## Early intervention in patients at ultra high risk of psychosis: benefits and risks.

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## Clinical overview

# Early intervention in patients at ultra high risk of psychosis: benefits and risks

de Koning MB, Bloemen OJN, van Amelsvoort TAMJ, Becker HE, Nieman DH, van der Gaag M, Linszen DH. Early intervention in patients at ultra high risk of psychosis: benefits and risks.

**Objective:** Prediction of transition to psychosis in the prodromal phase of schizophrenia has raised interest in intervention prior to the onset of frank psychosis. The aim of this review was to examine whether interventions in the prodromal phase have a favourable benefit/risk ratio.
**Method:** A literature search in PubMed, EMBASE and PsycINFO was performed.
**Results:** Three randomized clinical trials with antipsychotic medication and/or cognitive behavioural therapy as clinical intervention suggested a positive effect at the end of treatment, but no significant differences were found at the end of follow-up periods from 1 to 4 years. Naturalistic studies present a hypothesis about a possible preventive effect of antidepressive medication. The results of eight other studies are more difficult to interpret. Side-effects of antipsychotic medication and non-adherence with medication are essential problems.
**Conclusion:** At the present time, the data concerning the benefits and risks do not justify prodromal intervention as standard clinical practice.

**M. B. de Koning[1], O. J. N. Bloemen[1], T. A. M. J. van Amelsvoort[1], H. E. Becker[1], D. H. Nieman[1], M. van der Gaag[2,3], D. H. Linszen[1]**

[1]Department of Psychiatry, Academic Medical Centre, Amsterdam, [2]Department of Clinical Psychology, VU University, Amsterdam and [3]Parnassia BAVO Psychiatric Institute, The Hague, the Netherlands

Key words: psychotic disorder; prevention; treatment

M. B. de Koning, Department of Psychiatry, Academic Medical Centre, Room PA1-179, Meibergdreef 5, 1105 AZ Amsterdam, the Netherlands.
E-mail: m.b.dekoning@amc.uva.nl

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### Clinical recommendations

- Several treatments have been proposed for patients who are at ultra high risk (UHR) of developing a psychosis: different types of medication (antipsychotics: olanzapine, risperidone, aripiprazol, amisulpride, haloperidol; Selective Serotonin Reuptake Inhibitors; omega-3 fatty acids; glycine); CBT; skills training; psychoeducation and family interventions. Treatments are aimed at reducing the risk of transition to psychosis and/or treatment of the actual symptoms.
- A definitive conclusion about the efficacy and safety of all these interventions cannot be drawn at this moment.
- UHR patients should be monitored regularly and actively and defined comorbid syndromes such as depression and substance-use disorders should be dealt with adequately.
- A possible strategy when treating an UHR patient is providing extensive information about the possible benefit and risks of the different interventions and providing treatment based on the preferences of each individual patient.

### Additional comments

- Only a few randomized trials have been published, but pharmacological interventions and CBT have shown encouraging results that justify further research.
- Prediction algorithms might be improved, thus lowering the number of false positives. With improved prediction algorithms, the validity of efficacious and effective interventions might increase, and analysis of benefits and risks might be more favourable.
- Even with better prediction algorithms, the emphasis of the UHR criteria will be on attenuated psychotic symptoms and brief limited psychosis. Neurocognitive dysfunctioning and negative symptoms are core features of schizophrenia and of the UHR state which are until now far more difficult to influence.

## Introduction

Schizophrenia is a serious illness that usually manifests itself in adolescence or early adulthood. It has a potentially chronic course and the outcome is often poor. Over the last two decades, interest has grown in the potential benefits of intervention before the onset of psychosis. In this paper, the literature on interventions in the phase preceding the first psychosis will be reviewed, but first relevant concepts and preceding issues will be shortly addressed.

### Preventive interventions: definitions

Throughout medicine, the last decades have shown a movement towards prevention.

In 1994, Mrazek and Haggerty (1) described the difficulties with the traditional public health classification system of primary, secondary and tertiary prevention, which makes the classification system less useful for prevention of mental health disorders. They questioned the use of the term 'prevention' for situations in which a disorder is already present, as in 'tertiary prevention'. Furthermore, they pointed at the unclear definition of 'secondary prevention'. The term 'secondary prevention' is used in two different ways: i) early detection of a disease and preventing progression of the disease and ii) detection of prodromal symptoms of a disease and preventing full manifestation of the disease.

To overcome these difficulties, they described a mental health intervention spectrum, in which the term 'prevention' is reserved for interventions that take place when there is (still) no clinically diagnosable disorder. Then, the aim of prevention was to reduce the occurrence of new cases of a clinically diagnosable disorder (2).'Prevention' is divided into three subcategories: universal prevention, selective prevention and indicated prevention (1). Universal prevention is prevention in the whole population, selective prevention is prevention in a subgroup with risk factors but without any symptoms and indicated prevention is prevention in a group of persons with minimal but detectable symptoms but no clinically diagnosable disorder.

As the risk of developing a disorder increases along these three subgroups, the criteria for economically and ethically justified interventions get less strict. Universal prevention is acceptable when costs are low, the intervention is effective and the risk of adverse effects is low. Indicated prevention may be reasonable even at high costs and when there is some risk of adverse effects, especially if a serious disorder is implied and if the incidence of the disorder in the targeted subgroup is high (1, 2).

Universal and selective prevention are only possible when the aetiology of a disease is known, and when aetiological risk factors can be eliminated. In the case of psychosis, many risk factors are known, but each makes a small contribution to the total risk, and they are hard to influence. Effective universal and selective prevention strategies are, until now, not available (3, 4). In this paper, studies on indicated preventive interventions will be reviewed.

### The putatively prodromal state: operationalization criteria

In the phase preceding a first psychotic episode, many symptoms may be present: depressed mood, anxiety, irritability, changes in volition, cognitive changes (e.g. thought blocking), physical symptoms (e.g. sleep disturbances), behavioural changes (e.g. social withdrawal), impaired tolerance to normal stress and attenuated psychotic symptoms (5–7). Many of these symptoms are not specific for the psychotic prodrome and might also be the first manifestation of another disorder, for example a major depression (8). Attenuated psychotic symptoms occur late in the disease process (6).

As 'prodromal' is a retrospective concept (5), a patient with 'prodromal symptoms' actually has 'putatively prodromal symptoms' (9). Criteria had to be developed to operationalize this putatively prodromal state. Different research groups have developed different 'early detection instruments' and operationalization criteria, which will be discussed below. All different names used for the putatively prodromal state [e.g. 'ultra high risk' state (UHR), 'at-risk mental state' (ARMS), 'early initial prodromal state' (EIPS) and 'clinical high risk state' (CHR)] have their own definition, which are sometimes much alike, but almost never identical. The most widely used name is 'UHR': UHR patients and UHR state. Although this name originally referred to a specific set of operationalization criteria, nowadays it is often used to refer to the whole group of patients with putatively prodromal symptoms. Therefore, in this review, the name 'UHR' has been used, when referring to putatively prodromal symptoms or patients with these symptoms. For each described study, the specific operationalization criteria of the UHR state in that study have been mentioned.

