is a time matrix, in which, with the help of anchor events, the order in which symptoms, behavioural changes and signs of functional impairment occur and, as a result, the gradient of the early illness course are assessed from three sources: patients, family members and documents (case records provided by family doctors etc.). In general, both the early and the later illness course vary a great deal in duration and severity (Loebel et al. 1992; McGorry et al. 1996; Häfner and an der Heiden 2003) (Fig. 1). The low median durations are an indication of a highly skewed distribution. Under the present conditions (the ABC study) DUI lasts for over a year in 68 % of cases. It is these persons in particular to whom measures of early recognition and early intervention should be targeted. The small proportion of 15 % with acute-onset illness showing DUIs of four weeks or less from illness onset to beginning treatment do not need new therapy programmes. They are already detected and treated early.

Fig. 2 illustrates the temporal order of symptom appearance as based on four clinical symptom categories in the early course of schizophrenia. The onset of schizophrenia is mostly marked by depressive symptoms, depressive mood in particular, which appear several years before psychosis onset. Following the first depressive

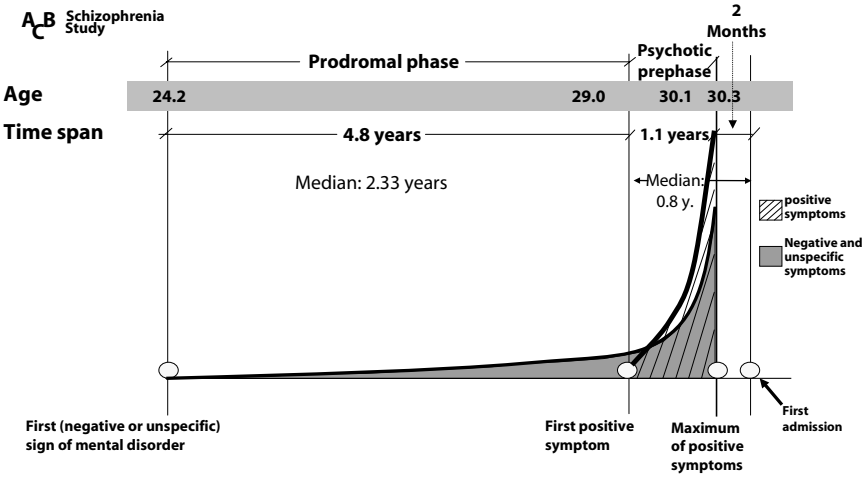

Fig. 1 The early stages of schizophrenia from first sign of mental disorder to first admission (ABC first-episode sample N = 232; (108 men, 124 women)); *Source:* Häfner et al. 1995

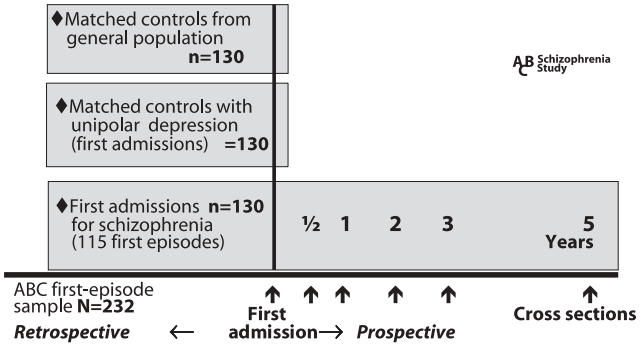

Fig. 2 ABC Schizophrenia Study Design for studying the development and early course of schizophrenia spectrum disorder (ICD 295, 297, 298.3, 298.4) and depression (ICD-10: F32, 33, 34.1, 43.2) in comparison with healthy controls from onset to 6 months to 5 years (only schizophrenia) after first admission

symptoms and in part overlapping them are first negative symptoms and indicators of functional impairment. But these mean values do not permit any conclusions about individual illness courses. The sequence of distinct symptom patterns seems to point to a stage model of the early illness course, as proposed by Conrad (1958) or Docherty et al. (1978). But an empirical testing of these two stage models, not described very precisely by the authors and not fully comparable with each other, on the basis of retrospective ABC study data on the early course failed to confirm them (Häfner et al. 2003 b).

Social consequences of the early course of schizophrenia

When the first sign of illness appears, the social development of persons with schizophrenia is not yet significantly inferior to that of controls matched by age, sex and residential area. When negative symptoms and social impairment increase, and that is the case before treatment beginning, most of the social consequences appear. They depend on the baseline – level of social development at illness onset (Häfner et al. 1999 a).

These results underscore the urgent need for early intervention. They also indicate that the targets should be the following: psychopathological and social change at the prepsychotic prodromal stage and the newly appearing positive symptoms in the psychotic prephase.

