Transition to Schizophrenia and Related Disorders: Toward a Taxonomy of Risk

by Wolfgang Maier, Barbara A. Cornblatt, and Kathleen R. Merikangas

Abstract

The early detection and prevention of schizophrenia and other psychotic disorders are receiving rapidly growing attention subsequent to the suggestion that poorer outcome is associated with delayed onset of treatment among patients in their first psychotic episode. Although the first generation of so-called "prodromal" research programs has produced encouraging preliminary results, more information is necessary on the conversion rates from prodromal states to schizophrenia in specific samples. Early recognition and prevention strategies require a new taxonomy that classifies subjects by their status of risk of imminent onset of psychosis. Without additional knowledge of the mechanisms through which particular constellations of vulnerability factors, precursors, and prodromal symptoms predict the onset of schizophrenia, it is difficult to judge the effects of existing programs. In this paper, we discuss three sets of issues that will need to be resolved before these preventive programs can be implemented into routine care: (1) optimization of predicting the onset of psychotic disorders; (2) development and evaluation of alternative treatment strategies depending on the presenting risk status; and (3) evaluation of costs and benefits of identifying subjects at risk of psychosis/schizophrenia and receiving a specific preventive treatment.

Keywords: Schizophrenia, vulnerability factors, prodromal symptoms, early recognition, early prevention, treatment strategies.


Early recognition and intervention programs in psychosis and schizophrenia are receiving increasing attention (Cornblatt and Malhotra 2001; Heinssen et al. 2001). One of the reasons for early interest is the limited impact of available treatment on the long-term course of symptoms and functional deficits in the majority of patients with already established illness. Despite insufficient theoretical and empirical evidence that early intervention may be beneficial, there is preliminary evidence from a few controlled early intervention studies that early post-onset treatment is only beneficial in the short term; there are no substantial changes in the long-term course of illness (Linszen et al. 2001).

Because of the generally unfavorable outcomes of post-onset interventions, there has been a shift toward early identification of individuals with psychosis/schizophrenia. As knowledge advances on the phenomenology of premorbid features in subjects who subsequently develop schizophrenia, pre-onset interventions are becoming feasible. These pre-onset strategies might provide a new chance to reduce the incidence, postpone the onset, and/or improve the long-term course of the disorder.

There is substantial variation in conceptual framework, designs, measures, and outcomes of current prodromal schizophrenia research programs. However, because this approach is in the early stages of development, there is little empirical basis on which to develop research methodology. This paper discusses the rationale for various approaches to identifying high-risk groups targeted in pre-onset recognition and treatment programs, as well as a number of ethical and practical considerations that constrain the design of these programs.

I. Risk Factors, Vulnerability Factors, "Prodromal" Symptoms

There is a fundamental distinction between precursors and prodromes (Eaton et al. 1995). Precursor signs and symptoms precede the disorder without predicting them with certainty and operate as predisposing risk factors. On the other hand, a prodrome is identified only retrospectively after the subject meets criteria for a full-blown disorder. Precursors are mainly identified by epidemiological
approaches and prodromes by clinical research approaches (Cornblatt et al. 2002).

Precursors. Epidemiological research has elucidated a number of risk factors for schizophrenia. General population and birth cohort studies have observed increases in risk for schizophrenia associated with family history, obstetric complications, urban residence, season of birth, low IQ, and delayed developmental milestones (Jones 2002). Family and twin studies have found evidence of deviant behavioral, neurocognitive, neurophysiological, and neuromorphological patterns among unaffected relatives of cases with schizophrenia (Tsuang et al. 2002). The finding that younger siblings of schizophrenia patients also exhibit some of these behavioral and neurobiological patterns suggest that they are truly precursors, or vulnerability factors, for the development of schizophrenia. The most informative designs for the elucidation of vulnerability factors are prospective high-risk studies (Erlenmeyer-Kimling et al. 2000) and comparisons between unaffected monozygotic and dizygotic twins of affected index cases (Cannon et al. 2000). Studies of discordant twins have found that prefrontally mediated brain functions such as working memory and divided attention define a genetically based vulnerability factor associated with risk for schizophrenia (Cannon et al. 2000). The New York High-Risk Study identified dysfunctional verbal memory and motor abilities during childhood as vulnerability factors with a moderate predictive power for schizophrenia-like psychosis later in life (Erlenmeyer-Kimling et al. 2000). Many of these vulnerability or risk indicators are distributed along a continuum, with mean differences observed between affected subjects, subjects at risk, and healthy low-risk controls. In fact, quantitative measures of risk often may be more powerful than arbitrary classification into high- and low-risk groups (Cannon et al. 2002).