*The UHR approach.* In 1994, the Personal Assessment and Crisis Evaluation (PACE) Clinic in Melbourne (Australia) started to develop the UHR approach. The researchers described a set of criteria, combining risk factors (age and family

history) with clinical symptoms. The symptom scores are based on subjective information from the patient and on observation by the rater. Individuals meeting a defined combination of risk factors are at UHR of developing a psychosis (5), indicating an increased risk for developing a first psychotic episode within a year.

Yung and McGorry (6) described the current UHR criteria as follows [for more details see Yung et al. (10, 11)]:

'The current UHR criteria require that a help seeking young person be aged between 14 and 29 years, is referred to a clinical service and meets criteria for one or more of the following groups:

i) Attenuated psychotic symptoms group (APS): have experienced sub-threshold, attenuated psychotic symptoms during the past year;
ii) Brief limited intermittent psychotic symptoms group (BLIPS): have experienced episodes of frank psychotic symptoms that have not lasted longer than a week and have been spontaneously abated;
iii) State and trait risk factor group: have schizotypal personality disorder or a first-degree relative with a psychotic disorder, and have experienced a significant decrease in functioning during the previous year'.

The PACE research team developed the first early assessment instrument 'Comprehensive Assessment of At-Risk Mental States (CAARMS)' in 1996 and refined it in the next 9 years (12). The CAARMS is a structured diagnostic interview on positive and negative symptoms, and other symptoms (e.g. cognitive changes, behavioural changes, emotional disturbances) that can occur in the prodromal state. The criteria for being at UHR were precisely defined, and consisted of thresholds for intensity, frequency and duration of the positive symptoms (for APS and BLIPS) and a precise definition of 'significant decrease in functioning' (for the state and trait risk factor group). Criteria for experiencing a psychotic episode (at present or in the past) were precisely defined as well and are based on intensity, frequency and duration of positive symptoms. Patients fulfilling the prodromal criteria in the CAARMS have been named 'UHR patients', but also 'ARMS patients' or 'patients fulfilling PACE criteria'.

Shortly after the development of the first version of the CAARMS in 1996, the Prevention through Risk Identification, Management, and Education (PRIME) prodromal research team at Yale University (USA) developed the Structured Interview for Prodromal Syndromes (SIPS), including the scoring list Scale of Prodromal Symptoms (SOPS) (13). The instrument was further developed in the next years (14). The SIPS and SOPS were based on the UHR approach developed in the PACE Clinic by Yung et al. (5). As in the CAARMS, the SIPS includes precisely defined criteria for the UHR state (the Criteria of Prodromal Syndromes, COPS) and for the psychosis-threshold (Presence of Psychotic Syndrome, POPS) (14). Patients fulfilling the prodromal criteria in the COPS have been named 'UHR patients', The structured interviews of the SIPS and the CAARMS have converged over the times, as have the UHR and psychosis criteria. Subtle differences are mainly found in frequency and duration criteria.

The UHR criteria (COPS or CAARMS) have been used by several research clinics besides the PACE clinic and the PRIME clinic (e.g. the Early Identification and Intervention Evaluation Clinic in Manchester, UK), sometimes with slight modifications. The 12-month transition rate to psychosis varies between 9 and 54% [for a summary see Haroun et al. (15)].

*The basic symptom approach.* Another early detection instrument was developed in Germany, and it originated from a different approach. Departing from the fundamental symptoms of schizophrenia as hypothesized by the Swiss psychiatrist Bleuler, the concept of basic symptoms was developed by the German psychiatrists Gross and Huber. The basic symptoms are *subjectively* experienced well-defined symptoms, amongst others cognitive symptoms, that were thought to be core signs of schizophrenia. They were translated to the Bonn Scale for the assessment of Basic Symptoms (BSABS) (16).

Klosterkotter et al. (7) studied the predictive capacity of basic symptoms with a shortened 66-item version of the BSABS in a group of 160 patients who were not psychotic but were referred by their clinician as being at risk for developing schizophrenia. During a follow-up period of 9.6 years, 79 of the 160 patients developed schizophrenia. The presence of at least one basic symptom at baseline had a positive predictive value of 0.70, and the absence of basic symptoms had a negative predictive value of 0.96. From the 66 BSABS items, 10 items fulfilled the criteria of sensitivity $> 0.25$ and a positive predictive value of $> 0.70$, that were defined on forehand (e.g. thought interference, thought blockages and acoustic perception disturbances).

Based on this study, the authors developed a new instrument, the BSABS – Prediction List (17), a list of nine symptoms, with a cut-off score for being at high risk of developing schizophrenia when two or more of these symptoms are present. The predictive

validity of this instrument is currently being examined in the European Prediction of Psychosis Study (18). Because the basic symptoms refer to subtle subjectively experienced abnormalities, they may refer to an earlier phase in the disease process than the UHR criteria in the CAARMS and the COPS.

### Potential benefits of prepsychotic intervention

There are, at least, three possible mechanisms for improving the course of the disease by intervention before onset of psychosis. First, it might be possible to prevent psychosis by intervening in a crucial phase of beginning symptoms.

Second, it might be possible to improve the course of the disease by improving the mental state in the prodromal phase or by postponing the first psychotic episode. It has been hypothesized that much harm is done already in the prodromal phase. This hypothesis refers to possible loss of grey matter at the time of transition to psychosis (19) and to functional decline (20). The major source of disability in schizophrenia is decline in social and work skills. By improving these skills in the prodromal phase and/or by giving a patient more healthy years in the crucial adolescent phase of building relationships and studying, functional decline might be limited (21).

Finally, the first psychotic episode might have a more favourable course after intervention in the prodromal phase, because the patient is already enrolled in a mental health treatment program: a psychosis will be discovered soon after onset, and the patient might be more willing to accept treatment, thus shortening the duration of untreated psychosis (22, 23).

### Potential risks of prepsychotic intervention

Risks of intervention primarily concern two issues: drug side-effects and stigma or anxiety because of the word 'psychosis' being used. Both risks are especially important because of the false-positive UHR subjects who will not develop a psychosis. In intervention studies, it is impossible to know the number of false-positive subjects, because there may be 'false false positives': subjects that do not make the transition to psychosis, but who would have if they had not been treated (10). False positives and 'false false positives' cannot be distinguished at follow-up, so it is impossible to know how many subjects have been treated unnecessarily.

The potential risk of stigmatizing has often been discussed. One should keep in mind, however, that UHR subjects are subjects who have psychological or psychiatric problems. They are help-seeking, often low-functioning individuals. In practice, researchers have found that good education about psychosis and about the risk and uncertainty of transition, is often accepted and does not seem to be stigmatizing (24).

### Earlier reviews on intervention studies in UHR subjects

The most recent reviews on this topic that were found, date from 2006: a Cochrane review (database search until March 2006) (25) and a comprehensive review article on prospective investigations of the prodromal state of schizophrenia by Olsen and Rosenbaum (database search until August 2005) (26).

Since then, many new results have been published, which justifies a new review. Furthermore, in the Cochrane review only three randomized controlled trials were included. The results of the Cochrane review were inconclusive. In the present review all available information will be included, because in clinical practice the need for knowledge about interventions in UHR subjects is high.