Constructing an early-recognition inventory

To practice early recognition both GPs or counselling teachers in nonspecialist settings and psychiatrists at early-intervention centres need appropriate instruments. Which indicators are suited to this purpose? One source for obtaining such indicators are generalisable results from controlled retrospective studies into the early course of schizophrenia. One such study is the afore-mentioned ABC Schizophrenia Study, in which prodromal signs, symptoms and indicators of impairment assessed in probands with schizophrenia were compared with the same phenomena in age- and sex-matched "healthy" controls in order to find indicators of diagnostically sufficient discriminatory power.

Table 1 shows the ten most frequent symptoms – based on their period prevalences in the early illness course from onset to first admission – for a representative subsample of 130 first admissions because of schizophrenia from the ABC study and for two age- and sex-matched control samples, n = 130 each, drawn 1) from the "healthy" population of the study area and 2) from among first admissions for depressive episodes (ICD-10: F32, 33, 34.1, 43.2).

The considerable and without exception highly significant differences between the two illness groups on the one hand and healthy controls on the other make plain that illness can be distinguished from health fairly clearly by the specific symptoms as early as the early illness course (see Table 1). The opposite is the case with depression and schizophrenia: the depressive core symptoms and negative symptoms are to be found in both illnesses either without significant differences or at fairly similar, high frequencies. Functional impairment, which is correlated with negative symptoms in schizophrenia, is very prevalent in severe depression, too.

The specificity of these initial symptoms is low for both schizophrenia and depression. These prepsychotic prodromal symptoms occurring in the early illness course are probably suited to predicting psychosis or severe mental disorder, but not yet to distinguishing between affective and schizophrenic psychosis at this early stage. However definitive answers will not be obtained until results from testing the diagnostic and predictive efficiency of the instruments construed on the basis of these symptom patterns become available. For this purpose a prospective design is needed that covers a sufficiently long period of risk to "catch" transitions to psychosis. To attain this goal, data from the ongoing assessments of the intervention and control groups have to be evaluated.

Another source for construing an early recognition inventory are prospective follow-up studies of the early illness course in persons at ultra-high risk for schizophrenia. For this purpose the ERIraos instruments "Checklist" and "Symptom List" include (self-perceived) BSABS items of high predictive power for schizophrenia from the Cologne Early Recognition – CER – Schizophrenia Study (Klosterkötter et al. 2001; Klosterkötter 2002). Assessed in the CER study were 385 patients referred to specialist outpatient services of psychiatric university hospitals for diagnostic clarification because of a suspected onset of a schizophrenic disorder. A total of 253 persons presented prodromal symptoms fulfilling the BSABS criteria. From the group with prodromal symptoms 110 patients and from the group without prodromal symptoms 50 patients were re-assessed within a mean period of 9.6 years of initial assessment. Of the prodromal group 70 % (77 from 110) had transited to a schizophrenic psychosis on average 5.6 years after the

Table 1 Comparison of the cumulative prevalences of the ten most frequent initial symptoms in the early course of schizophrenia, depression and among healthy controls – the symptoms were assessed retrospectively at age of first admission; symptoms with rank 1 to 10 in one of the three groups

Symptom	Schizophrenia		Depression		Normal controls		Sz vs. Dep	Sz vs. NC	Dep vs. NC
	%	Rank	%	Rank	%	Rank			
Worrying	74.6	9	94.6	4	26.9	6.5	***	***	***
Headaches, other aches and pains	49.2	–	66.9	–	30.8	4	**	**	***
Nervousness, restlessness	88.3	3	81.5	10.5	27.7	5	n. s.	***	***
Anxiety	88.1	4	81.5	10.5	26.9	6.5	n. s.	***	***
Difficulties of thinking, concentration	93.8	1.5	96.9	3	20.8	–	n. s.	***	***
Depressed mood	84.9	5	100.0	1	46.9	1	***	***	***
Loss of self-confidence	68.3	10.5	89.2	7	35.7	3	***	***	***
Social withdrawal, suspiciousness	79.8	8	90.8	6	13.8	–	*	***	***
Disturbed appetite and/or sleep	93.8	1.5	98.5	2	43.4	2	n. s.	***	***
Loss of energy/slowness	82.5	6	93.8	5	15.4	–	**	***	***
Irritability	65.4	–	68.5	–	26.2	8	n. s.	***	***
Delusional mood	68.3	10.5	4.6	–	0.0	–	***	***	*
Delusional misinterpretations, delusions of reference	80.3	7	6.2	–	0.0	–	***	***	**
Oversensitivity	22.3	–	52.3	–	25.4	9	***	n. s.	***
Dissocial behaviour	15.3	–	14.6	–	22.3	10	n. s.	n. s.	n. s.
Reduced spare-time activities	63.5	–	89.1	8	15.5	–	***	***	***
Reduced interests/citizen role	33.9	–	87.7	9	3.8	–	***	***	***