Prodromes. Retrospective follow-back studies in first onset patients with schizophrenia have observed a number of different prodromal syndromes and symptoms. Many precursors or risk factors occur in early childhood; however, they may not constitute realistic targets for early intervention programs. One study found that about 75 percent of patients with schizophrenia were found to have passed through three stages of prodromal symptoms in a fixed order (Hafler and An der Heiden 1997). That is, patients reported subthreshold psychotic symptoms in the year preceding onset, prominent negative symptoms in the 2 years preceding onset, and nonspecific affective and anxiety symptoms earlier. These retrospectively identified symptom patterns are used in a prospective manner to predict psychoses in early recognition programs. In this context, these symptoms and signs are used to define "at-risk mental states" (McGorry et al. 2001). However, prospective data would provide a much sounder basis for any intervention.

These concepts can be combined into a stage model of the progression to schizophrenia as displayed in figure 1. In this model, four phases are discriminated, moving from the most proximal to the most distal with respect to schizophrenia onset:

- A psychosis phase, which might progress to schizophrenia;
- A late prodromal phase, consisting of attenuated psychotic symptoms or brief, limited intermittent psychosis;
- An early prodromal phase, consisting of negative and unspecified, mainly affective symptoms as well as psychosocial impairment; and
- A premorbid phase without psychosocial impairment but with risk factors and vulnerability traits present.

Most of the empirical work on precursors and prodromes has emerged from studies targeting schizophrenia (defined by various classification schedules) as the outcome of interest. Figure 1 summarizes the putative precursors and prodromes of psychosis/schizophrenia. Although there are convergent tendencies between both types of predictors (mainly poor premorbid adjustment, psychosocial deterioration), five divergent aspects are noteworthy:

1. Differences in timing of appearance during development: The first vulnerability traits occur early in childhood or adolescence whereas prodromal states emerge later with or without an increasing aggregation of deviant behavioral/cognitive traits.
2. Differences in timing relative to the outcome of interest: Late, positive prodromal symptoms tend to predict an imminent onset of psychosis (Tsuang et al. 2002). Risk factors and vulnerability traits are associated with an increased risk for a lifetime-ever diagnosis of schizophrenia.
3. Differences in temporal stability: Late, positive prodromal symptoms fluctuate considerably over time, and thus represent state variables; vulnerability factors and negative prodromal symptoms are more persistent, representing mostly trait variables; risk factors are mainly stable over lifetime.
4. Different intrinsic scales: Many risk factors are categorical variables; vulnerability traits are mostly quantitative variables.
5. Different population base rates of precursors and prodromes: The prevalence of positive prodromal symptoms is quite high in the general population (van Os et al. 2000), whereas the negative symptoms and some of the vulnerability factors seem to be rare. Therefore, it is necessary to account for the necessary population base rates of these risk indicators.
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Figure 1. Indicators for elevated risk to psychosis