Olsen and Rosenbaum gave a complete overview of prospective studies until August 2005, focusing on operationalization criteria of the putatively prodromal state, and prediction of transition to psychosis in naturalistic studies, as well as on effects of interventions. They paid much attention to conceptual and methodological issues in the field. In contrast, the present review aims to examine whether interventions in UHR subjects have a favourable benefit/risk ratio, by giving a clinical overview that focuses on effects of interventions only, and especially on the meaning of research results for clinical practice.

### Aims of the study

The aim of this paper was to review all interventions in UHR subjects through a literature search. The main question is whether benefits of intervention during this phase outweigh the risks associated with intervention.

## Material and methods

We searched PubMed, EMBASE and PsycINFO databases from January 1980 to June 2008, using the keywords (early intervention OR prevent*) AND (psychosis) AND (ultra high risk OR prodrom*). Only publications in English or with at least an abstract available in English were included. The reference lists of retrieved articles were searched for additional articles. If a retrieved

article was part of a special theme issue on the subject, the whole issue was screened. Abstract books of conferences on the subject were screened from January 2005 to June 2008.

In line with the aim of this paper, we searched for studies that gave information about the efficacy of interventions in UHR subjects. We did not include: studies assessing the feasibility or tolerability of interventions or the feasibility of running a clinical service for UHR subjects, naturalistic studies describing the percentage of transition to psychosis and the prediction of psychosis, descriptions of UHR subjects at the point of inclusion in a study, and validation studies on operationalization criteria or early detection instruments. Neither did we include unpublished studies in progress,

### Inclusion of studies: design and quality

Because of the limited number of randomized clinical trials, studies with other methodological designs will also be reviewed. We included intervention studies without a control group, because these studies are often the first indication of a possible positive effect of an intervention and can prompt further research. We also included naturalistic studies in which the effects of different non-experimental interventions are compared retrospectively. Although this kind of design leads to a bias, it may generate interesting hypotheses. Finally, we included results presented in abstracts, which can provide important additional information, when there are so few trials with results published in full articles.

### Inclusion of studies: intervention

Different research groups have used – or evaluated, in the case of naturalistic, retrospective studies – several different interventions, sometimes in combination: different types of medication [antipsychotics: olanzapine, risperidon, aripiprazol, amisulpride, haloperidol; Selective Serotonin Reuptake Inhibitors; omega-3 fatty acids; glycine); different types of CBT; skills training; psychoeducation and family interventions. Therefore, it is difficult to compare the different studies. Because of the novelty of the field and the impossibility to decide on forehand which interventions are the most promising, every study will be reviewed, irrespective of the type of intervention used.

### Inclusion of studies: outcome measures

Two main outcome measures can be discerned: the percentage of transition to psychosis vs. acute treatment effects in the present phase. They will both be addressed in this review, because in clinical practice both outcome measures are important.

## Results

With the search in PubMed, EMBASE and PsycINFO, 56 articles could be retrieved that considered the subject. Of these 56 articles, 12 articles described the effect of an intervention. The other 44 articles were descriptions of study designs, descriptions of interventions and clinical settings, reviews, commentaries and case reports. By searching the reference lists of retrieved articles, special theme issues and abstract books, eight additional articles/abstracts could be retrieved that described the effect of an intervention. Three articles/abstracts described the same results; the most recent and complete description was selected. Thus, a total number of 18 articles/abstracts were found.

Studies focusing on the prevention of transition to psychosis are reviewed firstly and are listed in Table 1. Randomized controlled trials, trials without control intervention and naturalistic studies with retrospective comparisons of interventions are reviewed separately. Studies focusing on acute treatment effects are reviewed in secondly and are listed in Table 2.

### Prevention of transition to psychosis

The first study, to our knowledge, that focused on detection of possible prodromal symptoms was conducted by Falloon et al. (27). In an area of 35 000 inhabitants, they offered education, stress management techniques and low-dose antipsychotic medication to patients with possible prodromal symptoms (defined by DSM-III-prodromal symptoms and ten additional symptoms). The authors found a ten-fold reduction of the incidence of schizophrenia within the area, compared with a previous period. The study has multiple methodological limitations, of which the most important is the uncertain comparability with the historical control group (28). However, the results of this innovative and provocative study have inspired many researchers in the field of prepsychotic intervention.

*Randomized controlled trials*. Until June 2008, five research groups have reported results from randomized controlled trials evaluating the efficacy of different treatment approaches in reducing the transition rate from UHR symptoms to

Table 1. Studies on prevention of transition to psychosis

| Study | Inclusion criteria | Specific intervention (SI) | Control intervention (CI) | Primary outcome measure: transition to psychosis | | |
|---|---|---|---|---|---|---|
| | | | | Follow-up < 1 year | Follow-up 1 year | Follow-up > 1 year |
| PACE (23, 30) | UHR criteria (CAARMS) ($n$ = 59) | Risperidone 1–2 mg + CBT ($n$ = 31) 6 months | Needs-based intervention ($n$ = 28) 6 months | After 6 months: SI: 3/31 (10%) CI: 10/28 (36%) $P$ = 0.03 | After 12 months: SI: 6/31 (19%) CI: 10/28 (36%) NS | After 3–4 years: SI: 10/31 (32%) CI: 12/28 (43%) NS |
| PRIME (9) | UHR criteria (COPS) ($n$ = 60) | Olanzapine 5–15 mg ($n$ = 31) 12 months | Placebo ($n$ = 29) 12 months | | After 12 months: SI: 5/31 (16%) CI: 11/29 (38%) NS | |
| EDIE (29, 31) | UHR criteria (adaptation of PACE criteria based on PANSS) ($n$ = 60) 2 patients excluded from analysis | CT ($n$ = 35) 6 months | Monitoring ($n$ = 23) 6 months | | After 12 months: SI: 2/35 (6%) CI: 5/23 (22%) $P$ = 0.028 NB: NS if 2 excluded patients are included | After 3 years: Defined by PANSS: SI: 7/35 (20%) CI: 5/23 (22%) NS Defined by AP medication: SI: 5/35 (14%) CI: 8/23 (35%) $P$ = 0.024 |
| GNRS EIPS (32, 33) | = at least 1 basic symptom out of 10 basic symptoms with high predictive value, and/or 'state and trait risk factor' ($n$ = 128) | Comprehensive cognitive behavioural treatment (individual cognitive therapy, group intervention, cognitive remediation, psychoeducational family intervention) ($n$ = ?) 12 months | Supportive counselling ($n$ = ?) 12 months | | After 12 months: Transition to LIPS: SI: ?/? (3.2%) CI: ?/? (16.9%) $P$ = 0.008 Transition to psychosis: SI: ?/? (1.6%) CI: ?/? (13.8%) $P$ = 0.020 | After 24 months: Transition to LIPS: SI: ?/? (6.3%) CI: ?/? (20.0%) $P$ = 0.019 |
| Vienna, Austria (34, 35 ) | UHR criteria ($n$ = 81) (CAARMS) | Omega-3 fatty acids 1.5 g/day ($n$ = 41) 12 weeks | Placebo ($n$ = 40) 12 weeks | After 12 weeks: SI: 1/38 (2.6%) CI: 8/38 (21.2%) $P$ = 0.028 (5 patients excluded from analysis for unclear reason) | After 12 months: SI: 2/41 (4.9%) CI: 11/40 (27.5%) $P$ = 0.006 | |
| OPUS (36) | Schizotypal disorder ($n$ = 79) | Integrated treatment (ACT with family intervention and social skills training) ($n$ = 42) 2 years | Standard treatment ($n$ = 37) 2 years | | After 12 months: SI: 3/37 (8.1%) CI: 10/30 (25.0%) NB: 12 patients lost to follow-up not included in analysis | After 24 months: SI: 9/36 (25.0%) CI: 14/29 (48.3%) $P$ = 0.02 NB: 14 patients lost to follow-up not included in analysis |
| Szeged, Hungary (45) | UHR criteria ($n$ = 52) (CAARMS) | Low-dose haloperidol or risperidone 0.5–2.0 mg/day ($n$ = 52) 6 months | None | After 6 months: SI: 3/42 (7.1%) NB: 10 patients dropped-out | After 12 months: SI: 3/42 (7.1%) | |
| RAP (49) | Retrospective design: attenuated psychotic symptoms + pharmacological treatment = 8 weeks + follow-up at least 6 months ($n$ = 48) | Naturalistic design: 28 received AP medication, often with comedication (e.g. AD) 20 received an AD, but no antipsychotics | | | After maximum of 5 years: AP medication: 12/28 (43%) AD medication: 0/20 (0%) $P$ = 0.007 | |
| OASIS (50) | Retrospective design: UHR criteria (CAARMS) + pharmacological treatment with AD or AP + follow-up 2 years ($n$ = 48) | Naturalistic design: 35 received AP medication 13 received AD medication | | | After 2 years: AP medication: 10/35 (29%) AD medication: 1/13 (8%) No statistical analysis | |