onset of the prodrome, whereas the transition rate in the non-prodromal group was a mere 4% (2 from 50). As Table 2 shows, the ten BSABS items of high predictive power of > 0.70, already present at the initial assessment in more than a quarter of the patients later developing schizophrenia, belong to the cognitive dimension of psychopathology. In this study, too, depressive and other negative core symptoms occurred at considerably higher frequencies (68–92%), but their power for predicting a later schizophrenia episode did not attain significance. Although these results can be considered valid only for the high-risk group studied (Warner 2001), in view of their high predictive power it seemed reasonable to include the cognitive BSABS items in the early-recognition inventory, and all ten items from Table 2 were included.

Table 2 Prognostic accuracy of prodromal symptoms, which show a good predictive value and occur at least in a quarter of patients who later developed schizophrenia. Study population: 160 patients with suspected schizophrenia referred to university hospitals for diagnostic clarification; just under 50 % of these patients developed a schizophrenic psychosis during the observation period (mean: 9.5 years)

Prodromal symptom	Sensitivity	Specificity	PPP	NPP	% false positive predictions	% false negative predictions
Thought interference	0.42	0.91	0.83	0.62	4.4	28.8
Thought perseveration	0.32	0.88	0.71	0.57	6.3	33.8
Thought pressure	0.38	0.96	0.91	0.62	1.9	30.6
Thought blockages	0.34	0.86	0.71	0.57	6.9	32.5
Disturbances of receptive language	0.39	0.91	0.82	0.61	4.4	30.0
Decreased ability to discriminate between ideas and perception, fantasy and memories	0.27	0.95	0.84	0.57	2.5	36.3
Unstable ideas of reference	0.39	0.89	0.78	0.60	5.6	30.0
Derealisation	0.28	0.90	0.73	0.56	5.0	35.6
Visual perception disturbances	0.46	0.85	0.75	0.62	7.5	26.9
Acoustic perception disturbances	0.29	0.89	0.72	0.53	5.6	35.0

PPP positive predictive power, NPP negative predictive power
Source: Klosterkötter 2002

A multi-step approach to early recognition

The aim of the GRNS Project Network I projects is to develop an early-recognition instrument that is both of high discriminative and predictive efficiency and suited to be widely used for screening at-risk persons in the general population. The items obtained from retrospective and/or prospective assessments of high-risk individuals or the early-recognition instruments containing them require prospective validation. An important indicator of their efficiency is a both economically and ethically acceptable NNT.

A one-time assessment of at-risk persons is ineffective due to the low base rate of schizophrenia. And it would be uneconomic to administer a full assessment instrument to a great number of persons at no or slightly elevated risk. For this reason a multi-step approach is needed:

- a "self-selected", preferably representative population at least at slightly increased risk, e. g. patients of general practices, clients of counselling services etc. who seek help or treatment because of mental problems.
- These individuals are screened with an instrument of a high sensitivity, but only of a slightly increased risk threshold (e. g. the ERIraos Checklist construed for this purpose).
- The at-risk persons identified in this way are referred to an early-intervention centre for a detailed risk assessment by means of a full early-recognition inventory (the ERIraos Symptom List including various modules supplemented by neuropsychological tests and, if necessary, neurobiological parameters).

The ERIraos Checklist (Table 3) – available both as a questionnaire and an interview – first asks about 13 unspecific signs. In order not to exclude cases near to psychosis onset or unrecognised cases, three late prodromal items and one psychotic item (no. 14–17) follow. Two more questions concern 1) the most distressing symptom and 2) gradient of change (deterioration) of the most distressing symptom. Three further questions inquire about persisting risk traits: 1) obstetric complications 2) occurrence of mental disorder in the family and 3) type of mental disorder in the family. The items are weighted: unspecific symptoms are rated 2, prepsychotic 4 and psychotic symptoms 6 (certainty or probability of symptom presence is rated 1, 2 and 3). Persons attaining a preliminary cut-off (= 6) are referred to a specialist service (early-recognition centre) for assessment by the comprehensive early-recognition instrument, including neuropsychological tests and neurobiological examination.

