Preventing progression to first-episode psychosis in early initial prodromal states


Background
Young people with self-experienced cognitive thought and perception deficits (basic symptoms) may present with an early initial prodromal state (EIPS) of psychosis in which most of the disability and neurobiological deficits of schizophrenia have not yet occurred.

Aims
To investigate the effects of an integrated psychological intervention (IPI), combining individual cognitive–behavioural therapy, group skills training, cognitive remediation and multifamily psychoeducation, on the prevention of psychosis in the EIPS.

Method
A randomised controlled, multicentre, parallel group trial of 12 months of IPI v. supportive counselling (trial registration number: NCT00204087). Primary outcome was progression to psychosis at 12- and 24-month follow-up.

Results
A total of 128 help-seeking out-patients in an EIPS were randomised. Integrated psychological intervention was superior to supportive counselling in preventing progression to psychosis at 12-month follow-up (3.2% v. 16.9%; \( P = 0.008 \)) and at 24-month follow-up (6.3% v. 20.0%; \( P = 0.019 \)).

Conclusions
Integrated psychological intervention appears effective in delaying the onset of psychosis over a 24-month time period in people in an EIPS.

Declaration of interest
None.

Early detection and intervention strategies have led to substantial improvement in the prognosis of a number of non-psychiatric medical conditions.1–3 The chronicity of schizophrenia provides the primary rationale for adapting these strategies for schizophrenia. In recent years, criteria based on subthreshold levels of psychotic symptoms (ultra-high-risk criteria) have been found to predict psychosis onset within 12 months in 20–30% of cases.4–6 This approach has provided the opportunity of indicated prevention efforts in individuals at imminent risk of schizophrenia in order to reduce or prevent the devastating effects of the disorder.7

Five randomised controlled trials (RCTs) in the ultra-high-risk population have been completed so far. They have included evaluations of low-dose risperidone and cognitive–behavioural therapy (CBT) combined,8 CBT alone,9,10 olanzapine alone11 and omega-3 fatty acids.12 Although the results of the treatment phase were statistically borderline or significant in favour of the respective experimental condition, these effects were not sustained at 12-,9 24-11 or 36-month13,14 follow-up. The increased rate of conversion and return of prodromal symptoms to significantly higher levels after removing the specific intervention led some authors to conclude that interventions in the ultra-high-risk population merely delay conversion to psychosis rather than prevent it.11

One of the reasons for the limited efficacy of indicated prevention efforts might be that individuals who meet ultra-high-risk criteria already present with symptoms similar to psychotic symptoms. Thus, in the ultra-high-risk population most of the symptoms, disability and neurobiological deficits associated with schizophrenia might already be present.15 However, certain subtle, self-experienced thought and perception deficits (basic symptoms) have been described in initial prodromal states of schizophrenia, which may precede the onset of subthreshold psychotic symptoms.15,16 Furthermore, prospective data of people with basic symptoms \((n = 160)\) indicate that the 12-month conversion rate to psychosis is lower (19%) and the long-term conversion rate higher (70% after 5.4 years) than the 12-month transition rate of the ultra-high-risk population (20–30%).4–6 Moreover, cross-sectional data indicate that levels of psychopathological symptoms, disability, neurophysiological and neuropsychological deficits are lower in patients with basic symptoms than in patients who fulfil ultra-high-risk criteria.17–19 Therefore, it has been hypothesised that people with basic symptoms might be in an early initial prodromal state (EIPS) of psychosis in which symptoms, disability and biological deficits are less severe than in the ultra-high-risk population, and that the EIPS population may therefore be more responsive to preventive interventions than people who already fulfil ultra-high-risk criteria.20,21

However, to date, no information on the efficacy of interventions in people in the EIPS is available. Therefore, the present RCT study has been undertaken to test the efficacy of a specifically devised integrated psychological intervention (IPI) compared with supportive counselling in individuals in an EIPS. Integrated psychological intervention consists of individual CBT, modified social skills training, cognitive remediation and multifamily psychoeducation. It was chosen as the experimental condition because (a) the applied strategies have been found to be effective in individuals at ultra-high risk and patients with psychosis;22–24 (b) there is no risk of exposing false positives to possible pharmacological side-effects; and (c) it is an established treatment for anxiety, depression and several other syndromes which are regularly present in the pre-psychotic phase.25,26 Supportive counselling was designed to provide a minimal level of support for individuals who were seeking help and clearly in need of support as a result of psychiatric symptoms or concerns relating to functional domains.