psychosis. Definitive results have been published for three of the five trials (9, 23, 29); for two of these, long-term follow-up results have also been published (30, 31). Results of the fourth and fifth trial have only been presented orally and in abstracts (32–35).

A sixth randomized controlled trial evaluated the efficacy of an intervention in reducing the transition rate from schizotypal disorder to psychosis (36). This is a different patient group, but we included the study because of the partial overlap between UHR criteria and criteria for schizotypal disorder.

*The PACE clinic study (Australia).* The first randomized trial compared the outcome in two groups of UHR participants, selected with the PACE criteria, which were later elaborated in the CAARMS: a group who received a combination of 1–2 mg risperidone plus CBT (specific intervention: SI, $n = 31$) and a group who received supportive psychotherapy only (needs-based intervention: NBI, $n = 28$) (23). The main outcome measure was transition to psychosis, operationally defined using threshold scores on the Brief Psychiatric Rating Scale (37) and the Comprehensive Assessment of Symptoms and History (38). Study participants and clinicians were not blind to treatment; research interviewers intended to be blind, but this proved to be difficult. Treatment was provided for 6 months with follow-up 6 months later. Follow-up in these 12 months was 100%.

When analysed by intention-to-treat, significantly more people in the NBI group had developed a psychotic episode by the end of the treatment phase than in the SI group (10/28 = 36% vs. 3/31 = 10%). This difference was no longer significant at the follow-up at 12 months because of the progression to psychosis of three more SI participants between months 6 and 12.

Levels of all symptoms improved in both groups. There was no difference in symptom improvement between the NBI and the SI group. Levels of functioning remained stable in both groups. Neuroleptic adverse effects were present in four patients and were relieved by dose reduction.

Follow-up interviews took place 3–4 years after study entry (30). Follow-up was 24/31 (77%) in the SI group and 17/28 (61%) in the NBI group. Between the 12-month and the 3–4-year follow-ups, two people from the NBI group and four people from the SI group developed psychosis.

There was no significant difference in the probability of developing psychosis between the NBI and the SI group over the entire duration of the study. Neither were there any differences in symptomatology or functioning between the groups.

*The PRIME study (USA).* The PRIME study is a randomized double-blind placebo-controlled trial which compared the outcome of UHR participants who received olanzapine 5–15 mg ($n = 31$) with participants who received placebo ($n = 29$) (24). The UHR state was defined by COPS criteria. The main outcome measure was transition to psychosis, operationally defined by the POPS (39). Treatment was provided for 1 year, with a further 1-year follow-up.

Participation at follow-up was low: 14/31 (45%) in the olanzapine group and 19/29 (66%) in the placebo group; the difference in drop-out rate was not significant. All drop-out took place in the first year.

In the olanzapine group, 5/31 participants became psychotic during the intervention (16%) and three more during the follow-up year (total 8/31 = 26%). In the placebo group, 11/29 participants became psychotic during the treatment year (38%) and two more during the follow-up year (total 13/29 = 45%). Although the rate of conversion to psychosis seemed higher in the placebo group during the first year, this difference was not significant. This may be due to a lack of power. Neither were there any significant differences between the two groups in changes in symptom and functioning scores, although after the treatment year the olanzapine group showed a greater improvement in positive symptoms than the placebo group, tending to significance. When analysed with a mixed-effects model repeated-measures analysis, significant between-treatment differences were observed between weeks 8 and 28, when the reductions in positive symptom scores were significantly greater for the olanzapine patients.

At follow-up, positive symptom scores worsened significantly in the former olanzapine group. During the treatment year, fatigue was reported by 29% of patients in the olanzapine group and 3% of patients in the placebo group; this difference was significant. The difference in weight gain was also significant: 8.8 kg in the olanzapine group vs. 0.3 kg in the placebo group.

*The Early Detection and Intervention Evaluation study (EDIE) (UK).* This randomized trial compared the outcome in two groups of UHR participants. UHR was operationally defined using an adaptation of the PACE criteria, based on the Positive and Negative Syndrome Scale (PANSS) (40). The treatment group received cognitive therapy (CT) ($n = 37$) and the control group received only monitoring ($n = 23$) (29). The main outcome measure was transition to psychosis, operationally defined based on the PACE criteria and the PANSS, and/or prescription of antipsychotic medication, and/or a DSM-IV diagnosis.

Participants and clinicians could not be blinded because of the nature of the intervention. Research interviewers intended to be blind, but this proved to be impossible. Treatment was provided for 6 months with follow-up 6 months later. Two of the 37 participants in the CT group were excluded from analysis because at the first postrandomization assessment, they both reported having had concealed psychotic symptoms at baseline.

In the CT group, 26/35 (74%) completed CT and follow-up. In the monitoring group, 16/23 (70%) completed follow-up.

The authors reported a significant difference between the CT and monitoring group in percentage of transition to psychosis at follow-up at 12 months [2/35 (6%) and 5/23 (22%) respectively], suggesting that CT significantly reduced the likelihood of developing psychosis.

However, the omission of two participants from analysis because of having been psychotic at the time of randomization, is questionable, and might not be compatible with true intention to treat analysis. When included in the analysis and counted as transitions to psychosis, the transition rate in the CT group is 4/37 (11%) and the difference is no longer significant (25).

Positive symptoms diminished in both groups during the 12-month trial, significantly more in the CT group than in the monitoring group. There were no differences in levels of functioning between the groups.

Follow-up interviews took place 3 years after study entry (30). Follow-up rates were quite low: 17/35 (49%) in the CBT group and 10/23 (43%) in the monitoring group.