The ERIraos symptom list contains 110 symptoms and indicators of functional and social impairment and includes a time matrix. As mentioned, included in the symptom list are the IRAOS and BSABS items of high diagnostic and/or prognostic power. In addition, a few

Table 3 ERIraos Checklist/Interview

Interview Guidelines	
1	• **Do you feel that you have turned into a loner or have become less talkative?** *Examples:* Do you prefer to spend most of your time by yourself? Have you started to withdraw from your group of friends? Have you stopped doing things with others?
2	• **Have you become shy and timid, and feel more and more insecure or embarrassed in contact with other people?**
3	• **Has your mood been rather depressed, sad, subdued or desperate over weeks?**
4	• **Has your sleeping-pattern changed? Or has your appetite or sexual interest changed?** *Examples:* Difficulties falling asleep, or sleeping through the night or early wakening. Appetite/sexual desire significantly increased or decreased.
5	• **Do you feel like your thinking, speaking or movements have been slowing down noticeably?**
6	• **Has your persistence, motivation or quality in your main occupation**/search for work **deteriorated? Do you show less interest or commitment in your main occupation**/search for work?
7	• **Do you neglect one of the following areas: Personal hygiene, clothes, manners, nutrition or health?** Do you keep your home/room tidy?
8	• **Do you frequently feel nervous, restless or tense?** Do you feel jumpy, edgy or do others think that you appear this way and have remarked on it?
9	• **Are you unusually irritable or angry or do you find yourself more involved in arguments with your relatives, friends or others lately?**
10	• **Does it happen that different thoughts are getting mixed up and whirling in your mind?** *Example:* Do you find it very difficult to control, structure or stop your thoughts?
11	• **Do you lately often have the impression that other people are trying to take advantage of you or deceive you?**
12	• **Do you increasingly feel that certain everyday events or actions of other people are exclusively addressed to you, even if you know at the same time that this is unlikely?** *Examples:* Do you have the feeling that other people talk or laugh about you? Or do you receive messages through the radio, TV, newspapers containing some special meaning for you or hints that they are exclusively addressed to you?
13	• **Do your usual surroundings occasionally appear to be transformed, unreal or strange?** *Examples:* Do landscapes, animals or people occasionally appear to be particularly magnificent, impressive, moving, threatening or unreal?
14	• **At any time in your life, did you ever experience that people or things in your environment appeared to be changed?** *Examples:* Did you experience that your hearing or vision was outstandingly intense or supernaturally clear? Or sometimes people and things seem changed with regard to their colour, shape or magnitude? Or did you perceive things particularly intensive or glaring?
15	• **At any time in your life, did you sometimes experience that your train of thoughts was suddenly interrupted or disturbed by other thoughts?**
16	• **At any time in your life sometimes you felt observed, persecuted or threatened by something or somebody?**
17	• **At any time in your life sometimes you could see, hear, smell or taste things that other people could not sense. You couldn't explain these experiences in terms of natural causes?** *Example:* Did you sometimes hear noises or voices while on your own?

prodromal symptoms were taken from internationally accepted instruments designed for the early recognition of schizophrenia (Maurer and Häfner 2002). Four modules are included: 1) pharmacotherapy, 2) substance (drug) use, 3) delinquency and 4) functioning in "daily life". (Questions about schizophrenia in the family are included in the IRAOS). Associated are instruments assessing: 1) obstetric complications (modelled on the OCS of Lewis & Murray 1987) and 2) childhood developmental delays or anomalies (modelled on the PAS for parents, Cannon-Spoor et al. 1982). The validity of the early-recognition inventory is being tested in the GRNS projects and additionally on German and male and female Israeli conscripts as well as in an Italian intervention study. These three studies are associated GRNS projects.

The predictive efficiency of the items can be enhanced by taking into account item patterns or typical sequences of occurrence and increases in number and severity. Increasing functional impairment in combination with certain symptom patterns significantly enhanced predictive power in a study conducted by McGorry et al. (2000).

The efficiency of early-recognition instruments limited to assessing psychopathology and behaviour can be improved by neuropsychological and neurobiological risk indicators.

Neurocognitive impairments precede the onset of schizophrenia and may help to predict its occurrence (Davidson et al. 1999). In order to enhance the predictive validity of the psychopathological research criteria, putatively prodromal subjects included in the treatment programme are tested with a neuropsychological battery, including tests of verbal, declarative memory (Auditory Verbal Learning Test), working memory (Self Ordered Pointing Task, SOPT; and Letter-Number Sequencing), attention (Continuous Performance Test-Identical Pairs), verbal fluency and visual-motor functioning (Digit Symbol Substitution, Trail Making Test) (project leader: M. Wagner, Bonn). Research projects on morphological and functional imaging (project leader: K. Vogeley, Bonn) and genetics (project leader: W. Maier/Bonn) complement the range of possible indicators of psychosis risk and the neurobiological test results at the onset and in the early course of schizophrenia.