This paper presents the 12-month (post-treatment) and 24-month follow-up results of the RCT. The primary outcome

Declaration of interest
None.
measure was progression to psychosis (incidences of subthreshold psychosis, first-episode psychosis and first-episode schizophrenia) at 12-month and 24-month follow-up. It was hypothesised that IPI would significantly reduce progression to psychosis compared with supportive counselling.

### Methods

This was a multicentre, prospective, randomised trial with two parallel groups assigned to alternative out-patient interventions. Randomisation was achieved by using computer-generated block randomisation stratified by centre. Both interventions were delivered over a 12-month period. Follow-up of participants was conducted for up to 24 months after intake. The protocol was approved by the respective institutional review boards at the Universities of Cologne, Bonn, Dusseldorf and Munich, Germany. All participants provided written informed consent prior to any research activity. This study is registered with Clinicaltrials.gov (registration number NCT00204087).

### Setting

The study took place at four early detection and intervention centres located in the Departments of Psychiatry and Psychotherapy at the Universities of Cologne, Bonn, Dusseldorf and Munich, and was funded within the German Research Network on Schizophrenia. All centres serve as specialised out-patient departments and are designed to provide a low-threshold, non-stigmatising environment. An awareness programme was conducted, which aimed to engage ‘at risk’ individuals with the early intervention services. Referrals were made from primary healthcare, mental health professionals, counselling services and other youth support services.

### Participants

We used a two-step approach to identifying individuals at risk of psychosis created by Hafner et al.

First, a checklist was provided. For those who met threshold criteria in the checklist, an interview using a specially designed instrument based on the Interview for the Retrospective Assessment of the Onset of Schizophrenia (IRAOS) was performed at the respective centre. This instrument, called the Early Recognition Inventory (ERIraos), indicated whether the individual at risk fulfilled EIPS or subthreshold psychosis criteria.

#### Inclusion criteria

Inclusion criteria were met when patients presented with at least one of ten thought or perceptual basic symptom (Appendix 1), which have been found to predict psychosis in 19% of cases within 12 months and in 70% of cases within 5.4 years. A decrease in functioning in conjunction with presentation of a genetic risk within 12 months and in 70% of cases within 5.4 years. A decrease whether the individual at risk fulfilled EIPS or subthreshold (IRAOS) was performed at the respective centre. This instrument, the Retrospective Assessment of the Onset of Schizophrenia. All centres serve as specialised out-patient centres and are designed to provide a low-threshold, non-stigmatising environment. An awareness programme was conducted, which aimed to engage ‘at risk’ individuals with the early intervention services. Referrals were made from primary healthcare, mental health professionals, counselling services and other youth support services.

#### Exclusion and exit criteria

In accordance with the concept that the EIPS precedes subthreshold psychotic symptoms (attenuated or brief intermittent psychotic symptoms), the development of subthreshold psychotic symptoms or psychosis served as exit criteria for the trial (see Appendix DS1 for full exclusion and exit criteria).

### Treatments

The same research therapists delivered IPI and supportive counselling, except in Cologne, where 7 patients assigned to supportive counselling were treated by 2 additional psychiatrists, and in Munich, where supportive counselling was delivered to 11 patients by a clinical psychologist and a psychiatrist who were not involved in IPI. No formal measures of adherence to the manual or of therapists competence were employed in the IPI or supportive counselling conditions.

The therapists delivering IPI were CBT-trained clinical psychologists and psychiatrists with at least 2 years of experience in CBT delivery. At the start of the study the therapists were trained in IPI in a comprehensive workshop lasting for several days, and at least once yearly throughout the study. At each site, therapists received expert and/or peer supervision at least once every 2 weeks.

