Prediction and Prevention of Psychosis in Youth at Clinical High Risk

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Abstract
Most individuals with schizophrenia retrospectively report a prodromal period characterized by increasing problems in thinking, feeling, and behaving. However, it is less clear how many individuals who display prodromal symptoms will subsequently develop a psychotic illness. Thus, a precondition for early intervention in psychosis is the accurate detection of those who may be at true risk of developing a psychotic illness. The aim of this article is to review current work addressing prediction and prevention in the prodrome to psychosis. First, we describe research efforts to develop and test operational criteria for prospectively assessing psychosis liability over time. Second, the clinical, functional, and biological features of the prodrome are presented, along with a discussion of the variables most frequently associated with psychosis onset. Next, treatment studies are reviewed. The review concludes with a framework for future early identification and treatment studies.
INTRODUCTION

Detection and intervention very early in the course of illness are considered to be the field’s best practical hope for realizing substantive improvements in the outcome of schizophrenia spectrum disorders. In many mental health systems worldwide, specialized intervention programs offer services for individuals experiencing a first episode of psychosis, with the twin goals of promoting symptomatic and functional recovery (Addington 2007). Indeed, most individuals who receive adequate trials of antipsychotic medication following the first episode of psychosis experience high rates of remission of positive symptoms (Bradford et al. 2003). Adjunctive psychosocial interventions during this period can bring about better adaptation to illness, improved social functioning, and increased quality of life (Penn et al. 2005). Unfortunately, later symptomatic relapse is common even among well-treated individuals, and difficulties in everyday functioning can persist despite rehabilitative intervention (Addington et al. 2003). These sobering findings have shifted the focus of intervention research in schizophrenia to the period before psychosis becomes apparent, when positive symptoms and functional impairments may be less entrenched and more responsive to treatment.

Much research and clinical work in schizophrenia over the past decade has explored the possibility of intervention before the onset of the full disorder, in the hope that preemptive efforts may produce superior clinical outcomes. This work focuses on the prepsychotic or “prodromal” stage of illness, which has been defined as the period marked by changes from a person’s premorbid mental state and level of functioning up to the appearance of psychotic features (Yung & McGorry 1996a,b). Figure 1 presents a composite view of the changes in cognition, affect, and behavior reported to precede the onset of frank psychotic symptoms in retrospective and prospective studies.

Although not every ill person reports a prodrome, approximately 80% to 90% of patients with schizophrenia describe a variety of subacute symptoms in the months and years preceding psychosis, including changes in drive, perception, beliefs, attention, concentration, mood, affect, and behavior (Yung & McGorry 1996a,b). It is believed that much of the disability associated with schizophrenia develops during the prodromal period, in which social withdrawal and emerging negative
symptoms form the foundation on which psychosis later develops (Hafner et al. 1999).

Although most individuals with schizophrenia retrospectively report a prodromal period characterized by increasing problems in thinking, feeling, and behaving, it is less clear how many individuals who display prodromal symptoms will subsequently develop a psychotic illness. Thus, a precondition for early intervention is the accurate detection of prodromal states, i.e., knowing who may be at true risk of developing a psychotic illness. In this review we describe the efforts of researchers in Australia, North America, and Europe to develop and test operational criteria for prospectively assessing psychosis liability over time. These efforts suggest that it is possible to reliably identify an “at-risk mental state” in which individuals have an elevated risk—e.g., 25% to 35%—of developing a diagnosable psychotic illness over several years (Cannon et al. 2008). The clinical and functional characteristics of the prodrome risk syndrome are then presented, along with discussion of the variables most frequently associated with psychosis onset. Next, pharmacotherapy and psychological treatment studies are reviewed. The review concludes with a framework for future research in early identification and treatment and ideas about how these findings may be applied to improve the effectiveness of real-world intervention programs for persons at risk for developing psychosis.

ASSESSING THE PRODROME
Comprehensive Assessment of At-Risk Mental States

McGorry and Yung in Melbourne, Australia were the first researchers to define putative risk criteria for psychosis. These criteria, which reflect an ultra-high-risk state for developing a psychotic disorder in the near future, include attenuated positive symptoms, brief intermittent psychotic states, and genetic/familial risk for psychotic illness coupled with recent and dramatic decline in functioning (Yung & McGorry 1996a,b). The Comprehensive Assessment of At-Risk Mental States (CAARMS) is the diagnostic interview and rating system developed by Australian researchers to assess psychosis risk criteria prospectively (Yung & McGorry 1996a,b; Yung et al. 1996). The CAARMS manual (Yung et al. 2005) provides detailed definitions, questions, and anchor points for eliciting and rating 27 symptoms across seven dimensions of psychopathology, including positive symptoms, negative symptoms, deterioration of role functioning, sleep disturbance, and impaired tolerance to normal stress.

An early version of the CAARMS demonstrated good reliability and predictive validity (Yung et al. 1996, 2003), and a revised version, the CAARMS II, demonstrates good to excellent concurrent, discriminative, and predictive validity as well as excellent interrater reliability (Yung et al. 2005). In early studies using CAARMS criteria, the risk of developing a psychotic disorder increased from the expected rate of approximately 10% in family high-risk groups (Cornblatt & Ouchowski 1997) to approximately 30% to 50% in clinical high-risk samples followed for one to two years (Yung et al. 1998). Furthermore, these studies supported the view that putatively prodromal persons were both highly symptomatic and at imminent risk for psychosis (Schaffner & McGorry 2001).

Structured Interview of Prodromal Symptoms

Building upon Yung and McGorry’s conceptual framework, McGlashan and Miller in the United States developed the Structured Interview of Prodromal Symptoms (SIPS), which elicits information regarding the presence and severity of 19 symptoms across four domains of psychopathology, including positive, negative, disorganization, and general symptoms (Miller et al. 2002, 2003). Information on family history, global functioning, and schizotypal personality disorder is also gathered. Operational criteria are provided for three prodromal syndromes including attenuated positive symptoms, genetic risk and deterioration, and

Schizophrenia: a mental disorder characterized by a disintegration of thought processes and of emotional responsiveness. Most commonly manifests as auditory hallucinations, paranoid or bizarre delusions, or disorganized speech and thinking and is accompanied by significant social or occupational dysfunction.