Assessing schizophrenia risk before sufficiently valid early-recognition inventories are available

Before valid, diagnostically and predictively powerful early-recognition instruments are in hand, suitable symptoms and characteristics must be selected as inclusion criteria on a consensus basis at the state level. At this same level stages of early illness course must be identified for indicated interventions. In the intervention project focusing on the early prodromal stage, the prepsychotic prodromal phase, the highly predictive BSABS items from Klosterkötter's study (2002) were chosen as inclusion criteria (cf. above). The prognostic power of these "state indicators" can be improved by supplementing them by "persistent trait indicators". Relevant in this respect are the aetiological risk factors occurring at sufficient frequencies: 1) at least one first-degree relative with schizophrenia, 2) individual load of pre- and perinatal complications and 3) diagnosis of schizotypal personality (Table 4). The intervention project focusing on the late prodromal state uses inclusion criteria similar to those applied by the Melbourne group (Phillips et al. 2000) (Table 4).

This procedure has the advantage of enriching risk while reducing the NNT. Its disadvantage is that the at-risk persons included represent only a limited section out of the total spectrum of schizophrenia risk, a problem that cannot be solved at this premature stage of knowledge.

Preliminary results on early recognition

Based on a preliminary evaluation of GRNS Project Network I data (as of October 2003), the following results cannot be considered definitive. Data were analysed for 125 probands, who had filled in the Checklist and who had been administered a full ERIraos interview at inclusion in one of the two early-intervention studies. As Fig. 3 illustrates, the number of symptoms and the checklist score increased steadily over the 12 months preceding entry in the intervention studies. Of the probands 72.8 % attained the cut-off score as early as one year before inclusion. Consequently, most of the persons studied were apparently at rather late prodromal stages.

The rates for the risk traits "obstetric complications" and "familial load" (Fig. 4) are in line with results reported from epidemiological studies (Geddes and Lawrie 1995; McNeil and Cantor-Graae 2001; Mortensen et al. 1999).

Especially neuropsychological tests, which give an objective representation of cognitive impairment and can presumably be easily carried out by specialists in private practice, turned out to be informative. Preliminary results show that, compared to healthy controls matched for age, sex, handedness and education, subjects with prodromal symptoms have deficits in several domains of functioning (Fig. 5). Interestingly, subjects fulfilling the research criteria for the late prodromal stage have stronger cognitive deficits. This would be consistent with the hypothesis that this group is closer to the onset of psychosis. Alternatively, it may be due to the fact that more "true" cases are included in the late prodromal group, owing to the better diagnostic sensitivity and specificity of the psychopathological criteria for this group. The follow-up of the subjects will enable us to decide between these alternatives and to test whether a brief neurocognitive assessment can enhance the sensitivity and specificity of the diagnostic signs and symptoms presently used to define the high-risk groups.

Table 4 Criteria for the intervention studies

Inclusion criteria:

a) Early Prodromal State (EPS)
One or more of the following *basic symptoms* appeared in the last 3 months, several times a week:

- Thought interferences
- Thought perseveration
- Thought pressure
- Thought blockages
- Disturbances of receptive language, either heard or read
- Decreased ability to discriminate between ideas and perception, fantasy and true memories
- Unstable ideas of reference (subject-centrism)
- Derealisation
- Visual perception disturbances
- Acoustic perception disturbances

and/or

Reduction in the Global Assessment of Functioning Score (DSM IV) of at least 30 points (within the past year) *and* at least one of the following risk factors:

- First-degree relative with a lifetime-diagnosis of schizophrenia or a schizophrenia spectrum disorder
- Pre- or perinatal complications

b) Late Prodromal State (LPS)
Presence of at least one of the following Attenuated Positive Symptoms (APS) within the last three months, appearing several times per week for a period of at least one week:
– ideas of reference,
– odd beliefs or magical thinking,
– unusual perceptual experiences,
– odd thinking and speech,
– suspiciousness or paranoid ideation

and/or

Brief Limited Intermittent Psychotic Symptoms (BLIPS), defined as appearance of one of the following psychotic symptoms for less than one week (interval between episodes at least one week), resolving spontaneously:
– Hallucinations
– Delusions
– Formal thought disorder
– Gross disorganised or catatonic behaviour

Exclusion and exit criteria:

APS or BLIPS (EPP study)

Present or past diagnosis of a schizophrenic, schizophreniform, schizoaffective, delusional or bipolar disorder according to DSM IV

Present or past diagnosis of a brief psychotic disorder according to DSM IV with a duration equal to or of more than one week or within the last 4 weeks regardless of its duration

Diagnosis of delirium, dementia, amnestic or other cognitive disorder, mental retardation, psychiatric disorders due to a somatic factor or related to psychotropic substances according to DSM IV

Alcohol or drug abuse within the last three months prior to inclusion according to DSM IV

Diseases of the central nervous system (inflammatory, traumatic, epilepsy etc.)