1: Dysbindin gene
2: Neuregulin gene
3: G72 gene
4: DAAO gene

A: Family hx
B: Birth complications
C: Urbanicity
D: IQ
E: Season of birth

<table>
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<tr>
<th>Source:</th>
<th>Risk factors</th>
<th>Vulnerability factors</th>
<th>Precursors, prodromes</th>
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<tr>
<td>Case-control (general population)</td>
<td>a) Family high-risk samples</td>
<td>Mainly retrospective; few prospective studies (clinical samples)</td>
<td></td>
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<tr>
<td>Mainly categorical or ordinal</td>
<td>b) Longitudinal population cohorts (record linkages)</td>
<td>Mainly categorical symptoms</td>
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<th>Measure of predictive potency:</th>
<th>OR (lifetime), attributable risk (lifetime)</th>
<th>Quantitative group differences</th>
<th>Transition rates, predictive power (specificity/sensitivity)</th>
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<td>Lifetime perspective</td>
<td>Relatives or affecteds vs controls</td>
<td>Immediate risk</td>
<td></td>
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<tr>
<th>Predictive potency (psychosis):</th>
<th>Combined &gt; 40% / lifetime (calculated/no prospective validation)</th>
<th>a) Modest / lifetime in combination with familial loading for selected measures</th>
<th>40-60% / year in combination with psychosocial impairment (or risk factors)</th>
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Increasing Positive Predictive Value

Despite the variability across studies of prodromes for schizophrenia and other psychoses, it will be critical to integrate both sources of predictive variables in order to increase diagnostic sensitivity as well as specificity. Prodromal symptoms might qualify for diagnostic entities but mostly different from psychotic symptoms (figure 2); the specificity of the possible premorbid diagnoses for progression to psychosis/schizophrenia is very limited. Clusters of risk factors and prodromal features may yield greater specificity for future prevention and intervention efforts. Protective influences (e.g., supportive family environment, good premorbid functioning [Tienari et al. 2000]) might also improve the predictive potency.

Since the prognostic variables in figure 1 were identified retrospectively in clinical samples of psychotic patients, the information on the diagnostic specificity (e.g., schizophrenia vs. other disorders such as schizotypal personality disorder or schizoid personality disorder) is limited.

The selection of prodromal symptoms is critical for the predictive potency of schizophrenia; e.g., the negative symptoms listed in DSM-III-R as prodromal signs of schizophrenia are common in the general population and would be expected to have only very limited predictive power (McGorry et al. 1995, 2000) relative to attenuated or temporally limited psychotic symptoms (Phillips et al. 2000). It has been proposed that other signs and symptoms not considered in the conventional diagnostic manuals or checklists might add predictive power: e.g., the so-called "basic symptoms" (Klosterkötter et al. 2001) or signs emerging from a detailed phenomenological analysis of individual prodromal states (Moller and Husby 2000). Thus, Klosterkötter et al. (2001) used the basic symptom concept in patients with uncertain diagnostic status and found that basic symptoms such as thought interference, disturbances of receptive speech, visual disturbances or decreased ability to discriminate between ideas, and perception predicted schizophrenia with a very low false-positive rate.

In summary, future studies could evaluate the potential generalizability of the precursors and prodromes that are the most potent predictors of schizophrenia. This approach could eventually yield a new taxonomy of risk in which different combinations of precursors, prodromal symptoms, and risk factors could be identified with distinct predictive relationships to a number of psychotic disorders as well as their timing of onset. This taxonomy would have great heuristic value for theories of the causal...
mechanisms involved in these disorders and pragmatic significance for ascertainment and preventive intervention strategies.

II. Therapeutic Versus Preventive Treatment

The symptom-based variants of prevention may be particularly efficient, enabling us to establish a “check-in” strategy also labeled as “indicated prevention” (McGorry et al. 2001). In contrast, prevention programs targeting asymptomatic subjects at risk in the general population (e.g., children of probands with the disorder) seem to be less efficient, as many probands are required to be treated for a long time in order to prevent one proband from developing the disorder (Woods et al. 2001). In addition, it is ethically questionable to apply pharmacological treatment in asymptomatic subjects before their individual risk status can be established with a high level of confidence. Therefore, recently initiated pre-onset recognition and prevention programs are following the concept of “indicated prevention” (McGorry et al. 2001). Nevertheless, certain population-wide prevention measures might be effective and timely, such as the improvement of medical care to pregnant women in order to reduce obstetric and birth complications (Warner 2001).