Psychosis: a loss of contact with reality, usually including false beliefs about what is taking place or who one is (delusions) and hearing or seeing things that aren’t there (hallucinations).

Prodrome: a prodrome is an early symptom (or set of symptoms) that might indicate the start of a disease before specific symptoms occur.

CAARMS: Comprehensive Assessment of At-Risk Mental States.

SIPS: Structured Interview of Prodromal Symptoms.
brief intermittent psychotic symptoms (Miller et al. 2002). The attenuated positive symptoms syndrome requires the presence of at least one positive psychotic symptom (i.e., unusual thought content, suspiciousness, grandiose ideas, perceptual abnormalities, or disorganized communication), but at a level beneath the threshold for overt psychosis. Genetic risk and deterioration symptoms syndrome requires a combination of both functional decline and genetic risk; genetic risk in this instance defined as having either schizotypal personality disorder or a first-degree relative with a schizophrenia spectrum disorder. The brief intermittent psychotic symptoms state is defined as the presence of any one or more positive psychotic symptoms that cross the threshold for psychosis, but at a frequency too brief to meet diagnostic criteria for a psychotic disorder.

The goal of the SIPS interview—and the associated Criteria of Prodromal Syndromes (COPS)—is to identify operationally the presence of a prodromal state, to measure symptom severity over time, and to evaluate conversion to actual psychosis. Initial studies of the SIPS/COPS demonstrate excellent interrater reliability (Miller et al. 2002), which has promoted widespread use of the instrument within the clinical high-risk research community. The SIPS/COPS has been used in a large multisite study of psychosis risk states in North America with excellent interrater reliability and acceptable predictive validity (Addington et al. 2007, Woods et al. 2009). This study, which includes the largest sample of prospectively followed clinical high-risk (CHR) subjects worldwide (N = 291), found that approximately 25% of individuals who met COPS criteria initially developed a psychotic illness within one year, and 35% within two years (Cannon et al. 2008).

Bonn Scale for the Assessment of Basic Symptoms

Researchers in Germany have proposed an alternative approach for identifying individuals at clinical risk for psychosis based on the concept of basic symptoms. Starting in the late 1960s, the Bonn Scale for the Assessment of Basic Symptoms (BSABS) was developed by Huber (Gross 1989) and later elaborated on by Klosterkötter and colleagues (Klosterkötter et al. 2001a) to describe a variety of emerging problems experienced by individuals who later developed schizophrenia. This approach originated with the observation that individuals with schizophrenia often perceive subjective difficulties in basic psychological functions years before the first manifestation of psychotic symptoms. These are mild, often subclinical, but troublesome self-experiences of diminished drive and affect; problems with thought, speech, and perception; motor difficulties; and early vegetative symptoms (Klosterkötter et al. 2001a).

The Cologne Early Recognition (CER) study prospectively examined basic symptoms in 160 patients whose presenting problems suggested the likelihood of a subsequent psychotic episode. Within this at-risk sample, 49.4% developed schizophrenia during the 10-year follow-up period, with certain basic symptoms predicting a later diagnosis of schizophrenia with a probability of 70% (Klosterkötter et al. 2001a). A notable difference between the BSABS and the Melbourne/COPS criteria is that basic symptoms appear to identify individuals at an earlier stage of the psychosis prodrome than is possible with the Melbourne/COPS criteria (Klosterkötter et al. 2008, Schultze-Lutter et al. 2010). It is possible that utilizing the two assessment approaches together may allow risk stratification that separates individuals in the earliest stages of the psychosis prodrome from those at imminent risk for an initial psychotic episode (Ruhrmann et al. 2010).

Schizophrenia Proneness Instrument for Adults

Building upon prior work with the BSABS and the CER study, the Schizophrenia Proneness Instrument for Adults (SPI-A) is aimed at identifying early rather than late prodromal symptoms. Based first on a hierarchical cluster
analysis of BSABS data from the CER study and then upon a subsequent confirmatory construct validation project with a large inpatient sample, the SPI-A represents a streamlined approach for assessing basic symptoms (Klosterkötter et al. 2001b). The instrument has 32 items that cluster into six dimensions; patient responses are elicited in a semistructured interview via general guiding questions that are followed by increasingly specific inquiries. Operational definitions for prepsychotic deviations related to SPI-A items are provided in a newly published English-language manual (Schultze-Lutter et al. 2007a) along with examples of typical statements made by patients. Only subjectively experienced symptoms that were not present in what the person considers his/her premorbid stage are assessed as a definite basic symptom. The SPIA has good interrater reliability (Schultze-Lutter et al. 2007b) and good construct and predictive validity (Schultze-Lutter et al. 2007b, 2008).

Prodromal criteria based on the CAARMS, the COPS, and the BSABS/SCI-A have been validated in a range of studies (Schultze-Lutter 2009, Woods et al. 2009, Yung et al. 2008), and these three assessment tools are the most widely used in current CHR research.

CLINICAL AND FUNCTIONAL CHARACTERISTICS OF THE PRODROME

Clinical Features
Young people who meet criteria for clinical high risk are generally help-seeking adolescents or young adults and often present with a multitude of concerns in addition to complaints of attenuated positive psychotic symptoms. Many have comorbid diagnoses, in particular anxiety, depression, and substance use disorders that are clinically debilitating (Woods et al. 2009; Yung et al. 2007a, 2008). High levels of negative symptoms, significant impairments in academic performance and occupational functioning, and difficulties with interpersonal relationships are often observed (Addington et al. 2008b, Ballon et al. 2007, Lencz et al. 2004, Yung et al. 2008). It is often the case that these problems have been present for some time but recently worsened, triggering concern in family members or friends who have recommended professional evaluation.