Aged below 18 and above 36 years

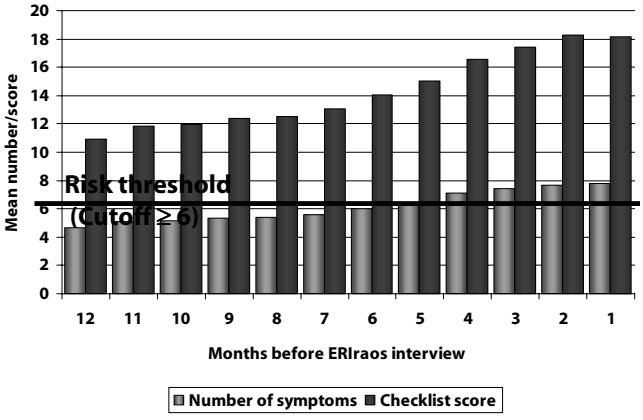

Fig. 3 Accumulation of 17 symptoms from the Checklist over 12 months preceding ERIraos interview (n = 125) (72.8 % of the probands fulfilled the cut-off criterion ≥ 6 12 months before interview)

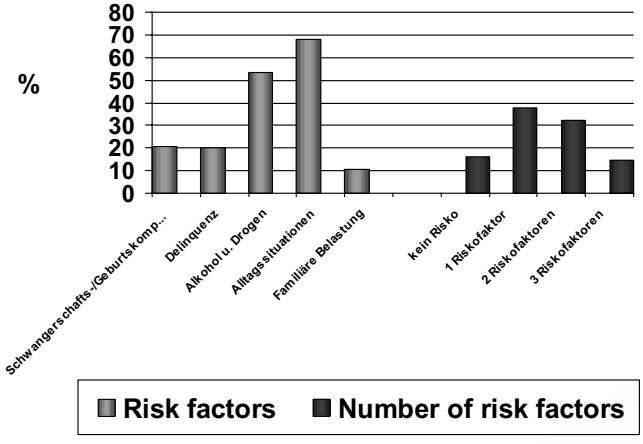

Fig. 4 Frequency (%) of additional risk factors in the early-intervention group (n = 125 patients)

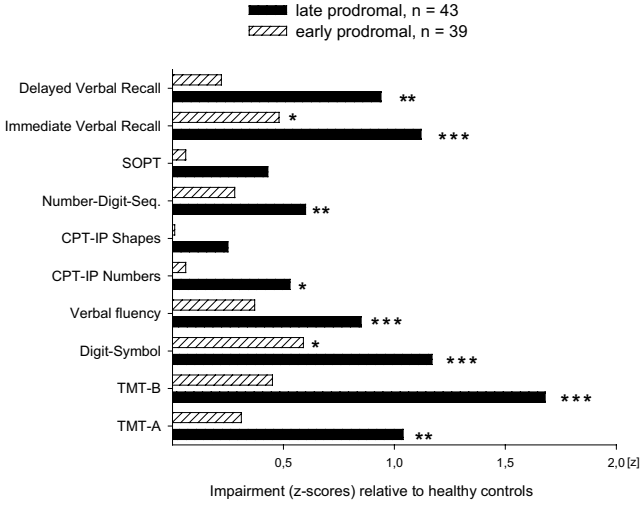

Fig. 5 Neuropsychological impairments in prodromal subjects relative to matched healthy controls (n = 33)

Intervention at the early (prepsychotic) prodromal stage

(Project leader: A. Bechdolf, Cologne; M. Wagner, Bonn; J. Klosterkötter, Cologne)

The inclusion criteria used in this project are – as long as a valid predictor algorithm based on the early-recognition inventory is lacking – at least one of the self-perceived indicators of thought disorder and perceptual change (predictive "basic symptoms" according to Klosterkötter 2002) occurring several times a week in the last three months (see Table 2). Alternatively, a reduced GAF score and presence of at least one of the risk factors listed in Table 4 qualified for inclusion in the study.

Patients meeting the early prodromal state criteria are asked to take part in a randomised controlled intervention trial. Patients who have given informed consent are randomised to receive either a comprehensive cognitive behavioural treatment (CBT) as experimental condition or clinical management (CM) as control condition for 12 months. The specially developed CBT intervention comprises individual (30 sessions) – and group treatment (15 sessions), cognitive remediation (12 sessions) and psychoeducation of relatives (3 sessions). The interventions of both conditions follow a detailed manual containing the aims of the sessions, examples of interventions and model responses for the therapist (Bechdolf et al. 2002).

The aims of the intervention are

- improvement of present prodromal symptoms,
- prevention of social decline or stagnation and
- prevention or delay of progression to psychosis.