#### Integrated psychological intervention (IPI)

**Model.** The stress–vulnerability model of schizophrenia serve as the framework of IPI. Thus, improving coping resources and stress management are underlying strategies of the intervention. Given empirical evidence that cognitive thought and perception disorders may precede negative affective states, social withdrawal and decline, a specific cognitive model of the EIPS was developed, as an extension of the stress–vulnerability model based on recent cognitive models of psychosis.

In this model, biological, psychological, social stress and vulnerability factors are presumed to interact to render the person at high risk for the subsequent development of prodromal symptoms. The prodromal symptoms become manifest on exposure to a range of additional stressors, which again may be social, psychological or biological. The occurrence of self-experienced cognitive thought and perception deficits (basic symptoms) could then serve as triggering events for the appraisal of negative beliefs and assumptions. Self-experience of basic symptoms may result in emotional disturbances, such as depression or anxiety, social withdrawal and decline, which jointly contribute to the development and maintenance of symptoms and distress.

**Treatment components.** The interventions draw on established strategies for first-episode or recurrent schizophrenia, anxiety and depressive disorders.

**Individual cognitive–behavioural therapy (CBT).** Individual CBT was at the core of IPI. Based on our integrative cognitive model, the individual CBT followed the basic principles of cognitive therapy described by Beck as being formulation driven, structured, based on shared problems and goals, educational, utilising guided discovery as the engine for change, involving homework and being time limited. Depending on the problems presented and the case formulation, therapists adapted the modules described in a manual (see Table 1 for modules and strategies applied).

**Skills training.** Scheduling and monitoring of mastery and pleasure activities, ‘keeping well’ strategies, social perception and social skills training and training in problem-solving were offered in a group format. Each therapy session followed a detailed protocol which outlined the aims of the session, examples of interventions and model responses for the therapist.

**Cognitive remediation.** Cognitive remediation was offered to address thought and perception deficits (basic symptoms) directly.

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It was computerised and based on cognitive exercises from the COGPACK software (Marker Software, Mannheim, Germany), a multimedia cognitive rehabilitation software designed for use with individuals with compromised brain functioning. In each session, three to six tasks were performed, involving repeated practice of exercises for attention, memory and executive functioning. Patients received performance scores, which were recorded and referred to in order to reinforce performance progress. Task parameters were initially made sufficiently easy for each patient to do well. After session 6, tasks were made more difficult, according to the next level of difficulty (low to medium, or medium to severe).

Psychoeducational multifamily groups. In addition, psychoeducational multifamily groups for family members or key persons were offered. These groups provided information on symptoms, course and treatment of at-risk mental states, as detailed in a manual. These sessions aimed to increase the family's understanding of the EIPS and to reduce stress and interpersonal conflicts.

Procedures and manual. Integrated psychological intervention was initially commenced with individual CBT delivered weekly or every 2 weeks, which was then consecutively supplemented by cognitive remediation and psychoeducation of family members or key persons. Following the assessment and engagement phase, and formulation and goal setting, group skills training was offered to participants, depending on availability of places in the group. While participants were attending the weekly group sessions, the frequency of individual sessions was reduced to crisis intervention, and only maintained in individuals who were clinically judged to have a particularly high risk of developing psychosis or dropping out. During the treatment phase of individual CBT, before or after the group intervention, CBT sessions were planned to be weekly, with a reduction in their frequency during the termination phase towards the end of the overall treatment at 12 months. However, the frequency and duration of sessions were intended to be flexible, depending on arrangements made between patients and therapists, as well as being contingent on the mental state of individual patients.

The IPI was detailed in a manual of 137 pages including an overall treatment model, aims of the treatment components and sessions, problem-specific treatment modules, examples of interventions and model responses for the therapist. Additionally, 80 pages of working material for patients were provided. Further details of IPI and case examples are presented elsewhere.