Social and Role Functioning
Several studies have demonstrated that as in schizophrenia, poor social functioning is commonly observed in those at CHR and is linked to later onset of psychosis (Mason et al. 2004; Yung et al. 2003, 2004). Yung and colleagues, for example, reported that a global assessment of functioning (GAF) score of 50 or below at baseline was associated with psychosis at 12-month follow-up (Yung et al. 2003). Other studies report unexpectedly low levels of employment among CHR individuals (Fusar-Poli et al. 2009), and impairments in interpersonal functioning and role performance are similar to those seen in the early stages of psychosis (Addington et al. 2008b, Ballon et al. 2007). Thus, even at the prepsychotic phase of the illness, these young people demonstrate significant social and instrumental dysfunction long before the onset of psychotic symptoms.

Most measures of functioning in schizophrenia research have been designed to study individuals with an established psychotic illness and are ill suited for work with the generally younger and less-disabled CHR population. Two new measures of global functioning have been developed for the CHR period, namely the Global Functioning: Social (GFS) and the Global Functioning: Role (GFR) scales (Cornblatt et al. 2007a). The measures were designed to represent parallel, well-anchored scales that account for age and phase of illness, distinguish social functioning from role performance, and detect functional changes over time. The GFS scale emphasizes age-appropriate social contacts and interactions outside the family, with a particular focus on social withdrawal and isolation. Ratings on the GFR scale are based on demands of the role and the level of support provided to the
Social cognition involves the perception, interpretation, and processing of social information and involves mental operations that underlie social interactions including the human ability and capacity to perceive the intentions and dispositions of others.

Cognitive Functioning

Over the past several years there has been an accumulation of data examining cognition in those at elevated risk for psychosis (Brewer et al. 2006, Seidman et al. 2010). Although these studies are limited by small samples, lack of power to detect differences, a limited longitudinal framework, and intermittent use of antipsychotics among CHR subjects, some conclusions can be drawn.

Findings from cross-sectional studies that include CHR subjects consistently document the presence of widespread cognitive deficits intermediate to healthy control and first-episode psychosis samples (Brewer et al. 2006; Hawkins et al. 2004, 2008). When a cognitive factor or overall cognitive score is used, CHR individuals consistently demonstrate significant cognitive impairment in comparison to normal controls (Seidman et al. 2010). Results are mixed for many individual tasks, but enough converging evidence supports the assertion of relative impairments in verbal IQ, verbal memory and fluency, and attention for individuals at risk for psychosis. Cognitive functioning in CHR individuals appears to be stable over time in some domains and to improve in others, but studies generally do not report evidence of progressive cognitive decline. Finally, a number of studies suggest that CHR individuals who go on to develop psychosis appeared to be more impaired at baseline assessment on a composite score of cognition (Seidman et al. 2010). However, no clear consensus has emerged on which individual cognitive tasks may or may not predict conversion. A comprehensive review of cognition in the prodrome is beyond the scope of the current review; for an outline of cognitive studies completed to date, with references, see Supplemental Table 1 (follow the Supplemental Materials link from the Annual Reviews home page at http://www.annualreviews.org).

Social Cognition

Research into social cognitive functioning among persons at risk for psychosis is under way, with projects examining emotion recognition in faces and voices as well as early studies on theory of mind and attributional style. Facial affect studies (Addington et al. 2007, Amminger et al. 2011) demonstrated that those at CHR have deficits relative to controls and performance difficulties similar to those observed during the first episode of psychosis. Deficits in theory of mind have also been reported (Chung et al. 2008) relative to healthy controls. Using the Ambiguous Intentions Hostility Questionnaire, An and colleagues (2010) reported that both first-episode and CHR participants demonstrated perceived hostility bias. For first-episode patients, this bias was related to persecutory symptoms, whereas in the CHR group, attribution bias for perceiving hostility was linked to an unfolding paranoid process.

A recent study by Green et al. (2011) assessed measures reflecting three domains of social cognition. The Relationships Across Domains task assesses models or rules for interactions, the Awareness of Social Inference Test (part II) assesses capacities to understand others’ minds, and the Mayer Salovey Caruso Emotional Intelligence Test 2.0 assesses emotional communication. Three samples, each with its own carefully matched control group, were examined: a group of patients with a more chronic course of schizophrenia, a first-episode psychosis group, and a CHR group. Results of this study demonstrated impairment in social cognition across all three phases of psychotic illness and that age had a limited effect on
performance for both clinical and comparison groups. What was most interesting, however, was a lack of evidence suggesting progression or improvement over the three phases of the illness. Thus, this study provides additional support for the notion that social cognitive impairments begin in the earliest phases of a psychotic illness and remain stable over time.

**Associations Among Cognition, Social Cognition, and Functioning**

There is evidence that social cognition potentially mediates the relationship between neurocognition and poor functioning in both first-episode psychosis patients and those with a more chronic course of schizophrenia (Addington et al. 2010). Such relationships are just beginning to be explored in CHR samples. CHR individuals who experienced significant cognitive deficits on tasks requiring speeded information processing and memory appear to experience a level of functional disability that is similar to that of patients with an established psychotic illness (Niendam et al. 2006). Although the degree of neurocognitive deficit at baseline in CHR patients does not predict psychosocial outcome, the course of neurocognitive change over the first eight months of follow-up does differentiate patients with good and poor functional outcomes (Niendam et al. 2007).

Emotion awareness was recently examined in a Dutch study (van Rijn et al. 2010) in which CHR adolescents showed difficulties in identifying and verbalizing their own emotions, independent of intelligence scores. Emotion awareness problems were related to social inadequacy and schizotypal traits in the high-risk group. These findings suggest that CHR adolescents may have reduced emotion awareness, independent of intellectual functioning. The relationship with socially inadequate behavior fits with the idea that emotion awareness is a prerequisite for the regulation of emotions in social contexts. Studying emotion processing alongside cognitive abilities might increase our understanding of at-risk developmental pathways and identify early vulnerability markers of risk for psychosis.