Between the 12-month and the 3 year follow-up period, there were five more transitions to psychosis in the CT group and none in the monitoring group, when transition was defined by PACE/-PANSS and DSM-IV criteria. There was no significant difference anymore between the two groups in transition rate. However, when defining transition by being prescribed antipsychotic medication, there was a significant difference with a lower percentage of transitions in the CT group. These findings are difficult to interpret because of the different methods used for defining transition. Prescription of antipsychotic medication might be considered to be the most objective measure of transition because it does not rely upon self-report data from interviews. On the other hand, antipsychotic medication is increasingly used in clinical practice for other disorders or UHR symptoms (41).

At the 3 year follow-up, no results were published about symptom or functioning levels.

*The German Research Network on Schizophrenia (GRNS): Early intervention in the Initial Prodromal State (EIPS) (Germany).* The GRNS study is different from the other three studies, because it combines the 'UHR approach' with the 'basic-symptom approach', thus distinguishing two different putatively prodromal stage phases:

i) EIPS: presence of at least one basic symptom of 10 basic symptoms that were found to have a high sensitivity and positive predictive value for developing schizophrenia in a 9.6-year follow-up period (7) and/or a 'state and trait risk factor'. The 'state and trait risk factor' in this study is a combination of a reduction in Global Assessment of Functioning (GAF) score of at least 30 points within the last year and one of the following risk-factors: first-degree relative with diagnosis of schizophrenia, a schizophrenia spectrum disorder in the help-seeking person or pre- or perinatal complications.
ii) Late Initial Prodromal State (LIPS): attenuated psychotic symptoms (APS) and/or BLIPS.

The EIPS patients ($n$ = 128) were randomized to receive either a comprehensive CBT or supportive counselling (SC) for 12 months. The CBT was a multimodal treatment programme comprising individual CT, group intervention, cognitive remediation and psychoeducational family intervention. The LIPS patients ($n$ = 124) were randomly assigned to a needs-focused intervention (NFI) or to NFI plus amisulpride.

For the LIPS group, only results on short-term acute treatment effects have been published, which will be summarized below.

For the EIPS group, preliminary results concerning prevention of psychosis have been published without statistical analysis (3, 42). Definitive results have only been described in abstracts and presented at conferences (32, 33).

The risk of transition from EIPS to LIPS was lower in the CBT group than in the SC group at month 12 (3.2% vs. 16.9%, $P$ = 0.008) and at month 24 (6.3% vs. 20.0%, $P$ = 0.019). The risk of transition from EIPS to psychosis was also lower in the CBT group than in the SC group at month 12 (1.6% vs. 13.8%, $P$ = 0.020). At month 24, no results of transition from EIPS to psychosis have been published.

*Medical University of Vienna: omega-3 fatty acids (Austria).* A research group of the Child & Adolescent Psychiatry Unit of the Medical University of Vienna, in cooperation with The

Schlössli Clinic, Ötwil am See (Switzerland) and ORYGEN's Research Centre, Parkville (Australia), has chosen a different intervention to evaluate. They hypothesized that omega-3 fatty acids might be effective in preventing psychosis in UHR individuals, based on earlier studies which implicate that fatty acid deficiencies may contribute to neurodevelopmental disorders (43).

They conducted a randomized, double-blind, placebo-controlled trial testing the effects of 1.5 g/day omega-3 fatty acids in 81 adolescents (mean age 16.4; range 13–24 years) with UHR symptoms for developing psychosis. UHR state was defined by CAARMS criteria.

Supplementation was administered for 12 weeks; follow-up was 12 months. The primary outcome measure was transition to psychosis, operationally defined using PANSS criteria, and criteria for frequency and duration of symptoms. Secondary outcome measures were PANSS scores and GAF scores.

Preliminary results have been described in two abstracts and presented orally (34, 35):

i) Results at 12-week follow-up have been described for 76 of the 81 adolescents. In the omega-3 fatty acids group, one of 38 adolescents (2.6%) made the transition to psychosis in 12 weeks, compared with eight of 38 adolescents (21.2%) in the placebo group. This difference was significant ($P = 0.028$). There were also significant differences at week 12 in changes from baseline on PANSS scores (positive symptoms and global symptoms) and GAF score, in favour of the treatment group. No side-effects were observed.
ii) Results at 1-year follow-up were described for the whole group. In the omega-3 fatty acids group, two of 41 adolescents (4.9%) had made the transition to psychosis, compared with 11 of 40 (27.5%) adolescents in the placebo group. This difference was significant ($P = 0.006$).

*OPUS trial, Copenhagen (Denmark).* The OPUS trial compared integrated treatment vs. standard treatment in 547 patients who recently got a ICD-10 diagnosis in the schizophrenia spectrum (schizophrenia, acute or transient psychotic disorder, schizoaffective disorder, other delusional disorders, and schizotypal disorder) (44). The majority of these patients had already experienced a first psychotic episode, a diagnosis beyond the scope of this review. Seventy-nine patients, however, received a diagnosis of schizotypal disorder and never had a psychotic episode. This group has been analysed separately (36). The criteria for schizotypal disorder in ICD-10 have some overlap with UHR criteria (e.g. odd beliefs or magical thinking, suspiciousness or paranoid ideas and unusual perceptions are among the criteria for schizotypal disorder and are items in the SOPS and the CAARMS). Patients with a schizotypal disorder are at a higher risk for developing a psychotic episode, which makes this group interesting to study for indicated prevention.

The integrated treatment in this trial consisted of Assertive Community Treatment (ACT) with programmes for family involvement and social skills training and lasted for 2 years. Medication prescription was based on the decision of the psychiatrist of the individual patient in each treatment condition.

The primary outcome measure was transition to psychotic disorder, defined as fulfilling the criteria of an ICD-10 diagnosis of a psychotic disorder. Secondary outcome measures were positive, negative and disorganized symptoms on the PANSS.

In the integrated treatment group, 37/42 patients (88%) completed 1-year follow-up, and 36/42 (86%) patients 2-year follow-up. In the standard treatment group, 30/37 patients (81%) completed 1-year follow-up and 29/37 (78%) patients the 2-year follow-up. Patients lost to follow-up were excluded from analysis.

After 1 year, 3/37 (8.1%) patients were diagnosed with a psychotic disorder in the integrated treatment group, compared with 10/30 (25.0%) in the standard treatment group. After 2 years, the number of patients diagnosed with a psychotic disorder was 9/36 (25.0%) in the integrated treatment group and 14/29 (48.3%) in the standard treatment group. In a multivariate analysis, integrated treatment significantly reduced the risk of being diagnosed with a psychotic disorder after 2 years (relative risk = 0.36, $P = 0.02$).

The level of positive and disorganized symptoms was not different between the two treatment groups. The level of negative symptoms was significantly lower in the integrated treatment group after 1 year, but not after 2 years.

Antipsychotic medication was prescribed to many patients: 68% and 61% of the patients in 1- and 2-year follow-up. As far as we know, no data have been published about the proportion of patients using antipsychotic medication in the group that made transition to psychosis and in the group that did not make transition to psychosis.

*Trials without control intervention Szeged, Hungary: haloperidol and risperidone.* This Hungarian study has been published in a Hungarian journal (45).

Only the English translation of the abstract was included in the present review.