The feasibility of the intervention was tested and confirmed in a pilot sample of 12 patients. The supportive counselling was designed to provide a minimal level of support for individuals who were seeking help and were clearly in need of support as a result of psychiatric symptoms or concerns relating to functional domains. Basic assessment, basic psychoeducation about the at-risk mental state and counselling in a supportive, warm, genuine, empathic and unstructured style were delivered. Supportive counselling was delivered on a one-to-one basis, manual based, regularly supervised and lasted for a maximum of 30 sessions over 12 months.

Assessments

Face-to-face assessment of the development of the primary outcomes – subthreshold psychotic symptoms, psychosis and schizophrenia – were undertaken at each individual treatment session (maximum of 30 assessments) during the treatment phase and at post-treatment (month 12). During the post-treatment phase, patients were regularly asked about the primary outcomes by telephone and by face-to-face interview during the 24-month follow-up. If the telephone interview indicated a deterioration of symptoms and/or an increased risk of conversion, an additional face-to-face interview was conducted. If patients did not attend assessments, every effort was made to follow them up and to complete assessments with regard to primary outcome variables by means of telephone calls and home assessments. If patients were not available for interviews, key persons and hospital admission data were approached to determine conversion status. Patients were classified as converters or non-converters by an independent consultant psychiatrist or senior clinical psychologist. The masking of these independent consultant psychiatrists or clinical psychologists was not formally measured.

Basic symptom inclusion criteria (Appendix 1) were assessed in a semi-structured interview by a short version of the symptom list of the ERIraos and the IROAS. Inclusion criteria were operationally defined as fulfilled if one of the ten basic symptoms was rated with a severity of at least 1 (corresponding to a mild
Integrated psychological intervention for the prevention of psychosis

A basic symptom total score was calculated by summing the scores of the ten basic symptom items defining the EIPS. Genetic risk of schizophrenia as part of the decreased functioning and risk factor criteria was assessed by the IRAOS. Obstetric complications were assessed by the respective ERIraos module, which was modelled on the Obstetric Complications, Scale (OCS).

The exit criteria to subthreshold psychosis and psychosis (Appendix DS1) were defined in accordance with definitions used by RCTs in the ultra-high-risk population. The exit criteria to the subthreshold psychosis syndrome ‘attenuated psychotic symptoms’ were assessed using the symptom list of the ERIraos, and were operationally defined as fulfilled if one of the symptoms was rated as present. The subthreshold psychosis syndrome ‘brief limited intermittent psychotic symptoms’ and psychosis criteria were assessed by the Positive and Negative Syndrome Scale (PANSS). In accordance with previous definitions the presence of brief limited intermittent psychotic symptoms or psychosis were operationally defined by cut-off points on PANSS subscales of 4 or more on hallucinations, 4 or more on delusions and 5 or more on conceptual disorganisation or formal thought disorder. After meeting exit criteria, patients were classified by an independent consultant psychiatrist or senior clinical psychologist into one of three categories: (1) subthreshold psychotic symptoms (see online Appendix DS1 for definitions); (2) DSM-IV psychosis diagnosis; schizophrenia/schizophreniform, schizoaffective disorder, major depression with psychotic features, bipolar disorder with psychotic features, delusional disorder, brief psychotic disorder, brief psychotic disorder not otherwise specified; or (3) DSM-IV schizophrenia/schizophreniform disorder diagnosis.

![CONSORT diagram](image-url)

EIPS, early initial prodromal state; IPI, integrated psychological intervention.
All assessors were experienced clinical psychologists or psychiatrists. They attended a comprehensive workshop lasting several days when the study commenced and yearly throughout the study. Reliability checks of the assessments were performed three times throughout the study with a total number of nine raters. Agreement with a gold standard rating on absence or presence of a symptom from the ERIraos symptom list among eight raters, who were sufficiently trained in the use of the schedule, were good to excellent[44] (kappa 0.64–0.77). However, one rater, who was still in need of further training, only achieved a kappa of 0.49 (for symptoms present at time of the interview). The reliabilities of the change assessments by the nine raters were good to excellent (kappa 0.63–0.87).

