

## Interventions in the initial prodromal states of psychosis in Germany: concept and recruitment\*

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**Background** The Early Detection and Intervention Programme of the German Research Network on Schizophrenia (GRNS) investigates the initial prodromal phase of psychosis in a multidimensional approach. Two intervention strategies are being studied by two large-scale multicentre projects.

**Aims** To present the concept of the intervention studies, and to provide an interim report of the recruitment procedure.

**Method** Comprehensive cognitive-behavioural therapy has been developed for patients in the 'early initial prodromal state'. For patients in the 'late initial prodromal state' the atypical neuroleptic amisulpride is explored. Both interventions are evaluated in randomised controlled trials using clinical management as the control condition.

**Results** Between January 2001 and March 2003, 1212 individuals seeking help for mental health problems were screened for putative prodromal symptoms at four university centres. More than 388 individuals fulfilled criteria for both interventions and 188 (48.5%) gave informed consent to participate in the trials.

**Conclusions** The screening procedure appears to be feasible and trial participation seems to be acceptable to a relevant proportion of people at increased risk of developing psychosis.

**Declaration of interest** The study on the late initial prodromal state is co-funded by a research grant from Sanofi-Synthelabo Germany.

The Early Detection and Intervention programme of the German Research Network on Schizophrenia (GRNS) was established in 2000 to promote research on the initial prodromal phase of psychosis. Early Detection and Intervention Centres at the outpatient departments of four university hospitals (Bonn, Düsseldorf, Munich and Cologne) are collaborating in intervention studies with Cologne acting as the coordinating centre.

An awareness programme (Köhn *et al*, 2002) is ongoing for psychiatric and primary healthcare services, families of patients with schizophrenia, several youth support services and the general population. It provides information about early symptoms of schizophrenia and the need for early intervention. The aims of the programme are to promote help-seeking and engagement with early intervention services for individuals at-risk of psychosis.

A two-step approach has been created in order to identify individuals at-risk for psychosis. A checklist (Häfner *et al*, 2004) has been used which serves as a low-threshold screening instrument for people who have approached general practitioners or counselling services, etc. because of mental health problems. The checklist includes criteria which indicate that a contact or a referral to one of the early intervention centres should be made. At the centre, a detailed assessment is made using a specially designed instrument, the Early Recognition Inventory (ERIRao; Maurer *et al*, 2004). The ERIRao indicates whether the individual at-risk of psychosis is in an 'early initial prodromal state' or a 'late initial prodromal state' (see below), as defined by the GRNS.

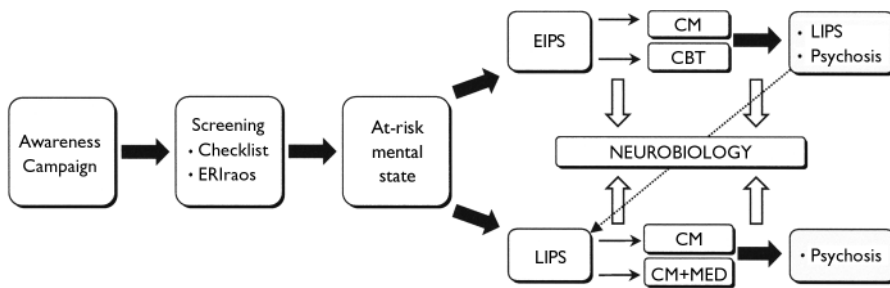
When there is evidence of an early initial prodromal state (EIPS), the at-risk individual is invited to participate in a

randomised controlled trial (RCT) on psychological early intervention. However, an at-risk person with evidence of a late initial prodromal state (LIPS) is asked if they will take part in an RCT with pharmacological intervention, using amisulpride. In addition to psychopathological and psychosocial assessments, individuals are asked to take part in GRNS neurobiological research projects. These comprise neuropsychological and neurophysiological assessments, brain imaging and molecular genetics (Maier *et al*, 2002). Furthermore, the effect of the awareness programme is investigated by pre- and post-assessments and comparison with regions in which the awareness programme does not operate (Köhn *et al*, 2002) (Fig. 1). Each study was approved by the respective local ethics committees.