A group of 52 UHR subjects (defined with PACE criteria) was treated for 6 months with low-dose haloperidol or risperidone (0.5–2 mg/day), together with psychoeducation and supportive psychotherapy, with a follow-up period of 6 months. There was no control group. Transition to psychosis was the primary outcome measure. The operational definition of transition is not mentioned in the abstract.

After 1 year, 42/52 (81%) patients completed the study. Of these 42 patients, three patients developed schizophrenia during the study (7.1%), all three during the first 6 months. Side-effects were mild and transient.

The authors conclude that low-dose haloperidol or risperidone seems to be effective in preventing or postponing transition to psychosis, because the transition rate is lower than the transition rate in UHR subjects who do not get any treatment, which is, according to the authors, 30–60%.

*Naturalistic studies.* Cornblatt and colleagues present a different vision on the subject (46–49). In 2001, they pointed out that information was lacking on several important topics in prodromal intervention research. For example, in their opinion knowledge was insufficient to make a rational choice which intervention to study, and to know how to measure the effectiveness.

They suggested that naturalistic studies were necessary to provide this information. In 2007, they conclude in a review that the situation is still very much the same. They point out the disadvantages of randomized controlled clinical trials for prodromal intervention research:

i) Lack of generalizability.
ii) Medication non-adherence is a major problem which often does not get enough attention in clinical trials. It is a potential confounder.
iii) In a clinical trial, one treatment option has to be chosen. Naturalistic studies are essential because the range of potential treatments is not limited. Results might show treatment options with promising results that can be evaluated in a randomized clinical trial afterwards.

The Hillside Recognition and Prevention (RAP) programme in New York is a clinical programme with a naturalistic treatment strategy, for adolescents (12–22 years) with UHR symptoms. A diagnostic algorithm is used that makes use of the SOPS, but with different operationalization criteria of the putatively prodromal state. The authors use the term 'CHR' for patients fulfilling their inclusion criteria. They discerned two CHR subgroups (48):

i) CHR− : patients that exhibited only attenuated negative symptoms (this group is not included in UHR criteria in CAARMS and COPS, and is considered by the authors to represent the earliest putatively prodromal stage);
ii) CHR+: patients that exhibited attenuated psychotic symptoms (APS, defined as in COPS).

The UHR categories 'BLIPS' and 'state and trait risk factor' are no inclusion criteria in the RAP programme.

From 1998 to 2005, 152 adolescents were enrolled in the programme, of which 30 already had a psychosis, but did not meet criteria for schizophrenia. Of the remaining 122, 44 only had attenuated negative symptoms (CHR−). Seventy-eight adolescents had APS (CHR+).

From these 78 adolescents, 48 were selected for analysis, with the following criteria: i) received pharmacological treatment for at least 8 weeks and ii) was followed up for at least 6 months (mean 30 months, maximum 60 months) (49).

Of these 48 adolescents, 20 never received antipsychotics (APs), but received antidepressants (ADs) alone or in combination with other medication (mainly mood stabilizers). Twenty-eight adolescents received a second-generation AP, often with an AD as co-medication.

During the follow-up of maximum 5 years, 12 of the 28 adolescents who used an AP converted to psychosis (43%), while none of the 20 adolescents who used an AD without an AP converted. This difference was statistically significant. A logical explanation of the high transition rate in the AP group would be that the AP group was a more severely ill group at baseline, being in a later phase of the prodrome, which could have been the exact reason they got prescribed an AP. However, the baseline symptom profiles of the two groups did not differ except for disorganized thinking which was more severe in the AP subgroup.

The high transition rate in the AP group could also be due to a high percentage of non-adherence. Seventeen of the 28 adolescents who used an AP were non-adherent. Eleven of the 12 converters to psychosis were non-adherent, thus only one adherent AP-using adolescent converted to psychosis. Non-adherence to APs was much higher than non-adherence to ADs (61% vs. 20%, $P = 0.005$).

The authors conclude that ADs might be an effective treatment for UHR subjects, possibly

because of the higher adherence to ADs than to APs. They emphasize that the naturalistic character of the study limits the comparisons that can be made between the AD and AP subgroup.

The results of Cornblatt et al. (49). prompted the research group of 'Outreach And Support In South London' (OASIS), a clinical service for people with UHR symptoms (defined by the CAARMS) in London, to do the same analysis in their group (50). At the OASIS clinic, patients are invited to make their own choice out of several interventions, amongst others symptom monitoring, CBT, antipsychotic medication and antidepressant medication, after being informed about the possible benefits and risks (51).

They found similar results: during a follow-up of 2 years, 10 of 35 adolescents who used an AP converted to psychosis (29%), while only one of the 13 adolescents who used an AD converted (8%) (50). No statistical analysis has been published. As in Cornblatt's group, the question is whether the AP group was more severely ill at baseline. Furthermore, intrinsic patient characteristics may have influenced the outcome, because the choice for an AP or an AD was based on the patient's preferences.

### Acute treatment effects in UHR subjects

The UHR state is characterized not only by symptoms and signs, but also by a decrease in functioning in a vast majority of patients (52). Therefore, some researchers focus on the syndrome itself and the acute treatment effects on symptoms and functioning, independently from a possible conversion to psychosis in the future. Furthermore, in studies with short follow-up periods (< 6 months) this focus on symptom levels and functioning is necessary, because of the often very small number of transitions to psychosis after such a short follow-up period. For example, in the four studies described below the follow-up period is 12 weeks or less.

*Olanzapine vs. placebo (PRIME study, USA).* The above-described double-blind, randomized, placebo-controlled trial of olanzapine in UHR subjects from McGlashan et al. (9) also generated acute treatment results. Results of the first 8 weeks were analysed separately (53). Drop-out was high in the first 8 weeks (11/31 = 35% in the olanzapine subgroup, 8/29 = 28% in the placebo subgroup).

The olanzapine group improved significantly more than the placebo group on different symptom scales. However, this was only the case when a mixed effect, repeated-measure analysis was used, combined with *post hoc* analyses. In 'last observation carried forward' analyses, which had been planned on forehand, the scores at endpoint were not significantly different, although there was a trend of more improvement in the olanzapine group. In the olanzapine subgroup, weight gain was significantly higher than in the placebo subgroup.

Table 2. Studies on acute treatment effects in UHR subjects

| Study | Inclusion criteria | Specific intervention (SI) | Control intervention (CI) | Primary outcome measure | Secondary outcome measures |
|---|---|---|---|---|---|
| PRIME (53) | UHR criteria (COPS) ($n$ = 60) | Olanzapine 5–15 mg ($n$ = 31) 8 weeks | Placebo ($n$ = 29) 8 weeks | SOPS total score: SI significantly more improvement than CI (but dependent on which statistical method used) | Weight gain: % of patients gaining more than 7% of their baseline body weight: SI: 56.7% CI: 3.4% $P < 0.001$ |
| GNRS LIPS (54) | Attenuated positive symptoms and/or BLIPS ($n$ = 124) 22 patients excluded from analysis | Amisulpride 50–800 mg + needs-focused intervention ($n$ = 58) 12 weeks | Needs-focused intervention ($n$ = 44) 12 weeks | Many scales: Positive symptoms, negative symptoms, general symptoms, depressive symptoms and GAF: SI significantly more improvement than CI | Weight gain: BMI increased slightly but significantly in the SI group, not in CI group (difference significant) |
| Woods et al. (55) | UHR criteria (COPS) ($n$ = 15) | Aripiprazole 5-30 mg ($n$ = 15) 8 weeks | No | SOPS total score: Significant improvement from week 1 | Side-effects: Mean weight gain 1.2 kg Acathisia in 8 patients |
| Woods et al. (56) | UHR criteria (COPS) ($n$ = 10) | Glycine 0.4 g/kg ($n$ = 10) 8 weeks | No | SOPS scores: Significant improvement on SOPS total scores and on all subscales except negative symptoms | |

*Amisulpride vs. a needs-focused intervention (GRNS: LIPS trial, Germany)*. The GRNS study has been described above. The patients in the LIPS ($n = 124$) were randomly assigned to an NFI ($n = 59$) or to NFI plus amisulpride, in a dose range from 50 to 800 mg ($n = 65$) (54). The study was open-labelled.

