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Editor's Introduction: The Empirical Status of the Ultra High-Risk (Prodromal) Research Paradigm

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Given the growth of prodromal research in the past 15 years, the time seems right for assessing whether the ultra high-risk (UHR) research paradigm has delivered on its promise as an approach to identification of individuals at risk for imminent onset of psychosis and as a platform for studies assessing protective benefits of early interventions and for elucidating predictive markers. As demonstrated by the 8 articles on this theme in the present issue, the empirical basis of the prodromal research area has advanced significantly. While there is a lower risk for transition to psychosis in recent studies compared with initial studies, most recent studies still show a 30%–35% risk for psychosis within 1–2 years of follow-up, a rate that is substantially higher than the incidence rate of psychosis among transition age youth in the general population. Moreover, the means with which to improve this predictive equation is rapidly developing, enabled by the collaborative integration of data across multiple sites, the employment of multivariate risk algorithms, and a longitudinal perspective on symptoms, cognition, and functioning. All the initial intervention studies have produced encouraging findings, albeit with small sample sizes and relatively large attrition rates. Nevertheless, the findings in this issue, together with others like them appearing at an increasing rate in the world literature, indicate that the prodromal research area is increasing in maturity and sophistication, providing a useful heuristic for early detection and intervention in those at risk for psychosis.

Key words: psychosis/prodrome/prevention

This issue of *Schizophrenia Bulletin* marks the third themed issue of this journal concentrating specifically on the prodromal phase of schizophrenia and other psychotic disorders. The first issue, published in 1996 and edited by T. McGlashan, provided an overview of the prodromal construct and initial evidence of the predictive validity of the operational diagnostic criteria for a prodromal or UHR clinical state. The second issue, edited by B.C., R. Heinssen, T.D.C., and T. Lencz and published in 2003, further developed the basic methodological framework and theoretical underpinnings for the UHR (also referred to as "clinical high-risk") research paradigm. The articles in the 1996 and 2003 issues have recently been indexed in PubMed and are now available online (www.oxfordjournals.com).

The prodromal field has now been active for about 15 years. During this period, dozens of clinical research programs specializing in early detection and intervention in the prodromal phase of psychosis have been created in Australia, North America, and Europe, and there are now actively developing sites in Asia as well. This area of research is also the focus of a professional society, the International Early Psychosis Association founded by P.McG., and a consortium of collaborating programs, the International Prodromal Research Network, founded and codirected by T.D.C. and B.C. Given the increasing interest in early intervention and the rapid growth of prodromal research, the editors of the current issue believe the time has come for a first assessment of the empirical status of the findings now emerging. Has this research paradigm, in effect, delivered on its promise as an approach to identification of individuals at risk for onset of psychosis within a 1- to 2-year time interval (ie, "incident cases") and as a platform for studies assessing protective benefits of early interventions and for elucidating biological and psychosocial markers of emerging psychosis?

The 8 articles selected for inclusion in this issue provide a representative, though clearly not exhaustive, perspective on this question. A key issue has continued to be the predictive validity of the prodromal or UHR selection criteria. Although early studies reported transition rates to a full psychotic disorder in the range of 40%–60% over 1-year of follow-up,[1–3] subsequent studies have generally observed more modest conversion rates, in the 20%–35% range, over comparable intervals.[4–6] Yung et al[7] probe

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this temporal trend within the Melbourne health system, finding evidence of a declining rate of transition within successive cohorts at this site, ranging from a high of 50% to a low of 12%. The sources of this declining rate of transition are not entirely clear. Given the evidence for protective benefits of both psychosocial[8] and pharmacological interventions (see McGlashan et al[9]),[10–12] it is possible that the more modest transition rates observed in recent cohorts reflect the influence of such treatments being more effectively applied in the study samples and/or increasingly applied in the community. While Yung et al[7] found no evidence for a lower severity of symptoms or functional impairment in more recent cohorts compared with earlier ones, they did detect a shortening of the time interval from onset of prodromal symptoms to ascertainment, a phenomenon that would be predicted with increased awareness in local populations as to the early warning signs and a decreased sense of stigmatization, both of which are targeted in community outreach efforts in Personal Assessment and Crisis Evaluation[13] and most other UHR programs (McGlashan et al[9]). These trends which have been accelerated by the evolution of the local service system to a broad spectrum youth mental model of care, may also have diluted the "true positive" rate within the sample accessed. Ascertainment of cases earlier in the period of risk for onset, and the recruitment of a more dilute sample, combined with increased exposure to and efficacy of the interventions within the subthreshold samples, may result in fewer cases in more recent cohorts making the transition to psychosis, at least in the short term (ie, 1 year).