### INTERVENTIONS IN THE INITIAL PRODROMAL STATES

The EIPS is defined by: (a) the presence of certain self-experienced cognitive thought and perception deficits ('basic symptoms' according to Huber & Gross, 1989), which were found to be predictive for transition to psychosis in 70% of the cases within 5 years (Klosterkötter *et al*, 2001); and/or (b) by the presence of a clinical decline in functioning in combination with well-established risk factors (Yung *et al*, 1998) (see Appendix for details). Estimating the risk/benefit ratio of intervening in the EIPS, a comprehensive cognitive-behavioural therapy (CBT) programme was developed (Bechdorf *et al*, 2003, 2005b) which has been influenced by the work of other investigators in this field (e.g. Kingdon & Turkington, 1994; Fowler *et al*, 1995; Chadwick *et al*, 1996). CBT can be useful in the early initial prodromal state, in particular because it is readily accepted by patients and little stigma is attached. Also, there is no risk of exposing false-positives to possible pharmacological side-effects. Since the efficacy of CBT in schizophrenia has been established for persistent psychotic symptoms in a number of investigations (see meta-analyses by Rector & Beck, 2001; Gould *et al*, 2002; Pilling *et al*, 2002; Cormac *et al*, 2003), one could hypothesise that such an approach is also effective in the prepsychotic phase. Moreover, CBT is an established treatment for anxiety, depression and several other syndromes, which are often present at this stage.

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**Fig. 1** Overview of the Early Detection and Intervention programme of the German Research Network on Schizophrenia. ERiraos, Early Recognition Inventory; EIPS, early initial prodromal state; LIPS, late initial prodromal state; CM, clinical management; CBT, cognitive-behavioural therapy; MED, antipsychotic medication.

The LIPS criteria are similar to the ‘ultra-high-risk’ measures used by current controlled intervention studies (McGorry *et al*, 2002; Woods *et al*, 2003; Morrison *et al*, 2004) (Appendix). Patients fulfilling LIPS criteria are highly symptomatic, functionally compromised (Miller *et al*, 2003) and have a risk between 36% and 54% of developing psychosis within 12 months (Miller *et al*, 2002; Yung *et al*, 2003, 2004; Mason *et al*, 2004). Taking this into account and also the significantly improved tolerability of the new neuroleptics, it seemed appropriate to investigate the possible benefits of pharmacological interventions for these patients. In the LIPS study, amisulpride was chosen for several reasons: at a low dose there are beneficial effects on depressive and negative symptoms, probably because of its primarily dopaminergic properties in the low-dosage range. At a higher dose it is an effective antipsychotic and data from schizophrenia studies lead us to anticipate very good tolerability with a side-effect rate no different from placebo at low doses and, not least, low weight gain (Ruhmann *et al*, 2003).

Aims of both intervention studies are: (a) improvement of present prodromal symptoms; (b) prevention of social decline/stagnation; and (c) prevention or delay of progression to psychosis.

**Intervention in the EIPS**

*Design*

Patients meeting EIPS criteria are randomised to receive either comprehensive CBT treatment or clinical management for 12 months. Interventions in both conditions follow a detailed manual, which defines the aims of the sessions, examples of interventions and gives model responses for the therapist (Bechdorf *et al*, 2002). The recruitment period is 3 years. Assessments take place pre- and post-treatment (12