Statistical analysis
Kaplan–Meier survival analysis assessed differences in time to conversion to subthreshold psychotic symptoms between the two treatment arms over the 24-month follow-up using the log-rank test. Estimated survival rates were compared at the 12-month and 24-month points on the survival curve using χ²-tests. Cox regression was applied to assess whether the effects of treatment on survival time remained constant when the impact of the basic symptom total score at baseline was accounted for. These primary survival analyses were performed on all available follow-up data. At 12-month and 24-month follow-up, a χ²-test was used to calculate the difference in proportions of patients who developed subthreshold psychotic symptoms, psychosis, or schizophreniform/schizophrenia disorders in the two treatments. The numbers needed to treat (NNT) with CBT to prevent one participant making a conversion were calculated by the reciprocal of the absolute risk reduction.[45] Two-tailed tests of significance were used in all analyses, with z set to 0.05.

Results
Enrolment and participant characteristics
Recruitment took place from January 2001 to January 2004. Figure 1 illustrates the flow of participant selection. Of 168 eligible individuals, 128 help-seeking out-patients in an EIPS were randomised. Only 15 of the 168 eligible patients (8.9%) refused to accept the offered interventions, with 25 patients not randomised for other reasons (Fig. 1). Table 2 indicates that the randomised participants were substantially symptomatic and functionally compromised, although patients did not score high on positive psychotic symptoms because these symptoms were among the exclusion criteria. The two treatment groups were reasonably comparable on sociodemographic, symptom and functioning measures at intake (Table 2), with the exception of total basic symptom score, which was slightly higher in the supportive counselling group. Although any differences between the groups are due to chance alone (since the participants were randomised to the treatment groups), it was decided to examine whether the effects of treatment on time to conversion remained constant when the impact of the basic symptom total score at baseline was accounted for.

Adherence to treatment and follow-up
After randomisation, two patients in the IPI group and one in the supportive counselling group failed to attend any treatment sessions. There were no statistical differences (χ² = 0.003, P = 0.956) in the number of participants who received less than 50% of the treatment between trial conditions (IPI, <20 sessions: n = 22, 33.8%; supportive counselling, <13 sessions: n = 20, 31.7%). Patients from the supportive counselling group (mean number of sessions 15.8 (s.d. = 6.8)) received significantly less treatment (P < 0.001) than those in the IPI group (23.7 (s.d. = 13.1)). After randomisation no patient was withdrawn from the study because of suicidal ideation or worsening of depression.

All 128 randomised patients were included in the primary survival analyses. The median follow-up interval for the entire study period for the 111 participants who did not convert to subthreshold psychosis was 730.0 days (s.d. = 256.6, range 10–952), while the median interval for the 17 participants who did convert was 237.0 days (s.d. = 13.1), range 10–952).

Psychosis incidence and time to conversion
By the end of the treatment phase, 2 of 63 patients in the IPI group and 11 of 65 patients in the supportive counselling group had converted to subthreshold psychosis. During the post-treatment phase, an additional two patients converted in each of the treatment groups. The cumulative conversion rates to subthreshold psychosis at 12 months were 3.2% for IPI and 16.9% for supportive counselling (odds ratio (OR) = 6.21, 95% CI 1.32–29.29) and at 24 months 6.3% for IPI and 20% for supportive counselling (OR = 3.69, 95% CI 1.13–12.01). These differences were significant (P = 0.008 at 12 months and P = 0.019 at 24 months, as indicated by a z-test at each of these points) (Fig. 2). The time to conversion for the entire study period was significantly shorter for the supportive counselling group than the IPI group (IPI: mean 887.1 days, 95% CI 849–925; supportive counselling: mean 784.2 days, 95% CI 702–866; log rank: χ² = 5.43, P = 0.020). The effects of treatment on time to conversion remained statistically significant (P = 0.042) when basic symptom total score at baseline was accounted for in a