Exit criteria from the trial are:

- transition to psychosis defined according to the criteria commonly used in the field (e. g. McGorry et al. 2002) as presence of at least one psychotic symptom from a list as described for BLIPS (Table 4) for longer than six days,
- diagnosis of a schizophrenic, schizophreniform, schizoaffective, delusional bipolar disorder or a brief psychotic disorder with a duration equal to or of more than one week according to DSM IV,
- presence of inclusion criteria of the late prodromal state.

The recruitment period will be three years. Assessments take place pre- and post-treatment (12 months) and at 24-month follow-up. Participating in the study are the GRNS early-intervention centres in Cologne, Bonn, Düsseldorf and Munich. The sample size planned is N = 200. For preliminary results see Fig. 6.

The current sample size is too small and the observation period too short to permit generalisable conclusions to be drawn from these preliminary analyses. However, the trend to a clearly decreased number of transitions to a late prodromal stage or to psychosis as compared with controls give reason to hope that it will be possible at least to delay psychosis onset by the cognitive behavioural intervention specially developed for this purpose.

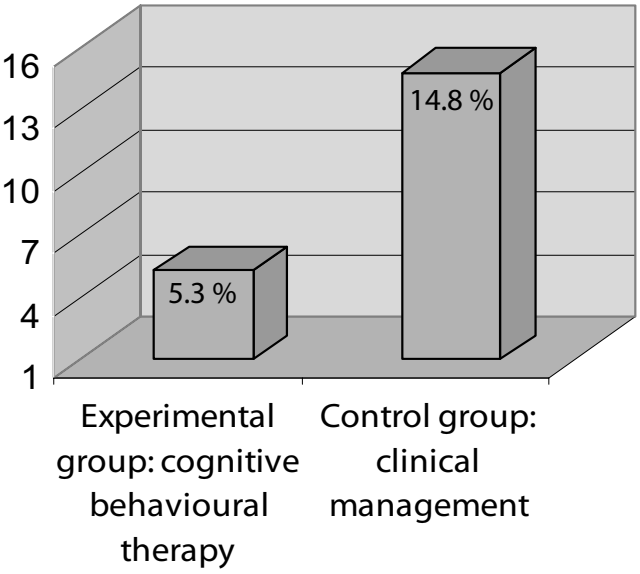

Fig. 6 Efficacy of intervention in the early prodromal state (preliminary data as of Oct. 16, 2003). Percentages of transitions to psychosis or the late prodromal state. Mean period of observation: CBT 16.3 months (SD 8.5 months), CM 9.2 months (SD 8.6 months). based on data for all patients who gave informed consent to participate in the trial (n = 123); *Source:* Bechdolf et al. 2004

Intervention at the late (early psychotic) prodromal stage

(Project leader: S. Ruhrmann, Cologne; J. Kosterkötter, Cologne; W. Maier, Bonn)

As long as a valid early-recognition inventory of sufficient diagnostic and prognostic power is lacking (following Phillips et al. 2000), "state" indicators (Table 4), i. e. attenuated positive symptoms (occurrence of at least one several times a week) are used as inclusion criteria by way of a consensus definition. Five symptoms are relevant (ideas of reference, odd beliefs or magical thinking, unusual perceptual experiences, odd thinking and speech, suspiciousness or paranoid ideation). A further inclusion criterion are "BLIPS" (Yung et al. 1998): presence of at least one of the following four symptoms for less than a week: hallucinations, delusions, formal thought disorder, gross disorganised or catatonic behaviour. No persistent trait indicators or gradients of change are included.

As intervention design a controlled randomised multicentre study was chosen. The treatment period lasts for two years. A sample size of N = 130 cases is planned. The control condition consists of clinical management (CM), including crisis intervention, family counselling, etc. restricted to a focused, supportive reaction to acute needs of the patients. In the experimental part of the

study this condition is combined with treatment with amisulpride. Dosage varies between 50 and 800 mg. Increase in dosage follows an algorithm based on clinical improvement and minimal time periods between changes of dosage. The effect intended by low doses of amisulpride is an increased dopaminergic neurotransmission associated with improved negative and depressive symptoms. Higher doses are expected to have antipsychotic effects based on their antidopaminergic action.

Participating in the study are the GRNS early-intervention centres in Cologne, Bonn, Düsseldorf and Munich. The objectives of the study are remission of symptoms, improved global functioning and prevention or at least delay of transition to full-blown psychosis.

The first 15 patients of the CM + amisulpride group were included in an interim analysis covering the first 12 weeks of treatment (Fig. 7). Three patients (20 %) dropped out, two did not wish to continue treatment and one moved too far away; there was no important adverse event. Thus, design and treatment were assessed as feasible and tolerable. The positive, negative, and global psychopathology PANSS scores were significantly decreased. The general level of functioning also improved significantly from the middle of the 'moderate' level to the upper limit of the 'mild' level.