Pre-onset recognition and intervention in premorbid and prodromal states aim at two targets: (1) symptoms and syndromes and (2) vulnerability factors as described below:

1. Symptoms and syndromes. Symptoms and syndromes can simultaneously be considered in a conventional clinical perspective. If they are associated with psychosocial disability they might define either actual disorders or, in the case of not meeting diagnostic criteria, subthreshold disorders that are in need of immediate therapeutic intervention in order to reduce current disability. Thus, two modes of intervention might be indicated:

- **Therapeutic intervention:** The goal is reduction and remission of the current symptoms and complaints emerging in the prodromal phase; another goal is the “repair” of psychosocial deterioration that took place during the prodromal phase.

- **Preventive intervention:** The goal is prevention of the manifestation of a psychotic disorder or of schizophreniform disorders/schizophrenia, as well as prevention of psychosocial decline; if prevention cannot be achieved, delay of the onset of these disorders is an alternative.

2. Vulnerability factors. Vulnerability factors may occur in symptomatic or asymptomatic states. In an asymptomatic individual, these signs may indicate an increased risk for a subsequent disorder, but do not necessarily imply that a person has a particular disor-
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These probands cannot profit from the intervention and thus, preventive treatment will inevitably be delivered to those who present with prodromal symptoms might be the main criterion, transitions to other severe mental disorders are also common but receive less attention. Although inclusion criteria vary, the majority of programs focus on prodromal symptoms (i.e., attenuated positive symptoms), augmented by a narrow range of selected risk factors (mainly family history) and/or functional deterioration. Most programs follow a “closed-in” strategy focusing on probands at incipient risk for developing psychosis. The programs differ by mode of therapy (atypical neuroleptics, antidepressants, or both, or/and psychosocial/psychotherapeutic intervention) either applied in a standardized or controlled manner. Some nonpharmacological programs also include patients with early prodromal symptoms (negative symptoms). The main outcome variable is binary (transition to psychosis in a prespecified temporal period). The conversion rate to psychosis is considered as the main criterion.

Conversion rates depend not only on the inclusion criteria but also on the population sampled and the treatments applied. Although conversion to psychosis is considered to be the main criterion, transitions to other severe mental disorders are also common but receive less attention.

As summarized in table 1, conversion rates to psychosis vary across various studies even though the samples were recruited through comparable criteria. The most elevated risk for psychosis or schizophrenia.” This knowledge might create anxiety and reduce self-confidence (self-stigmatization), and might induce stigmatization through the society and the family. Pharmacological treatments (mainly atypical neuroleptics) are associated with numerous side effects (e.g., sedation, metabolic syndrome, prolactin elevation, obesity, and motor symptoms). In contrast, psychological interventions are likely to induce less harm when given to “false positive” prodromal cases.

The establishment of pre-onset prevention programs can only be justified if the harm is minimized and if the benefits outweigh the risks. Benefits and risks may vary by age of the subject (intervention in young adolescents with uncertain diagnosis might additionally interfere with individual maturation and development and thereby increase the putative risks). Thus, it is imperative to minimize the number of probands who are included as false positives to optimize the accuracy of prediction of psychosis and schizophrenia and to balance advantages and disadvantages of an intervention.

III. Prediction of Psychosis

Present State of Knowledge of Conversion Rates to Psychosis. The already established early recognition and treatment programs in psychoses are developing rationales for detecting high-risk states and applying appropriate preventive interventions (Falloon 1992; Phillips et al. 2000; McGlashan et al. 2001; Cornblatt et al. 2002). Although inclusion criteria vary, the majority of programs focus on prodromal symptoms (i.e., attenuated positive symptoms), augmented by a narrow range of selected risk factors (mainly family history) and/or functional deterioration. Most programs follow a “closed-in” strategy focusing on probands at incipient risk for developing psychosis. The programs differ by mode of therapy (atypical neuroleptics, antidepressants, or both, or/and psychosocial/psychotherapeutic intervention) either applied in a standardized or controlled manner. Some nonpharmacological programs also include patients with early prodromal symptoms (negative symptoms). The main outcome variable is binary (transition to psychosis in a prespecified temporal period). The conversion rate to psychosis is considered as the main criterion.