<table>
<thead>
<tr>
<th>Table 2 Sample characteristics (n = 128)</th>
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<tbody>
<tr>
<td><strong>Integrated psychological intervention</strong> (n = 63)</td>
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<tr>
<td>Age, years: mean (s.d.)</td>
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<tr>
<td>Male, % (n)</td>
</tr>
<tr>
<td>Met basic symptom criteria, %</td>
</tr>
<tr>
<td>Met decreased functioning and risk factor criteria, %</td>
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<tr>
<td>Marital status, % (n)</td>
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<tr>
<td>Married/cohabiting</td>
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<tr>
<td>Living alone/divorced</td>
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<tr>
<td>Employment status, % (n)</td>
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<tr>
<td>Full/part time</td>
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<tr>
<td>Student/training</td>
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<tr>
<td>Unemployed/other</td>
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<tr>
<td>Housing status, % (n)</td>
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<tr>
<td>Independent</td>
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<tr>
<td>Primary family</td>
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<tr>
<td>Baseline severity of symptoms</td>
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<tr>
<td>Prodomal symptoms (basic symptom total score), mean (s.d.)</td>
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<tr>
<td>PANSS subscale score, mean (s.d.)</td>
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<tr>
<td>Positive</td>
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<tr>
<td>Negative</td>
</tr>
<tr>
<td>General</td>
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<tr>
<td>MADRS score, mean (s.d.)</td>
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<tr>
<td>Global Assessment of Functioning</td>
</tr>
</tbody>
</table>

PANSS, Positive and Negative Syndrome Scale; MADRS, Montgomery-Åsberg Depression Rating Scale.

a. For definitions see Appendix 1.

b. Six people had other living arrangements.

c. Symptom data are missing for 0–16 participants.
Cox regression model. At 24-month follow-up, significantly fewer patients in the IPI group than in the supportive counselling group had developed psychosis (3.2% vs. 15.4%; \( \chi^2 = 5.614, \) d.f. = 1, \( P = 0.018 \)) or schizophrenia/schizophreniform disorder (1.6% vs. 12.3%; \( P = 0.033 \)). Details of the participants classified as making conversion are shown in online Table DS1. The NNTs with IPI to prevent one person making the conversion were 8 (95% CI 6.4–21) for psychosis and 10 (95% CI 2.1–19.3) for subthreshold psychotic symptoms, 9 (95% CI 4.0–8.5) for subthreshold psychosis, and 15 (95% CI 2.1–19.3) for schizophrenia/schizophreniform disorder. The overall conversion rates did not differ between centres (exact \( P = 0.785 \)).

**Use of antidepressants**

At intake, 17.5% (\( n = 11 \)) of the IPI group and 20% (\( n = 13 \)) of the supportive counselling group were being prescribed antidepressants. At 12 months, 9.5% of the IPI group and 10.8% of the supportive counselling group and at 24 months, 15.0% of the IPI group and 9.75% of the supportive counselling group were being prescribed antidepressant medication. There were no significant differences in antidepressant use between treatment groups.

**Discussion**

To our knowledge, this is the first trial to evaluate a specific prevention strategy in individuals putatively in an EIPS. In accordance with our hypothesis, the incidence of and time to conversion to subthreshold psychotic symptoms, psychosis and schizophrenia/schizophreniform disorder during a 12-month treating period was significantly lower for patients who received specially designed IPI than for those who were treated with supportive counselling. This significant difference was maintained throughout the 24-month follow-up.

**Comparison with earlier trials in individuals at risk of developing first-episode psychosis**

The present study confirms that EIPS criteria define a clinically symptomatic and functionally compromised population whose risk of developing psychosis is several thousand times higher than the annual risk in the general population. A transition rate of 17% in the first year during supportive treatment is in line with a 19% transition rate in the original naturalistic Cologne Early Recognition study.\(^8\) In accordance with the aim of identifying an especially early stage of the illness, 12-month transition rates to psychosis in the control condition were lower in our EIPS trial than in RCTs which used ultra-high-risk criteria as inclusion criteria (17% vs. 22–38%).\(^8\)–\(^12\)