**CONVERSION TO PSYCHOSIS**

The Melbourne/COPS criteria reliably identify young people who are at high clinical risk for psychosis or who are in the earliest phase of acute psychotic illness. In the early CHR studies, the 12-month transition rate to full-blown psychosis of young people who met criteria approached 40% despite the provision of supportive psychotherapy and, where appropriate, antidepressant or anxiolytic medication (Cadenhead 2002, Mason et al. 2004, Miller et al. 2003, Morrison et al. 2003, Yung et al. 2003). This rate of progression to illness is much higher than the incidence rate in the general population of between 0.2 and 0.5 new cases per 1,000 population per year (Jablensky et al. 1992) and the 10% to 12% statistical risk that children of parents with schizophrenia have of developing the illness later in life (Gottesman 1991).

In their earlier studies (Yung et al. 2003), the Melbourne group found that predictors of psychosis were long duration of prodromal symptoms, poor functioning at intake, low-grade psychotic symptoms, depression, and disorganization. Two large multisite studies, one from North America and one from Europe, have aimed to better quantify the level of risk and also to identify particular predictors of transition to psychosis. In the first, a consortium of investigators from the United States and Canada pooled data from individual prodromal studies using identical CHR criteria. The eight research centers comprising the North American Prodrome Longitudinal Study (NAPLS) ascertained CHR individuals and followed them at regular intervals for a period of up to 2.5 years (Addington et al. 2007). Although originally developed as independent studies, the sites employed similar ascertainment and longitudinal assessment methods, making it possible to form a standardized protocol for mapping acquired data into a new scheme representing common components across sites (Addington et al. 2007).
2007). This exercise yielded one of the largest databases of longitudinally followed CHR cases worldwide.

Of the 370 subjects enrolled in the study, 291 (79%) had at least one follow-up assessment. Approximately 35% of these 291 subjects converted to psychosis over the 2.5-year follow-up period (Cannon et al. 2008). Five features assessed at baseline contributed uniquely to the prediction of psychosis: a genetic risk for schizophrenia with recent deterioration in functioning, higher levels of unusual thought content, higher levels of suspicion-paranoia, greater social impairment, and history of substance abuse. Algorithms combining two or three of these variables resulted in dramatic increases in positive predictive power (i.e., to 68% to 80%) compared with the prodromal criteria alone (Cannon et al. 2008), although this method reduces sensitivity, leading to a higher rate of false negatives. By comparing the 30-month transition rates in this sample with the incidence rates for all forms of psychosis in the general population during a comparable period (Kirkbride et al. 2006), it was possible to quantify the relative risk of psychosis at 405.

The European Prediction of Psychosis Study (EPOS) was a prospective, multicenter European study led from Cologne and included sites in the Netherlands, United Kingdom, Spain, and Norway (Klosterkötter et al. 2005). Inclusion criteria were the CHR criteria as used in NAPLS plus the cognitive symptom cluster from the SPI-A applied to help-seeking people ages 16 to 35. The aims of the EPOS study were to assess the rate of transition to psychosis over an 18-month follow-up plus to identify baseline variables predictive of conversion. From the total sample of 245 enrolled, 90% met CHR criteria on the SIPS. Of the 183 who were followed up over 18 months, conversion rates of 14% at 12 months and 19% over 18-month follow-up were seen. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) diagnoses following conversion were schizophrenia in 62%, mood disorder with psychotic features in 16%, and the remainder mainly divided between schizoaffective and schizophreniform disorder (Ruhrmann et al. 2010).

Multiple regression analysis, controlling for confounds, identified six baseline variables that independently predicted conversion. These were the overall severity of attenuated positive symptoms (based on the Scale of Prodromal Symptoms score), bizarre thinking, sleep disturbance, schizotypal personality, low functioning in the past year rated on the GAF scale, and years of education. Combining these into a four-class “prognostic index,” as is done with cancer staging, proved useful in refining predictive power. Relating the conversion rate data to known incidence rates in the reference population showed a relative risk over 18 months of psychosis in this group to be 364, similar to that of 405 shown in NAPLS (Ruhrmann et al. 2010).

Predictors of Conversion

Several cohort studies and clinical trials have reported on demographic, clinical, and other predictors of conversion in samples of help-seeking people who meet CHR criteria. Because different studies have collected different variables, there is only partial overlap in baseline measures that predict the onset of psychosis. The most well-replicated finding is the relationship of baseline-attenuated positive symptom severity with psychosis onset, whether this is measured by Positive and Negative Syndrome Scale (PANSS), CAARMS, or SIPS. This relationship was observed in NAPLS and EPOS as well as in cohorts from the Melbourne Personal Assessment and Crisis Evaluation (PACE) program and in treatment trials such as the Early Detection and Intervention Evaluation (EDIE) study (Morrison et al. 2004a,b). Severity of attenuated positive symptoms seems to predict both the likelihood of eventual psychosis and the length of time to conversion. In the PACE cohort, duration of symptoms also predicted conversion in that the longer that symptoms were present, the greater the risk for an initial psychotic episode.
In terms of individual psychotic symptoms, both NAPLS and EPOS reported that unusual thought content, suspicion/paranoia, and bizarre thinking (a disorganization syndrome feature) predicted conversion. PACE and NAPLS reported negative symptoms also to be predictive, although not as strongly as positive symptoms. Both NAPLS and EPOS reported that low functioning, as measured by changes in GAF scores over the previous year, predicted conversion (Velthorst et al. 2010). It might seem that street drug use, especially cannabis and amphetamines, would predict conversion; in the NAPLS study, however, a history of any substance use, including alcohol, was only a weak predictor.

Some research groups have begun to study hypothalamic-pituitary-adrenal (HPA) axis functioning in those at CHR. Thompson et al. (2007) reported higher cortisol levels among a small sample of CHR individuals who were depressed but did not go on to develop psychosis. On the basis of this finding, Thompson and colleagues speculate that dysregulated HPA axis functioning may be more related to concomitant depression than to psychosis risk in CHR samples. However, results from a more recent, larger study by Walker et al. (2009) fail to support this conclusion. Walker and colleagues used salivary cortisol measures to assess HPA axis integrity among CHR subjects over time. The researchers reported that CHR persons who eventually developed psychosis exhibited higher cortisol levels at several follow-up points prior to conversion as compared with those who did not. More studies are needed to clarify the seemingly contradictory findings from the two HPA axis research groups.