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Table 1. Conversion rates to psychosis in prospective studies in subjects with prodromal symptoms

<table>
<thead>
<tr>
<th>Study</th>
<th>Inclusion criteria for high-risk group</th>
<th>n</th>
<th>Conversion rate (sensitivity to psychosis)</th>
<th>Specificity</th>
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<tr>
<td>Yung and McGorry 1996</td>
<td>1) Psychosocial decline with positive family, or 2) two DSM-III-R prodromal symptoms, or 3) schizotypal or schizoid personality</td>
<td>33</td>
<td>21% in 20 months</td>
<td>?</td>
</tr>
<tr>
<td>Yung et al. 1998</td>
<td>1) BLIPS, or 2) subthreshold psychiatric symptoms, or 3) psychosocial decline with positive family history</td>
<td>49</td>
<td>41% in 12 months</td>
<td>?</td>
</tr>
<tr>
<td>Cornblatt and Malhotra 2001</td>
<td>Identical with Yung et al. 1998</td>
<td>22</td>
<td>14% after 6 months</td>
<td>?</td>
</tr>
<tr>
<td>McGorry et al. 2001</td>
<td>Identical with Yung et al. 1998</td>
<td>59</td>
<td>I. 36% in 6 months</td>
<td>?</td>
</tr>
<tr>
<td></td>
<td>l. Need-based intervention alone,</td>
<td></td>
<td>l. 36% in 12 months</td>
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<tr>
<td></td>
<td>II. Cognitive behavior therapy + atypical neuroleptics (6 months)</td>
<td></td>
<td>II. 10% in 6 months</td>
<td></td>
</tr>
<tr>
<td>McGlashan et al. 2001</td>
<td>Identical with Yung et al. 1998</td>
<td>29</td>
<td>54% in 12 months</td>
<td>100% in 12 months</td>
</tr>
<tr>
<td>Klosterkötter et al. 2001</td>
<td>Two cognitive &quot;basic symptoms&quot; in subjects with mental state at risk</td>
<td>385</td>
<td>97% with variable length of follow-up period (mean 9.6 years)*</td>
<td>59% in 6-9 years*</td>
</tr>
</tbody>
</table>

* Conversion to schizophrenia

Note.—BLIPS = Brief Limited Psychotic Symptoms; ? = unknown.

widely used criteria for inclusion for pharmacological pre-onset prevention programs, the Australian Criteria (Yung et al. 1998), predict conversion to psychosis with approximately 50 percent probability within 1 year under naturalistic treatment conditions. Thus, using the current criteria, if all patients enrolled in a prodromal research program receive antipsychotic drug therapy, a substantial number of patients would be exposed to neuroleptic treatment without being in need of it (Heinssen et al. 2001). Moreover, it remains unclear whether the main effect of neuroleptic pre-onset intervention is prevention or delay of onset.

Need to Optimize Diagnostic Accuracy and Predictive Potency. Early recognition and intervention programs promise a reduction of incidence and/or improvement of long-term course of psychosis and schizophrenia. Although there are promising pilot and preliminary reports (for overview: McGlashan et al. 2001; McGorry et al. 2001) since the pioneering study by Falloon (1992), additional empirical research is required to demonstrate the efficacy of this strategy. Meanwhile, implementation of these programs in routine clinical care cannot be justified because of ethical concerns (Cornblatt et al. 2001; Heinssen et al. 2001). Without strong evidence supporting the efficacy and specificity of such programs, they might induce harm to those who would not develop adverse outcomes in case of remaining untreated. Avoidance of any harm to participants in these studies is imperative. Therefore, a series of research issues must be resolved before these early recognition and intervention programs can be routinely implemented:

- The false negative rate needs to be clearly established; and
- Development of a rationale for a trade-off between benefits to those at high risk and risks for specific interventions in the program.