Of the 124 patients, 102 were considered for analysis. In the amisulpride group, seven patients were excluded from analysis: three because treatment had already started before baseline assessment (protocol violation) and four because they did not return after randomization.

In the NFI alone group, 15 patients were excluded from analysis: 10 because they did not return after randomization, one because of a serious somatic problem and four because at the baseline assessment they proved to be psychotic and/or used antipsychotic medication.

It is questionable if all these exclusions do not violate the intention to treat principle. In the remaining sample, drop-out was 15/58 (26%) in the amisulpride group and 15/44 (34%) in the NFI alone group. At week 12, scores on different symptom and functioning scales were reported, as well as side-effects.

Symptoms and functioning ameliorated in both groups during these 12 weeks. The NFI plus amisulpride group ameliorated significantly more than the NFI alone group on all measures.

The body mass index (BMI) increased significantly in the amisulpride group and not in the NFI alone group. Other side-effects were mainly associated with increased prolactin levels, like diminished sexual desire.

*Aripiprazole: an open-labelled pilot study*. Woods et al. (55) included 15 UHR participants with a mean age of 17.1 years. UHR state was operationalized by COPS criteria. The participants were enrolled in an open-labelled trial with aripiprazole treatment for 8 weeks, without control intervention. Aripiprazole dosing varied between 5 and 30 mg/day. During these 8 weeks, two participants dropped-out (13%).

The principal outcome measure was the severity of prodromal symptoms (SOPS total score). Improvement from baseline was statistically significant, with a mixed effect, repeated-measure analysis. No participant converted to psychosis during these 8 weeks. Mean weight gain was 1.2 kg. Acathisia emerged in eight participants.

The authors conclude that aripiprazole is possibly effective and relatively safe for UHR subjects, but they emphasize that placebo-controlled studies are needed.

*Glycine: an open-labelled pilot study*. Woods et al. (56) included 10 UHR patients with a mean age of 17.3 years. The UHR state was defined by COPS criteria. The participants were enrolled in an open-labelled trial with glycine 0.4 g/kg for 8 weeks, with follow-up of 16 more weeks, without control intervention. Glycine is an amino acid neurotransmitter that acts as a coagonist with glutamate at N-methyl D-aspartate (NMDA) receptors. It is no standard treatment for psychosis. It is hypothesized that NMDA hypofunction is associated with developing schizophrenia, which makes glycine an interesting potential treatment (56).

Outcome measures were changes on SOPS total scores, and positive, negative, disorganization and general symptom subscales.

To our knowledge, the results were only described in an abstract. During the 8 weeks of treatment, 3/10 patients dropped-out (one because of lack of efficacy and two because of transportation or family difficulties). Patients improved significantly from baseline on the SOPS total score ($P < 0.001$) and on all subscales except the negative symptom subscale.

The authors conclude that the NMDA-agonist glycine might be effective in prodromal patients and that placebo-controlled trials are necessary.

## Discussion

The main conclusion of this review was that we are unable to draw a final conclusion about the efficacy and safety of interventions for UHR subjects.

### Summary of the results

*Prevention of transition to psychosis*. In the PACE study, CBT + risperidone significantly lowered the transition rate to psychosis compared with the NBI group at the end of the 6-month treatment phase, but during the follow-period of 1–4 years this effect was no longer present (23, 30). This might suggest that the intervention is effective in delaying psychosis for months; that might be an indication for continuation of the intervention. The separate contribution of risperidone and CBT is not known. Neuroleptic adverse effects were present in four patients.

In the PRIME study, no significant effects were found of olanzapine compared with placebo on the transition rate to psychosis (9). Conversely, significantly higher adverse effects were reported in the olanzapine group (weight gain and fatigue mainly). Drop-out was high, especially in the olanzapine group. The study may have been

underpowered, because the transition rate seemed much lower in the olanzapine group, especially at the end of the treatment year.

In the EDIE study, 6 months of CT significantly lowered the transition rate to psychosis compared with the monitoring group after 1 year (29). However, a methodological discussion about the exclusion of two patients complicates this finding. At 3-year follow-up, the transition rate in the CT group was still significantly lower, but only when transition was defined as being prescribed antipsychotic medication, which was only one of the three operationalizations of the primary outcome measure (31).

Results of the GRNS trial have only been described in abstracts (32, 33). The absolute numbers and information about drop-out and other methodological issues have not yet been published, so no definitive conclusions can be drawn. Data thus far suggest that 12 months of this specially developed comprehensive CBT are effective in lowering transition from EIPS to LIPS and from EIPS to psychosis.

One study on the possible therapeutic effects of 12 weeks of omega-3 fatty acids was described in two abstracts (34, 35). Supplementation of omega-3 fatty acids for 12 weeks significantly lowered the transition to psychosis at week 12 and at 1-year follow-up. No side-effects were observed. These findings suggest that omega-3 fatty acids could be effective and safe in preventing psychosis in UHR subjects, possibly with a lasting effect after supplementation of only 12 weeks. As results have only been presented in abstracts so far, methodological issues will have to be evaluated after publication of a full article.

One study on the efficacy of integrated treatment (ACT with family intervention and social skills training) compared with standard treatment in patients with schizotypal disorder showed a significantly lower relative risk of transition to psychosis in the integrated treatment group (36). An important limitation of the study is the exclusion of dropped-out patients from statistical analysis. It is not clear if the significant effect would have been found with an intention to treat analysis. Another limitation is the prescription of antipsychotic medication to many patients, which can be a confounding factor. However, results of the intervention are promising. Although the patient group is different from patients fulfilling UHR criteria, the intervention could be of great importance for UHR patients also. Because of the study design, it is not possible to conclude what elements from the integrated treatment were the effective ones.

The last study on transition to psychosis found a transition of 7.1% in UHR subjects treated with low-dose haloperidol or risperidone for 6 months (45). There was no control group. Although this transition rate is lower than in many studies without a specific treatment, the variation in transition rates in naturalistic studies is high (15), and one cannot be sure that the studied subjects are comparable with subjects in earlier research groups with no treatment. A control group is necessary to be able to interpret the results.

Two naturalistic studies show a possible effect of ADs in patients with UHR symptoms, lowering the transition rate to psychosis (49, 50). It is possible that a low mood plays a causal role in the development of a psychosis because it leads to a more paranoid interpretation of beginning anomalous experiences (57). The major question is the possibility that the patients who were prescribed ADs were a subgroup with a better prognosis than the patients who were prescribed APs. In Fusar-Poli's group, the outcome may also have been influenced by intrinsic patient characteristics, because the choice for an AP or an AD was based on the patient's preferences (51). Randomized trials are necessary to test the possible therapeutic effect of ADs and to evaluate drug safety and tolerability (50).