Although the Melbourne/COPS criteria for CHR have been validated in a number of studies, it is not known whether particular syndromes or combinations of syndromes are associated with a higher risk of conversion to psychosis. An examination of 928 referrals to the PACE clinic suggests that conversion to psychotic illness over the ensuing six months is most likely when the initial diagnosis is brief intermittent psychotic states syndrome, followed by diagnoses of attenuated psychotic symptoms syndrome and genetic risk with deterioration syndrome, respectively (Nelson et al. 2011).

### Biomarkers of At-Risk Mental States

Current theories suggest that schizophrenia is a disorder of reduced or disrupted neural connectivity, such that impaired communication between brain regions leads to observable symptoms as well as problems in cognition and affect (Karlsgodt et al. 2010). A range of neuroimaging studies reveals alterations in brain structure, function, and chemistry in CHR individuals that are consistent with those typically associated with psychosis (Fusar-Poli et al. 2011, Karlsgodt et al. 2010, Smieskova et al. 2010). This evidence has contributed to a growing awareness that these measures of brain anatomy and function may represent vulnerability markers for increased psychosis risk (Borgwardt et al. 2011, Fusar-Poli et al. 2011, Smieskova et al. 2010).

Pantelis and colleagues (2009) discuss a number of potential biomarkers of incipient psychotic illness, drawing particular attention to indices of frontal and temporal cortex integrity. However, since these brain regions undergo rapid changes during normal maturation, any putative neurobiological markers of illness onset may be difficult to detect against this dynamic background. Instead, identification of valid risk markers may require longitudinal assessment to distinguish normal and abnormal trajectories of neurodevelopment. Certainly, further longitudinal imaging studies are required, but findings to date support the value of neuroimaging methods for illuminating the biological pathways to psychosis (Karlsgodt et al. 2010). A goal for future studies will be to explore the potential of combining different biological, clinical, and functional markers to enhance positive predictive power.

### Future Issues for Predicting Conversion to Psychosis

Several issues related to prediction will require attention in the next generation of CHR...
studies. First, as mentioned above, there is a need to combine biological, clinical, and functional markers into accurate and practical prediction tools like those already developed for cardiovascular disease. Such work is being addressed in the ongoing NAPLS 2 project, in which neurocognitive tests, neuroimaging methods, cortisol assays, electrophysiological measures, and genomics are being applied in conjunction with clinical and functional assessments to (a) create more powerful prediction algorithms and (b) explore potential biomarkers of psychosis. Second, although onset of psychosis has been a major outcome of interest, the point at which an individual actually converts to psychosis is somewhat arbitrary. To date, the point of conversion has been determined by clinical consensus, but it is unclear whether this threshold is supported by valid biological markers (Yung et al. 2010). Thus, a requirement for further progress in this area is biological testing that delineates the boundary between psychotic and nonpsychotic mental states.

Interestingly, as more studies that examine conversion to psychosis appear in the literature, a trend has developed suggesting lower conversion rates currently than those originally reported. Recent studies report rates of conversion to psychosis in the high teens or low twenties compared to those of around 35% to 40% reported a decade ago. The PACE clinic in Melbourne, for example, reports that rates of first-episode psychosis among CHR patients have declined 20% each year for several successive years (Yung et al. 2007b). Several factors may account for this phenomenon, including earlier identification and engagement of CHR individuals and more rapid initiation of supportive treatments. Alternatively, a growing number of false-positive cases, i.e., individuals who meet CHR criteria but who were never at true risk of psychosis, may contribute to a dilution effect (Yung et al. 2007b). Further studies are required to test whether early identification and early treatment, dilution effects, or other unknown factors are contributing to the declining conversion reported in CHR programs since 2005 (Yung et al. 2007b).

Outcomes Other Than Psychosis Onset

Several different outcomes are possible in a population considered to be at risk, including conversion to psychosis, symptomatic recovery, and stable presentation of prodromal symptoms. Several recent studies have focused on the longitudinal course of CHR individuals who do not convert, exploring outcomes other than onset of psychosis. For example, Schlosser and colleagues recently reported that although 30% of their CHR sample developed psychosis within two years, 36% experienced remission of symptoms, and 30% evidenced limited functional recovery (Schlosser et al. 2011). Other studies suggest that members of the third outcome group—i.e., the nonconverters—continue to display a range of psychiatric problems and functional difficulties over time. Many experience nonpsychotic DSM-IV Axis 1 conditions such as mood and anxiety disorders that warrant immediate intervention. Even when need-based treatments are offered, short-term outcomes for these CHR individuals are rarely positive, with up to 40% bothered by enduring attenuated positive symptoms as well as impaired social and role functioning (Addington et al. 2011a). Although it appears unlikely that these persons will go on to develop a subsequent psychotic illness, they are clearly not well and need help (Weiser 2011). Further work is required to discern the profile of risk indicators that will distinguish nonconverters from CHR individuals most likely to progress to psychosis (Schlosser et al. 2011).

TREATMENT

Many research programs investigating the prepsychotic period have developed mental health clinics for at-risk individuals that integrate both research and clinical services. Early in the development of this area of science, clinical services for at-risk individuals emphasized early identification, systematic assessment of risk status, longitudinal monitoring, and referral for treatment in the event
that prodromal symptoms worsened. As data accumulated about the predictive validity of clinical high-risk criteria, and the range of impairments and difficulties experienced by members of this young population, the research agenda progressed from early identification to pre-emptive intervention. The goal of this next wave of research was to study interventions designed to reduce symptoms and behavioral deficits associated with the prodromal stage of illness and to prevent or delay the onset of the first episode of psychosis. To date, only five controlled trials have been published that focus on individuals at clinical high risk for psychosis. These studies involving antipsychotic medications, cognitive behavioral therapy (CBT), and other novel strategies such as eicosapentaenoic acid (omega-3 fatty acid) are summarized in Table 1.