As regards acceptance of, and adherence to, offered interventions, our trial is reasonably comparable with the psychological intervention trial in an ultra-high-risk population by Morrison et al\(^7\) (8.9% vs. 2.8% refused treatment). This contrasts with prevention efforts involving treatment with anti-psychotics in ultra-high-risk individuals, which have proven less acceptable to patients (refusal rate of 35.9%)\(^8\) and have relatively low adherence rates (45.2% and 54.8%).\(^11\) The data on unwanted side-effects go along similar lines. There were no reports of side-effects in the psychotherapy studies (Morrison et al,\(^8\) Addington et al\(^9\) or our own study), but McGlashan and colleagues\(^1\) reported some instances of rigour and sedation due to risperidone treatment. In the McGlashan et al trial\(^1\) weight, pulse rate and fatigue increased significantly (by 8.8 kg and 9.5 beats/min for weight and pulse rate respectively) in the olanzapine compared with the placebo group. The acute treatment effects of the IPI intervention in comparison with supportive counselling were statistically significant, which was not the case in some trials of ultra-high-risk populations.\(^8\)–\(^11\),\(^13\)–\(^14\) Moreover, in contrast to the trials in ultra-high-risk populations,\(^8\)–\(^11\),\(^13\)–\(^14\) the conversion rates did not increase substantially after removing the specific intervention in the EIPS population. Both findings support the hypothesis that people in an EIPS might be more responsive to treatment than people in later stages of the prodromal phase.\(^8\)–\(^11\)

**Methodological considerations**

First, the overall sample size doubles those of earlier trials\(^8\)–\(^12\) and the methodological quality of the trial using the Clinical Trial Assessment Measure\(^46\) was high, which strengthens the validity of the findings. Second, no formal measures of therapists’ adherence to the manual were employed, nor did we use any formal assessments of therapists’ competence. However, we believe that the internal validity of the interventions was high, because the framework, setting and supervision differed between IPI and supportive counselling, and additionally, both interventions were detailed in specific manuals. Third, face-to-face contact with therapists within the trial was higher for patients in the IPI group than for patients receiving supportive counselling. Fourth, since all participants received some sort of treatment (IPI or supportive counselling) and there was no ‘no treatment’ condition, we cannot rule out that participants might have improved without treatment. Finally, since IPI covered a variety of psychological strategies, the trial design did not allow assessment of the relative contribution of the psychological strategies provided.

**Clinical consequences**

Despite the limitations mentioned above, the data presented indicate that specifically developed IPI was effective for delaying the onset of subthreshold, first-episode psychosis and schizophrenia over a 24-month time period. Moreover, the very small numbers of converters after termination of treatment raises the likelihood that interventions in the EIPS indeed prevent psychosis. Integrated psychological therapy was safe, well accepted...
and tolerated by patients, did not produce unpleasant side-effects and might have been helpful in reducing false positives as well. The NNTs of 8 (subthreshold psychotic symptoms) and 9 (psychosis) for IPI to prevent one conversion are clinically meaningful and contrast with for example, NNTs between 71 and 171 (depending on degree of illness) for the treatment of one stroke. Thus, IPI has the potential to improve the prognosis of many young people in an EIPS and could reduce the devastating consequences of schizophrenia for the affected individuals, their families and society.

References


13. A small number of the following basic symptoms in the past 3 months several times a week: (a) thought interferences (b) thought perseveration (c) thought pressure (d) thought blockages (e) disturbances of receptive language, either heard or read (f) decreased ability to discriminate between ideas and perception, fantasy and true memories (g) unstable ideas of reference (subject centrism) (h) derealisation (i) visual perception disturbances (blurred vision, transitory blindness, partial sight, hypersensitivity to light, etc.) (j) acoustic perception disturbances (hypersensitivity to sounds or noise, acoasms, etc.)

and/or decrease in Global Assessment of Functioning score of at least 30 points (within the past year) and at least one of the following decreases in functioning and risk factors: (i) first-degree relative with a lifetime-diagnosis of schizophrenia (ii) a schizophrenia-spectrum disorder (iii) pre- or perinatal complications.