*Acute treatment effects.* Summarizing four studies on acute treatment effects, we conclude that a significant symptomatic improvement was found for olanzapine and for amisulpride compared with a control intervention (53, 54). However, methodological issues complicate the findings: in the first study different statistical methods are used, and in the second study 22 patients are excluded from analysis on forehand for different reasons.

The third and the fourth study are studies without a control intervention, which makes conclusions about the effect of the medication (aripiprazol and the NMDA-agonist glycine respectively) impossible (55, 56).

In these four studies, drop-out varied from 13 to 35% in 8–12 weeks. Weight gain and acathisia were the main side-effects of the APs.

In conclusion, all treatment studies with antipsychotic medication and/or CT/CBT and/or family intervention and/or social skills training, suggest a positive effect of the intervention at the end of treatment. Omega-3 fatty acids give promising results, but publication of a full article has to be awaited to evaluate methodological issues.

For ADs and glycine, no conclusions can be drawn. The positive effect of antipsychotic

medication and CT/CBT seems to have disappeared at follow-up.

A methodological problem when comparing the different studies is the operational definition of the UHR state and of transition to psychosis. Different instruments have been used for this purpose.

### Potential benefits of antipsychotic medication and CT/CBT as prepsychotic interventions

The results suggest that, *if* there is a therapeutic effect, it seems to be delay of onset of psychosis, and not prevention, because the possible therapeutic effects disappear after the end of the intervention period. Hypotheses about improving clinical outcome after the first psychosis by delaying its onset have not been proven.

Furthermore, in all follow-up studies the functioning of the UHR subjects remained poor, even if they did not convert to psychosis. UHR symptoms seem to indicate a serious mental health problem. This might mean that treatment (e.g. antipsychotic medication or CBT) is necessary and should not be stopped after a certain period. However, until now, no studies with treatment periods longer than 2 years have been published.

### Potential risks of antipsychotic medication and CT/CBT as prepsychotic interventions

The known side-effects of second-generation antipsychotic medication are clearly present in UHR subjects, as are adherence problems (49). Extrapyramidal symptoms, weight gain and metabolic complications are major issues nowadays in the treatment of psychotic patients. When used as prepsychotic intervention, with no proven long-term effects, the benefit/risk ratio is even more unfavourable. Furthermore, antipsychotic medication may lead to upregulation of D2 receptors, which might raise the chance of transition to psychosis after stopping the medication.

These risks do not hold for CT/CBT, but the potential risk of stigmatizing or anxiety induction when using the word 'psychosis' does. However, in all studies the education about psychosis and about the uncertainty of transition seems to be very well accepted. Furthermore, Fusar-Poli et al. (50) found in their service that CBT is more easily accepted by their UHR subjects than any type of medication.

Finally, when intervening in the UHR state, the question when the intervention should stop, is very complex, and has not yet been answered. 'False false positives' cannot be discerned from 'false positives', so when a subject with UHR symptoms does not progress to psychosis, one does not know if that was because of the intervention or not. But even if it would be sure that a subject has not progressed to psychosis because of the intervention, it is not known for how long the intervention has to be continued. Prescribing an intervention for many years without knowing the answers to these questions is not ethical, especially when side-effects can be serious, as is the case for antipsychotic medication.

### Future developments: better prediction?

The transition of UHR symptoms and signs to a psychotic disorder is obviously uncertain, so the problem of false positives remains. Cannon and colleagues (41) have demonstrated that prediction algorithms can be improved, resulting in a positive predictive power (PPP) of 68–80%, which is much higher than the PPP of the criteria used until now. This improvement of PPP resulted from adding certain features to the prediction model, e.g. 'greater social impairment', 'history of substance abuse', 'higher levels of suspicion/paranoia'. If this finding of an increased PPP is replicated, the effect of interventions might increase as well, and the benefits and risks ratio might be more favourable. However, Yung (58) comments on Cannon's results, noting that the sensitivity may be reduced when the PPP is increased by adding certain selection criteria. It depends on the aim of the study if sensitivity should be sacrificed to minimize false positives.

Even with better prediction algorithms, the emphasis of the selection criteria will be on attenuated psychotic symptoms and brief limited psychosis, simply because they are the most specific putatively prodromal symptoms for psychosis. In the case of schizophrenia, these symptoms are probably not core risk factors, but the more dramatic manifestations of the disease. The core features of schizophrenia are probably neurocognitive dysfunctions and negative symptoms, which are far more difficult to influence (47). Therefore, delaying or even preventing transition to psychosis can be important, but may not be correlated with a long-term better clinical outcome. An interesting study would be the comparison between the outcomes of treated prodromal subjects who converted to psychosis and patients with a first psychotic episode who never received treatment during the prodromal phase, as suggested by Phillips et al. (30).

Furthermore, it is important to realise that, even with highly available early intervention services,

there will always be patients who present with a first psychotic episode without having sought help during the prodromal phase.

### Implications for clinical practice

Antipsychotic medication as prepsychotic intervention might delay the onset of psychosis, and might have therapeutic effects on the prepsychotic symptoms, but this has not yet been proven. On the other hand, serious side-effects and adherence problems are present, as is the risk that antipsychotic medication leads to upregulation of D2 receptors and raises the chance of transition to psychosis after stopping the medication. We conclude that the results are promising enough to justify further research, but that antipsychotic medication should be no standard clinical practice in the UHR state.

The therapeutic effect of CT/CBT and family intervention has not been proven either, but we think these are more suitable options, because side-effects have not been demonstrated. Antidepressive medication and omega-3 fatty acids might be promising alternatives, but further research is necessary.

As there is no conclusive evidence for one type of intervention, a possible strategy when treating an UHR subject is providing extensive information about the possible benefit and risks of social support, symptom monitoring, CBT, antidepressant and antipsychotic medication, family intervention, psychoeducation, and social skills training, and providing treatment based on the patient's preferences. The patient might choose only to receive social support and monitoring, but might also ask for CBT or even antipsychotic medication. For example, the OASIS clinic in London is following this strategy (51).

International clinical practice guidelines for early psychosis have been published in 2005 (59). An update will probably be published in 2009. Given the available research at present, these guidelines still seem to be valid. The most important advices in the guidelines for UHR subjects are (modified from) (59):

i) regular monitoring of mental state and offer support;
ii) specific treatment for syndromes, such as depression, anxiety or substance misuse, and assistance with problem areas such as interpersonal, vocational and family stress if present;
iii) psychoeducation;
iv) family education and support;
v) provide information in a flexible, careful and clear way about risks for mental disorders as well as about existing syndromes;
vi) antipsychotic medication is not usually indicated. Exceptions should be considered when rapid deterioration is occurring;
vii) the evidence of effectiveness of treatments aimed specifically at reducing the risk of transition psychosis (e.g. cognitive and family therapy, antipsychotic medication or experimental neuroprotective drug strategies) remains preliminary. More data are required and the risk/benefit ratio of various interventions needs to be determined.

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## Declaration of interest

None.

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