### Medication Trials

The first study to address intervention during the prepsychotic stage was carried out by McGorry et al. (2002) in Melbourne. Fifty-nine CHR participants (as defined by CAARMS criteria) were randomized to six months of active treatment (risperidone 1–3 mg/day plus modified CBT) or needs-based intervention (McGorry et al. 2002). By the end of six months, significantly fewer individuals in active treatment had progressed to a first-episode of illness.

<table>
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<tr>
<th>Study</th>
<th>Follow-up</th>
<th>Groups</th>
<th>Conversion rates</th>
<th>Diagnostic measure</th>
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<tr>
<td>PACE Trial 1</td>
<td>12 months</td>
<td>31 CBT + Risp</td>
<td>19.4%</td>
<td>CAARMS</td>
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<td>28 NBI</td>
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<td>PRIME North America</td>
<td>12 months</td>
<td>31 olanzapine</td>
<td>16.1%</td>
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<td>29 placebo</td>
<td>37.9%</td>
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<td>EDIE-1</td>
<td>12 months</td>
<td>37 CBT + monitor</td>
<td>5.4%</td>
<td>PANSS</td>
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<td>Morrison et al. (2004a)</td>
<td>12 months</td>
<td>23 monitor</td>
<td>21.7%</td>
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<td>Morrison et al. (2007a)</td>
<td>3 years</td>
<td>17 CBT + monitor</td>
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<td>18 months</td>
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<td>12.5%</td>
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<td>Omega-3</td>
<td>12 months</td>
<td>41 omega 3</td>
<td>4.9%</td>
<td>SIPS</td>
</tr>
<tr>
<td>Amminger et al. (2010)</td>
<td>12 months</td>
<td>40 placebo</td>
<td>27.5%</td>
<td></td>
</tr>
<tr>
<td>PACE Trial 2</td>
<td>6 months</td>
<td>43 CBT + Risp</td>
<td>4.7%</td>
<td>CAARMS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>44 CBT + placebo</td>
<td>9.1%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>28 ST + placebo</td>
<td>7.1%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>78 NBI</td>
<td>5.1%</td>
<td></td>
</tr>
</tbody>
</table>

CAARMS, comprehensive assessment of at-risk mental state; CBT, cognitive behavioral therapy; NBI, needs-based intervention; PANSS, Positive and Negative Syndrome Scale; Risp, Risperidone; SIPS, Structured Interview for Prodromal Syndromes; ST, supportive therapy.
Randomized controlled trial (RCT): treatment study that includes random assignment to conditions and assessments of the outcome; the gold standard for establishing treatment efficacy.

Psychotic disorder (9.7% versus 36%). However, six months after treatment ended, this difference was no longer significant, as more individuals in the active treatment group eventually developed psychosis (19% versus 36%). Non-adherence to medication emerged as a risk factor for poor outcome in the active treatment condition, as subjects who were noncompliant with antipsychotic medication were much more likely to develop psychosis than were compliant peers. Overall, results suggest that a combination of antipsychotic medication and CBT may delay the onset of psychosis in symptomatic high-risk subjects but does not necessarily prevent a first psychotic episode.

As with many early studies in emerging areas, there were some methodological limitations to the Australian project that should be acknowledged, including a small sample and clinical raters who were not blind to subjects' treatment assignments. Second, because pharmacologic and psychological treatments were combined in the active treatment group, it is impossible to determine the relative contributions of medication and CBT for delaying psychosis onset. Third, it was difficult to control for adherence to medication, which clouds interpretation of findings. Despite these limitations, the Australian effort represented a landmark study of selective prevention of psychotic disorders.

A more rigorous study, the PRIME trial, conducted in North America, was a randomized, double-blinded trial of the antipsychotic medication olanzapine for preventing or delaying the onset of psychosis (McGlashan et al. 2006). Sixty help-seeking patients in Canada and the United States who met COPS criteria were randomized to medication or placebo for one year, followed by no medications for the second year. After 12 months, more than twice as many placebo-treated participants than olanzapine-treated subjects had converted to psychosis (35% versus 16%), but this difference was not statistically significant (McGlashan et al. 2006). At 24 months, the rate of psychosis onset did not differ significantly between treatment and control groups. However, olanzapine was associated with significantly greater improvement in prodromal symptoms compared to placebo. As with the Australian study, interpretation of findings is likely limited by the small sample size, a problem compounded in the North American trial by high dropout rates in both conditions.

Taken together, results from the PACE and PRIME studies suggest that (a) the severity of prodromal symptoms can be reduced with atypical antipsychotic medications, and (b) it may be possible to delay the onset of the first psychotic episode by combining pharmacologic and psychological therapies. However, issues related to sampling, sample size, and acceptance of pharmacological treatment suggest caution in interpreting these findings. For example, more than half of individuals who met inclusion criteria for the Australian study refused participation in the randomized controlled trial (RCT) (56%), and for the Calgary site of the North American trial, only 14% of eligible individuals agreed to participate (Addington & Addington 2005). High rates of initial refusal raise the prospect of unknown biases in subject selection, which may have influenced results. Small samples may have limited statistical power to detect differences in conversion to psychosis between conditions, particularly considering that rates of psychosis onset vary widely in longitudinal studies of at-risk subjects (9% to 54%) (Haroun et al. 2006). Finally, medications were not universally accepted by subjects; nonadherence to medication was common in the Australian study (42%), and most subjects in the olanzapine arm of the North American trial dropped out of treatment (55%). Undoubtedly these limitations will be addressed in future studies. For now, however, findings from medication studies do not support broad adoption of pharmacotherapy as a first-line treatment approach with at-risk individuals.