Risk estimates obtained within a single study site are expected to have large confidence intervals, given the relatively modest sample sizes available. Thus, although Yung et al[7] present evidence that transition rates in more recent cohorts are statistically lower than those in previous ones, the 95% confidence interval for the transition rate in more recent cohorts still includes the 1-year transition rate averaged across all cohorts (ie, 31%). Clearly, much larger numbers of cases are required to provide statistically reliable modeling of the survival curve and estimates of the positive predictive power of existing prodromal criteria. Addington et al[14] describe the development of a collaborative study integrating information on risk predictors from prodromal and comparison samples across 8 prodromal research sites, known as the North American Prodromal Longitudinal Study (NAPLS). Such collaborative efforts are ideally designed and implemented prospectively. However, as Addington et al[14] demonstrate, even separately developed studies can achieve a relatively high degree of data integration if the same methods for case ascertainment and clinical evaluation have been used. The NAPLS database includes baseline information on 888 subjects, including 370 who are at UHR based on Structured Interview for Prodromal Syndromes (SIPS) criteria,[15] representing the single largest cohort of prospectively followed prodromal subjects worldwide. Analyses of this database, in progress, will determine the rate of conversion to psychosis in the NAPLS sample and assess the accuracy of a number of multivariate prediction algorithms. The development of an improved risk ascertainment algorithm continues to be a primary goal of the UHR research area, given that such criteria will enable more selective recruitment into preventive intervention programs (minimizing exposure of false-positive cases to potential adverse events) and facilitate studies attempting to elucidate neural, hormonal, and other changes proximal to the onset of psychosis.[16–18] A particular challenge for such integrative projects is to account for the influences of treatments which have been applied in non-standard ways across sites.

McGlashan et al[9] review the history of the prodromal construct and describe how treatment-seeking prodromal patients are currently recruited and treated in prodromal clinics worldwide. While atypical antipsychotics were the focus of the initial wave of preventive intervention studies in UHR cases, psychosocial interventions, including cognitive behavior therapy (CBT), have also been evaluated in randomized, controlled trials.[19] Morrison et al[8] report on a 3-year follow-up of the Early Detection and Intervention Evaluation trial, finding that treatment with CBT was associated with a lower risk for prescription of antipsychotic drug treatment (a putative marker of disease progression) over the follow-up interval but was not associated with a reduced risk for transition to full psychosis according to Comprehensive Assessment of At Risk Mental States (CAARMS) criteria.[20] However, when cognitive risk factors targeted by the CBT approach were taken into account, a statistical effect in favor of CBT on preventing full psychotic symptoms emerged. While the findings must be interpreted with caution, given the small initial sample size ($n = 58$) and high rate of attrition (53%) over the 3-year period, the findings are provocative in suggesting that 6 months of treatment with a relatively low-risk, cost-effective intervention such as CBT is associated with a reduction in severity of illness and perhaps also with a reduced likelihood of illness progression. Psychosocial interventions such as CBT, psychoeducational multifamily groups,[21] and adolescent skills training are likely to target-specific aspects of social and role functioning, in addition to emerging psychotic-like symptoms. Given that impairments in social and role functioning, along with cognitive deficits, are the features most resistant to drug treatment and represent the most costly and debilitating aspects of chronic schizophrenia, future studies are encouraged to determine whether psychosocial interventions in the prodromal phase of psychosis deflect the course of illness toward forms with relatively favorable long-term outcomes.

The measurement of social and role functioning in the prodromal population presents some unique challenges.

The subjects in these studies span a relatively large age range (eg, 12–35 years), and the standards for optimal functioning vary considerably from childhood/adolescent samples to adult samples. Moreover, the range of functioning in these groups is generally higher than that of samples of chronic schizophrenia patients, thus making instruments developed for the latter subjects less than ideal. Cornblatt et al[22] present 2 new scales designed specifically for use in transition age and perionset populations, the Global Scale of Functioning: Social and the Global Scale of Functioning: Role. These scales are clinician-rated and easy and brief to administer. They show excellent interrater reliability and convergent-divergent validity. In addition, social functioning in particular is shown to be a relatively stable marker of vulnerability to psychosis, with baseline scores on this measure predictive of conversion to psychosis within the first year of follow-up.