months) and at 24-month follow-up. After the intervention period, monthly telephone interviews are conducted to check if there is transition to psychosis. Main rating instruments are the Early Recognition Inventory (ERiraos; Maurer *et al*, 2004), Positive and Negative Syndrome Scale (PANSS; Kay *et al*, 1987), DSM-IV Global Assessment of Functioning Scale (GAF-F; American Psychiatric Association, 1994) and the Montgomery-Åsberg Depression Rating Scale (MADRS; Montgomery & Åsberg, 1979). At yearly intervals, the Social Adjustment Scale-II (SAS-II; Schooler *et al*, 1979) is administered. Transition to psychosis is defined by commonly used criteria (e.g. McGorry *et al*, 2002; Morrison *et al*, 2004), such as the presence of at least one psychotic symptom from a list for brief limited intermittent psychiatric symptoms (BLIPS, see Appendix) for longer than 6 days. In accordance with our differential intervention approach the presence of inclusion criteria for the LIPS served as additional exit criteria from the EIPS intervention trial.

*CBT intervention*

The experimental intervention is based on a CBT model (Larsen *et al*, 2003). Individual therapy forms the central part of the early intervention programme. A combination of psychoeducation, symptom, stress and crisis management modules is adapted to the specific needs of each client. Although putative prepsychotic symptoms serve as inclusion criteria for therapy, the interventions are problem-oriented, collaborative, educational and involve the therapist and the client working together on an agreed problem list. This may also include problems other than basic symptoms, such as anxiety, depression, family or occupational problems. Apart from the treatment of the psychopathological symptoms, one major treatment aspect focuses

on attributional styles that underpin symptoms. Psychoeducation and cognitive techniques are used to challenge self-stigmatisation and self-stereotypes, helping the person to protect and enhance self-esteem, and to come to terms with understanding the illness and pursuing life goals. A special group intervention, cognitive remediation and a short psychoeducational multi-family intervention are also parts of the programme (Table 1).

**Intervention in the LIPS**

*Design*

The LIPS project is a pharmacological phase III study conforming to good clinical practice and has a controlled, open-label, randomised, parallel group design. In the first condition, patients receive a psychologically advanced clinical management programme, including, where necessary, crisis intervention, family counselling, etc. Its primary aim is providing very focused, supportive care for the patient’s acute needs (psychotherapy is not allowed). In the second condition, similar clinical management is combined with amisulpride. The dose can range between 50 mg and 800 mg per day, the increase in dose follows an algorithm based on clinical improvement and minimal time periods between changes of dosage. The treatment period is 2 years with weekly visits during the first 4 weeks, then bi-weekly until week 12, and monthly, thereafter.

Main rating instruments are ERiraos, PANSS, GAF-F and, at yearly intervals,

**Table 1** Psychological intervention in the early initial prodromal state

Module	Topics
Individual therapy (30 Sessions)	Assessment and engagement Psychoeducation Stress management Symptom management Crisis management
Group therapy (15 Sessions)	Positive mood and enjoyment Social skills Problem-solving
Cognitive remediation (12 Sessions)	Concentration, attention, vigilance and memory
Information and counselling of relatives (3 Sessions)	Psychoeducation of multi-family group

SAS-II. Among other instruments are the MADRS, the Extrapyramidal Symptom Rating Scale (ESRS; Chouinard *et al*, 1980) and the UKU Side Effect Rating Scale (UKU; Lingjaerde *et al*, 1987).

## RECRUITMENT

Between 1 January 2001 and 31 March 2003, 1212 individuals who were seeking help for mental health problems were examined using the checklist. This was administered by general practitioners, counselling services, psychiatrists and psychotherapists in private practice, psychiatric out-patient units at hospitals or the early intervention centres themselves. A total of 994 individuals fulfilled criteria for further assessment at the early recognition and intervention centres – 993 out of 994 were assessed. A total of 388 individuals fulfilled at-risk criteria. Of these, 190 fulfilled early initial prodromal state criteria and 109 (57.4%) gave informed consent to participate in the psychological intervention study. A total of 198 individuals met late initial prodromal state criteria and 79 (39.9%) gave informed consent to participate in the pharmacological intervention study. The main reasons why individuals fulfilling at-risk criteria were not included in the trials were: continued substance misuse, pre-treatment with neuroleptics, past history of psychotic episodes, refusing enrolment in research studies, refusing psychopharmacological treatment, living out of the catchment area, moving out of the area.