Appendix 1

Inclusion criteria (early initial prodromal state)

Self-experienced thought and perception deficits (basic symptoms): one or more of the following basic symptoms in the past 3 months several times a week:

- (a) thought interferences
- (b) thought perseveration
- (c) thought pressure
- (d) thought blockages
- (e) disturbances of receptive language, either heard or read
- (f) decreased ability to discriminate between ideas and perception, fantasy and true memories
- (g) unstable ideas of reference (subject centrism)
- (h) derealisation
- (i) visual perception disturbances (blurred vision, transitory blindness, partial sight, hypersensitivity to light, etc.)
- (j) acoustic perception disturbances (hypersensitivity to sounds or noise, acoasms, etc.)

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The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.


Online supplement

Appendix DS1

Exclusion criteria

(a) Attenuated or brief limited intermittent psychotic symptoms
(b) Present or past diagnosis of a schizophrenic, schizophreniform, schizoaffective, delusional or bipolar disorder according to DSM-IV
(c) Present or past diagnosis of a brief psychotic disorder according to DSM-IV with a duration of more than 1 week or within the past 4 weeks regardless of its duration
(d) Diagnosis of delirium, dementia, amnestic or other cognitive disorder, mental retardation, psychiatric disorders due to a somatic factor or related to the consumption of psychotropic substances according to DSM-IV
(e) Alcohol or drug dependence within the past 3 months according to DSM-IV
(f) Organic brain disease (inflammatory, traumatic, epilepsy, etc.)
(g) Previous treatment with antipsychotics
(h) Acute suicidality
(i) Aged below 17 and above 35 years.

Exit criteria

Subthreshold psychotic symptoms

(a) Attenuated psychotic symptoms: one or more of the following symptoms appearing several times a week for a period of at least 1 week and/or
(b) brief limited intermittent psychotic symptoms: one or more of the following psychotic symptoms for less than 1 week resolving spontaneously and/or
(c) psychosis: one or more of the following psychotic symptoms for more than 1 week.
Table DS1  Details of participants classified as converting to subthreshold psychosis

<table>
<thead>
<tr>
<th>Participant</th>
<th>Age, years</th>
<th>Gender</th>
<th>Entry route</th>
<th>Allocation</th>
<th>Time to conversion, months</th>
<th>Probable DSM-IV psychosis diagnosis a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>19</td>
<td>Male</td>
<td>BS</td>
<td>SC</td>
<td>5</td>
<td>Schizophrenia/schizophreniform</td>
</tr>
<tr>
<td>2</td>
<td>18</td>
<td>Female</td>
<td>BS</td>
<td>SC</td>
<td>2</td>
<td>Schizophrenia/schizophreniform</td>
</tr>
<tr>
<td>3</td>
<td>35</td>
<td>Male</td>
<td>BS+DF/R</td>
<td>IPT</td>
<td>7</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>19</td>
<td>Male</td>
<td>BS+DF/R</td>
<td>SC</td>
<td>11</td>
<td>Schizophrenia/schizophreniform</td>
</tr>
<tr>
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BS, basic symptoms (for definitions see Appendix 1); DF/R, decrease in functioning and risk factors (for definitions see Appendix 1); SC, supportive counselling; IPT, integrated psychological therapy.

a. None: subthreshold psychotic symptoms (attenuated psychotic symptoms, brief limited psychotic symptoms; see Appendix 1 for definitions); psychosis: DSM-IV psychotic diagnosis (schizophrenia/schizophreniform, schizoaffective disorder, major depression with psychotic features, bipolar disorder with psychotic features, delusional disorder, brief psychotic disorder, brief psychotic disorder not otherwise specified); schizophrenia/schizophreniform: probable DSM-IV schizophrenia/schizophreniform disorder diagnosis.
Preventing progression to first-episode psychosis in early initial prodromal states

Andreas Bechdolf, Michael Wagner, Stephan Ruhrmann, Susan Harrigan, Verena Putzfeld, Ralf Pukrop, Anke Brockhaus-Dumke, Julia Berning, Birgit Janssen, Petra Decker, Ronald Bottlender, Kurt Maurer, Hans-Jürgen Möller, Wolfgang Gaebel, Heinz Häfner, Wolfgang Maier and Joachim Klosterkötter


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