The converse also appears to be true: functional improvement during the year after ascertainment is a highly positive prognostic indicator among UHR patients. Niendam et al[23] found that about half of 35 UHR cases showed significant (>20%) improvement in social and role functioning over an 8-month follow-up interval, while the other half remained stably impaired or declined in functioning. The group showing functional improvement also showed significant improvements in processing speed and visual memory on neurocognitive testing, and significant decreases in clinical symptoms, during this interval. This pattern suggests that there is a subgroup of UHR individuals in whom psychotic-like symptoms and cognitive and functional deficits represent state-specific factors associated with diffuse psychological distress and that these factors ameliorate rapidly with treatment. Such individuals may thus be "false positives" from a psychosis risk prediction standpoint; they stand in contrast to those cases in whom psychotic-like symptoms and cognitive and functional deficits are more treatment resistant, trait like, and enduring, a pattern also seen in patients with first-episode schizophrenia, suggesting that the latter group is likely to contain a higher proportion of "true positives." Of course, it is also possible that the subgroup of patients showing cognitive, clinical, and functional improvement may have also contained some true positives (or "false false positives") who have responded to the earlier intervention.

The question of whether neurocognitive functioning deteriorates among UHR cases who convert to psychosis compared with those who do not has not been resolved. In the Niendam et al[23] study, poorer clinical outcomes were associated with stability or deterioration in neurocognition in the first 8 months of follow-up, but this effect was accounted for primarily by cases in whom cognitive deficits were present stably, and relatively few cases showed evidence of cognitive deterioration. That some degree of deterioration may occur is suggested by the study performed by Simon et al[24], who found that neurocognitive deficits in UHR patients are intermediate between those in patients with established illness and those in treatment-seeking patients who are not at risk for psychosis. Among the UHR group, those at UHR based on SIPS or CAARMS criteria show more deficits than those at UHR based on the presence of basic symptoms. Overall, the deficits seen in UHR patients are in the same domains as those in patients with full psychosis, with relatively greater impairments in auditory working memory, verbal fluency/processing speed, and declarative verbal memory. While these cross-sectional results showing differential degree of deficit based on phase of illness hint at the possibility of neurocognitive deterioration as one moves from a prodromal to fully psychotic clinical state, it is important to keep in mind that the UHR group at baseline is clinically heterogeneous, containing a mixture of cases who will and will not progress to psychosis. Thus, rather than necessarily implying intraindividual deterioration in neurocognition, the finding that UHR cases are, as a group, intermediate between fully psychotic patients and controls in terms of neurocognitive functioning could also be explained by more severe deficits in the UHR cases who will later convert to psychosis compared with those who will not.

The ultimate *Diagnostic and Statistic Manual of Mental Disorders, Fourth Edition* diagnostic outcomes of UHR individuals who convert to psychosis include schizophrenia, schizoaffective disorder, and affective forms of psychosis, including bipolar disorder or recurrent major depression with psychotic features.[25] Although the prodrome criteria are thus sensitive to a range of psychosis outcomes, they were nevertheless developed for schizophrenia-spectrum conditions in particular. Correll et al[26] present a parallel approach to the early identification of individuals at risk for onset of bipolar disorder, irrespective of psychotic symptoms. The content and format of the risk indicators are highly parallel to those used by the SIPS[15] and CAARMS[20] for psychosis risk. Correll et al[26] demonstrate that the first manic episode is preceded by a surprisingly long and insidious period of low-grade symptoms (ie, a prodrome) and that the nonpsychotic mania prodrome differs very little from the prepsychotic mania prodrome, except for a greater likelihood of attenuated positive symptoms proximal to the first manic episode in the latter.

In conclusion, the empirical basis of the field of prodromal research has advanced significantly during the past few years. While confidence intervals around conversion rates in individual studies are quite wide, collapsing across the available studies, there is a central tendency for a 30–35% risk for psychosis within 1 to 2 years of follow-up among UHR cases, a rate that is substantially higher than the incidence rate of psychosis among transition age youth in the general population. Improving prediction of psychosis is a focus of current efforts, which

involve the collaborative integration of data across multiple sites, the employment of multivariate risk algorithms, and a longitudinal perspective on symptoms, cognition, and functioning. Although the initial wave of intervention studies with the UHR population have been limited by small sample sizes and relatively large attrition rates, these studies have produced encouraging findings in regard to the likely beneficial effects of early psychosocial and pharmacologic interventions on symptom severity. It thus appears that the prodromal research paradigm provides a useful heuristic for early detection and intervention in those at risk for psychosis, one that is increasing in maturity and sophistication. The next wave of natural history and treatment studies will be better powered and integrate biological as well as psychiatric, psychosocial, and neurocognitive measures.

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