## DISCUSSION

The Early Detection and Intervention programme of the GRNS investigates the initial prodromal phase of psychosis in a multidimensional approach including two intervention studies.

In the first 2 years of the project over 1200 help-seeking individuals were screened for at-risk mental state and almost 190 patients in the initial prodromal phase were recruited and assessed with regard to psychopathology, psychosocial and neurobiological parameters at four recently established Early Detection and Intervention centres. With almost 50% of the at-risk individuals, a high number of participants have been recruited for the psychological and pharmacological intervention trials.

Baseline assessments within the two studies indicated that help-seeking individuals with prodromal symptoms, who were randomised to receive a clinical intervention, were clinically symptomatic and functionally compromised (Ruhmann *et al*, 2003; Häfner *et al*, 2004; Bechdolf *et al*, 2005a). First interim evaluations of both interventions are promising as the two approaches seem to be successful regarding the first two aims of the interventions: (1) improvement of early or late prodromal symptoms; and (2) improvement of social or occupational functioning (Ruhmann *et al*, 2003; Häfner *et al*, 2004; Bechdolf *et al*, 2005a). A preliminary analysis of the EIPS study indicated advantages of CBT regarding transition to late initial prodromal state and psychosis (Häfner *et al*, 2004).

In summary, the GRNS Early Detection and Intervention programme, including awareness campaigns and a two-stage screening approach, appears to be feasible and effective in recruiting at-risk individuals with putatively prodromal symptoms for interventions in the initial prodromal phase. The programme will be completed by the end of 2005 and will provide a sound data-set regarding the efficacy of intervening in the initial prodromal state, the prediction of psychosis, putative underlying neurobiological variables and the effects of awareness campaigns.

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## APPENDIX

### Inclusion criteria for intervention studies on the early initial prodromal state and the late initial prodromal state

#### Early initial prodromal state

One or more of the following basic symptoms appeared in the last 3 months, several times a week:

- Thought interference
- Thought perseveration
- Thought pressure
- Thought blockage
- 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 disturbance
- Acoustic perception disturbance

#### and/or

Reduction in the DSM-IV Global Assessment of Functioning score 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.

### Late initial prodromal state

Presence of at least one of the following attenuated psychotic symptoms (APS) within the last 3 months, appearing several times per week for a period of at least 1 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 1 week (interval between episodes of at least 1 week), resolving spontaneously:

- Hallucinations
- Delusions
- Formal thought disorder
- Gross disorganised or catatonic behaviour

### Exclusion and exit criteria

- APS or BLIPS (early initial prodromal state).
- 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 1 week or within the last 4 weeks regardless of its duration.
- Diagnosis of delirium, dementia, amnesic 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 misuse within the last 3 months prior to inclusion according to DSM-IV.
- Diseases of the central nervous system (inflammatory, traumatic, epilepsy, etc).
- Aged <18 years and >36 years.

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## CLINICAL IMPLICATIONS

■ A programme including awareness campaigns and a two-stage screening approach seems to be feasible and effective in recruiting at-risk individuals with putative prodromal symptoms for interventions in the initial prodromal phase.

■ For patients presenting with psychosis-predictive basic symptoms and/or a clinically relevant decline of social functioning in combination with established risk factors (early initial prodromal state) a comprehensive cognitive–behavioural therapy (CBT) was developed, which is evaluated in comparison with clinical management in a randomised controlled trial (RCT).

■ In patients presenting with attenuated and transient psychotic symptoms (late initial prodromal state) an RCT is being conducted comparing amisulpride and clinical management and clinical management alone.

## LIMITATIONS

■ Of the population identified with an at-risk mental state, 51.5% did not participate in the related RCTs.

■ First results of both treatment approaches have to be cautiously interpreted, as they are based on preliminary data obtained from early interim analysis.

■ Because the two large-scale RCTs are ongoing no final results can be presented.

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