Psychological Treatment Trials

Concerns with medication for those at CHR led to a logical case for considering the application of psychological treatments for psychotic symptoms during the emergent phase of psychotic
disorders. Only two RCTs of psychotherapeutic interventions have been published to date; both studies tested the efficacy of CBT compared to an alternative nonpharmacologic intervention (Addington et al. 2011b; Morrison et al. 2004a,b). The cognitive therapy utilized in these trials was based on an empirically validated cognitive model of psychosis (Morrison 2001). The therapy adheres to the structure and principles of cognitive therapy (Beck & Rector 2000), being time limited (up to a maximum of 26 sessions over six months; average number of sessions was 12), problem oriented, collaborative, and involving the use of homework tasks and guided discovery. Initial stages of therapy include a cognitive-behavioral assessment, the development of a shared list of problems and goals, and the generation of a case formulation based on the cognitive model. Common techniques, which are collaboratively selected on the basis of a shared case formulation, include the examination of advantages and disadvantages associated with particular ways of thinking and behaving, consideration of evidence, generation of alternative explanations, and the use of behavioral experiments to evaluate beliefs.

There are several arguments to support why CBT may be a beneficial psychological intervention for young people at CHR (French & Morrison 2004). First, CBT has demonstrated effectiveness for those with schizophrenia to cope with psychotic symptoms and to reduce associated distress (Lewis et al. 2002, Pilling et al. 2002, Sensky et al. 2000, Tarrier et al. 1998) as well as the risk of relapse (Birchwood et al. 1989, Gumley et al. 2003). Thus, CBT is likely to help with both the attenuated and brief intermittent psychotic symptoms associated with the prodrome. Second, CBT was originally developed for mood disorders and has an extensive evidence base for the treatment of anxiety disorders, which are common in the CHR group (Woods et al. 2009, Yung et al. 2003). This means that a CBT approach would be a valuable intervention for the nonspecific emotional problems that are often observed during this period of CHR. Third, CBT approaches have also been useful in addressing substance use, which is believed to be a common and important contributing factor in the development of psychosis in those at risk (van Os et al. 2002). Fourth, increased problems with metacognitions and self-schemas, which are psychological processes typically targeted during CBT, have also been observed in the CHR population (Morrison et al. 2007b). Finally, CBT interventions fit very well within a stress-vulnerability model and offer numerous coping strategies that may offer protection against environmental stressors that are likely to precipitate conversion to psychosis (McGorry & Singh 1995, Roberts 1991).

The collaborative nature of CBT, in that it is problem-oriented and involves working toward shared goals, may make it more acceptable to young adults, particularly since they often express a preference for psychological interventions and a willingness to participate in trials of psychological interventions (Addington & Addington 2005, Morrison et al. 2004b). In sum, it appears that CBT could be the model of psychological intervention that holds the greatest promise for being effective in (a) addressing the range of symptoms and concerns present in the CHR period and (b) teaching potentially effective strategies to protect against the impact of environmental stressors that may contribute to the emergence of psychosis.

The first trial that explored the value of a fully psychological intervention with CHR patients was the Manchester Early Detection and Intervention Evaluation (EDIE) (Morrison et al. 2004a,b). EDIE was a single-blinded, randomized trial of CBT with individuals at high risk for psychosis. Fifty-eight patients were randomized to either CBT or symptom monitoring. CBT was provided for the first six months, and all patients were monitored on a monthly basis for 12 months. CBT significantly reduced the likelihood of progression to psychosis over 12 months as defined by (a) PANSS scores (6% versus 22%), (b) being prescribed antipsychotic medication (6% versus 30%), and (c) meeting DSM-IV diagnostic criteria for a psychotic disorder (6% versus 26%). The CBT group
demonstrated improved positive symptoms, depression, and anxiety over time (French et al. 2007), and some benefits were maintained at three-year follow-up (Morrison et al. 2007a). Of note, 95% of eligible subjects consented to participate in the RCT, and dropout rates were considerably lower than in the Australian and North American medication trials. A three-year follow-up study (Morrison et al. 2007a) showed that the initial effects of therapy largely disappeared, although follow-up rates were only 50% of the original sample.

A recently published Canadian study, Access, Detection and Psychological Treatments (ADAPT), compared the effectiveness of CBT to supportive therapy (Addington et al. 2011b). Fifty-one patients who met COPS criteria were randomized to treatment and followed for 18 months. Only three individuals experienced a first psychotic episode during the study period, all in the supportive therapy condition. However, the difference in conversion rates between supportive therapy (12.5%) and CBT (0%) was not significant. Both treatments were equally effective in bringing about significant improvements in attenuated positive symptoms, anxiety, and depression, but neither treatment impacted negative symptoms or poor functioning.

To the best of our knowledge these are the first published results of an RCT that compared two different nonpharmacological treatments for those at CHR. The lack of differences between treatment groups was unexpected. There are several possible explanations for the nonsignificant differences, including: (a) both treatments may be equally effective in reducing the risk for imminent psychosis; (b) both treatments may be equally ineffective, and participants may have recovered despite the interventions; (c) the study is underpowered to detect group differences; (d) the number of overall sessions tended to be low, and the CBT group may have received an inadequate dose of treatment; and (e) since CBT was individualized to patients’ presenting problems, areas of improvement varied considerably across participants. One recommendation for future CBT trials is that the intervention should be directed at targeting and improving attenuated positive symptoms. Finally, the overall conversion rate within this sample (6.25% over 18 months) was much lower than expected. This latter finding, which is consistent with results from other prodromal clinics worldwide (Yung et al. 2007b), suggests that samples for future treatment studies will have to be considerably larger than samples utilized in the PACE, PRIME, EDIE, and ADAPT trials summarized here.

Other Treatments

Only one study to date has been designed to explore whether pharmacological or psychological treatments alone or in combination are effective treatments for young people at risk for psychosis (Phillips et al. 2009, Yung et al. 2011). In this study, the main outcome measure was conversion to psychosis, although changes in symptoms, functioning, and quality of life were measured during the 12-month treatment and 12-month follow-up phases. All participants were between 14 and 30 years of age and met one or more of three prodromal syndromes based on the CAARMS (Yung et al. 2005). One hundred and fifteen participants were randomized to one of three treatment groups, which included (a) CBT plus antipsychotic (up to 2 mg risperidone) (n = 43), (b) CBT and placebo (n = 44), and (c) supportive counseling and placebo (n = 28). A monitoring group (n = 78) consisted of individuals who met criteria for CHR but did not agree to be randomized. Family education and support were offered to all participants if deemed necessary, regardless of treatment group.