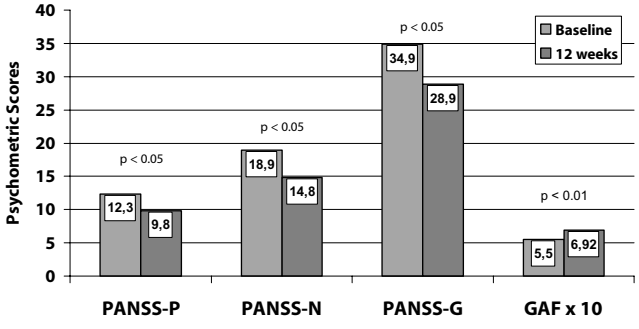

Fig. 7 Psychopathological results of an interim analysis of feasibility performed within the medicated group (n = 15). GAF scores have to be multiplied by ten; *Source:* Ruhrmann et al. 2002

Discussion

A considerable number of early intervention studies into the secondary prevention of psychosis or schizophrenia are currently being conducted all over the world. But the number of studies completed or from which generalisable preliminary results are available is still small.

The randomised, controlled trial conducted by McGorry et al. (2002) was based on 59 "ultra-high risk" individuals included in the study by complex state, trait and gradient criteria and who were primarily at late prodromal stages close to psychosis onset or very recent-onset cases.

The experimental condition extended over six months and consisted of low doses of risperidone (Ø 1.3 mg/d), targeted cognitive therapy and social support. Control condition consisted of "clinical management". To both conditions patients were assigned randomly. Assessments were conducted at the end of the treatment phase – 6 months – and one year after treatment beginning. The result showed (Table 5) significantly fewer transitions to psychosis among compliant probands of the experimental group and, hence, a delaying effect of early intervention on psychosis onset. A noteworthy result of the study was that almost a third of those transiting to psychosis developed affective or other psychosis instead of schizophrenia. As the two modes of therapy, psychological and pharmacological, were administered simultaneously, it is impossible to tell to what extent each of them contributed to the effect. We hope that GRNS intervention study 1 will provide answers to this question. Several comparable studies are underway and will hopefully yield informative results in the next few months or years.

Summary

The common objective of the projects subsumed in GRNS Project Network I on organisational grounds and for reasons of research logic is to develop instruments and criteria for diagnosing and predicting schizophre-

Table 5 Experimental shortening of DUI by randomised controlled intervention in high-risk prodromal stages (McGorry et al. 2002)
Design: 6-month treatment, 1-year outcome (transition to full-blown psychosis)
Index cases (n = 31): cognitive behavioural therapy and low-dose (ø 1.3 mg/day) risperidone
Controls (n = 28): non-specific therapy

		One-year outcome		
		Transition to psychosis	Diagnostic outcome:	
Index cases n = 31	6 = 19.9 %	Compliant with medication n = 14 1 = 7.1 %*	psychosis Schizophrenia	16 7
		Not fully compliant n = 17 5 = 29.4 %	Psychotic (NOS) Psychotic (brief) Psychotic (substance induced)	1 1 1
Controls n = 28	10 = 35.7 %*		Affective disorder (psychotic features) (uni-/bipolar)	 3 3

* Compliant index cases compared with controls (Fisher exact test): p = 0.032
Source: Based on data from McGorry et al. 2002

nia in clinical practice as well as effective and practical early-intervention programmes. The precondition for early intervention at the prepsychotic prodromal or early psychotic stage are early detection and recognition of persons at risk. In a first step toward this goal awareness programmes with the aim of increasing knowledge and help seeking as well as programmes combating social stigma are being conducted. In a second step a two-step easy-to-use early-recognition inventory of sufficient diagnostic and prognostic power is needed. The empirical basis for creating such an inventory and first results from validity tests were discussed. In addition, neuropsychological tests conducted at the early illness stage and preliminary results on their discriminatory and prognostic power were reported. They seem to be able to increase predictive accuracy based on psychological indicators.

Preliminary data suggest that a cognitive-behavioural intervention administered at the early prepsychotic prodromal stage and an intervention combining psychotherapeutic and psychopharmacological amisulprid treatment at the late prodromal stage are effective on all the main dimensions targeted. In spite of the tentative nature of these results the prospects of GRNS Project Network I attaining its objectives appear fairly good.

If it were possible to delay psychosis onset by psychosocial intervention at the prodromal stage, to reduce severity of psychosis or prevent psychosis altogether, a new promising perspective of high public-health relevance would open up. There would then also be hope of reducing the early social consequences, which determine the further illness course, and of improving the patients' chances in life.

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