Two major issues for future research should be a priority in reviewing the value of early intervention programs:

1. Improvement in accuracy of predicting the first psychotic episode: Combining all putatively predictive variables with the prodromal symptoms might add to the sensitivity and specificity of the proposed inclusion criteria. Inclusion of risk and vulnerability factors, and also of protective variables, might in particular improve the specificity of the prediction. A series of state and trait variables predicting immediate or lifetime risk of schizophrenia-related psychosis could be combined into "trait plus state" risk factors (Yung et al. 1998):

- prodromal signs, symptoms and traits, and their duration;
• indicators of recent deterioration of psychosocial functioning;
• predisposing risk factors (such as age, obstetric complications, familial loading, grown up in cities, or reduced intelligence);
• vulnerability traits (such as personality features, psychophysiological abnormalities, neuroimaging-assessed brain abnormalities, neuropsychological deficits, genetic factors) (Comblatt and Malhotra 2001; Tsuang et al., 2002);
• protective factors (e.g., intelligence or supportive family environment) as emerging from recent adoption studies (Tienari et al., 2000).

For example, current research programs are under way to measure these putatively predictive variables in a follow-up program of subjects at risk who have asked for consultation and treatment (e.g., the RAP program in New York [Comblatt et al. 2002] or the German Research Network on Schizophrenia [Wölwer et al. 2003]).

2. **Assessment of benefits and disadvantages of a pre-onset recognition and prevention program for psychosis:** The quantification of long-term benefits and costs depending on the targeted population, the at-risk status, and the mode and the duration of intervention must be justified before the widespread application of early intervention programs. A systematic evaluation of exit rules is also needed in this context. In addition, units of measurements of costs and benefits must be developed (e.g., based on the quality-adjusted life years) and systematically applied in ongoing indicated prevention programs.

### IV. Need for a New Taxonomy of Predictive Assessment

The current classification employs definitions of symptoms, syndromes, and disorders rather than a system designed to define therapeutic interventions. Symptoms that are co-occurring and contributing simultaneously to the impairment and disability are grouped together in syndromes and disorders that define indications for therapeutic treatment. Preventive intervention requires a taxonomy of “at-risk states” in order to define indications for intervention:

1. At-risk states are defined by patterns of predictive variables, including not only symptoms but also signs, vulnerability patterns, and risk factors, as well as protective factors. Recency of onset of prodromal signs and symptoms is critical and requires specification.

2. These patterns of variables should fit two conditions for an optimal decision of inclusion into a preventive program:
   - They should enable optimal predictive accuracy for the targeted disorder within a defined temporal interval (1–2 years) in terms of sensitivity as well as of specificity in specific populations.
   - They should provide a basis for estimating benefits and disadvantages of correct and incorrect classification of high-risk status with respect to a specific preventive treatment. Thus, “at-risk states” should be conveyed by estimates for the future occurrence of a disorder.

The derivation of a generally accepted and empirically based taxonomy of “states at risk” requires large-scale empirical longitudinal research in clinical populations taking all putatively predictive variables into account. Current consensus is still based on a small amount of research that has focused only on a tiny sector of putatively predictive variables. An increase of research efforts in this field is highly needed.

### Conclusion

Early recognition and intervention programs for psychosis/schizophrenia are now being established or planned in diverse international settings. However, evidence for the positive predictive values of risk factors and prodromal manifestations is still insufficient to warrant integration of these programs into routine care settings; they must still be considered as experimental, clinical research activities. There is an ethical imperative to deliver those programs in clinical care outside of a research context only after benefit has been maximized and risk has been minimized. In order to attain this goal:

- the accuracy of the predictive value and specificity of premorbid risk factors for psychosis/schizophrenia must be optimized; and
- a taxonomy classification of risk states must be developed in order to provide clear, empirically justified indications for each mode of early intervention.

There is still much empirical research required to accomplish these goals. Large-scale multicenter studies should be established or modified to provide a context in which to resolve the predictive power and specificity of the prodrome-precursor measures. Maximal standardization of assessment tools between centers, and a broad application of clinical, biological, psychological, and social indicators of elevated risk for psychosis would improve the variability across studies and would generate sufficient power to provide a strong basis for early intervention.
References