To date, only the six-month follow-up data from this trial have been published (Yung et al. 2011). At the six-month follow-up, eight of the 115 participants (7%) had developed a psychotic disorder: two in the CBT + risperidone group, four in the CBT + placebo group, and two in the supportive therapy + placebo group. There were no significant differences between the groups in the proportion of participants who converted to psychosis. All groups
showed significant improvement on ratings of psychopathology, and with the exception of the CBT + risperidone group, all showed significant improvements in functioning.

An interesting new development in the CHR intervention arena is a 12-week trial comparing eicosapentaenoic acid, more commonly known as omega-3, with placebo (Amminger et al. 2010). At 12 months, only 4.9% (2/41) of individuals in the eicosapentaenoic acid group developed psychosis, compared to 27.5% (11/40) of individuals in the placebo group. Furthermore, there were significant group differences in positive and negative symptoms at 12 weeks and 12 months in favor of the treatment group.

Future Issues for Treatment

Preti & Celli (2010) recently reviewed RCTs that tested approaches aimed at preventing onset of psychosis in at-risk individuals. A meta-analysis of five trials involving pharmacologic and nonpharmacologic interventions suggests that focused treatments are effective in reducing the risk of transition to full-blown psychosis over a 12-month period, but that over longer intervals (i.e., ≥2 years), time-limited interventions are less effective and may only delay transition to psychosis. The current group of published RCTs underscore critical points that now need to be considered in future trials, including alternative approaches to pharmacotherapy and for psychological treatments, that treatments are clearly distinguished from one another, and that level of therapist expertise is defined. For all types of interventions, the dose and duration of treatment must be adequate, and desired outcomes must be clearly operationalized.

In considering already-tested treatments for this young at-risk population, it may be that antipsychotics are potentially useful in the later phases of the prodromal period, when attenuated psychotic symptoms are clearly evident and the individual is potentially on the edge of a conversion to full threshold psychosis. However, it appears that community practitioners are already prescribing antipsychotic medications to at-risk individuals well before psychotic symptoms emerge (Walker et al. 2009). Clearly, more research about the proper timing, dosing, and duration of antipsychotic medications is required. In addition, alternative pharmacologic approaches should be explored, including antidepressants (Cornblatt et al. 2007b), lithium, and biologics such as glycine (Woods et al. 2006) and essential fatty acids (Amminger et al. 2010). RCTs are under way for many of these agents, including an international effort to replicate the promising finding regarding eicosapentaenoic acid as a potentially low-cost, easily administered, and low-stigma prevention strategy.

In contrast to antipsychotic medications, psychological interventions might be expected to be most promising at earlier and less-symptomatic stages of the prodrome. In fact, in the early stages of the prodromal period, presenting symptoms are not only less severe but also less specific, as individuals often present with a wide constellation of concerns. For example, persons at CHR frequently need to understand their perceptual difficulties; manage their stress, depression, anxiety, sleep disturbance and decline in functioning; and feel supported through this difficult period of their lives (Yung et al. 2003). Given this mélange of symptoms, McGorry and colleagues (2010) suggest a staged model of treatment that could begin with a period of observation, followed by evidence-based treatment of presenting psychiatric disorders and ongoing monitoring. Functional deterioration and/or worsening of subthreshold psychotic symptoms would lead to more specific treatment, such as CBT for attenuated positive symptoms, and finally antipsychotics if rapid worsening occurred. Other reasons to institute low-dose atypical antipsychotics would include failure to respond to nonspecific treatment, prolonged subthreshold psychotic symptoms, and suicidality and dangerousness coupled with subthreshold psychosis.

Although psychological trials to date have focused exclusively on CBT, other treatment approaches are beginning to be explored for
the prodromal stage of psychotic illness. These include group and family work, substance use prevention, and cognitive remediation (Addington et al. 2006). In the case of family work, investigators working with the CHR population are building upon treatment strategies found to be highly effective in established schizophrenia (e.g., Gingerich & Bellack 1995). For example, O’Brien and colleagues demonstrated that lower expressed emotion among family members was related to symptomatic improvement in at-risk individuals (O’Brien et al. 2007). Furthermore, the better the problem-solving and communications skills were between CHR persons and their relatives, the lower the symptom ratings were at follow-up (O’Brien et al. 2009). Results such as these suggest that the family environment should be a specific target for treatment. Studies examining the impact of a family intervention on conversion, and symptomatic and functional improvement, are under way.

Other forms of cognitive therapy can be imagined that target the basic information-processing deficits, social cognitive impairments, and attention biases common among at-risk individuals. For example, intensive computerized neuroadaptive cognitive training has been proposed as a strategy for “normalizing” cognitive deficits frequently observed among CHR youth—e.g., processing speed, working memory, verbal learning—with the goal of preventing onset of psychosis and improving overall adaptive functioning (Genevsky et al. 2010). Likewise, social cognitive rehabilitation methods (Eack et al. 2009) may be relevant for improving the problems in affect recognition and theory of mind that have been reported in CHR samples (Addington et al. 2007, Amminger et al. 2011, Chung et al. 2008). Computer-delivered programs that promote attention disengagement from threatening stimuli have proven effective in anxiety disorders (Amir et al. 2009) and may be useful for modifying attentional biases that underlie suspiciousness and attenuated paranoia in some CHR youth (An et al. 2010).

Several questions need to be addressed when considering new techniques or modifying existing treatments. How much therapy would be enough to make a difference? Should CBT be used specifically to target attenuated positive symptoms, and should other therapies be used for different problems such as general distress, information-processing difficulties, and social skills deficits? That is, simple interventions offering support and problem solving may be helpful for these young people at CHR when they first seek help, augmented by more specific interventions when warranted. Structured CBT strategies possibly requiring more experienced therapists should be reserved for targeting specific problems such as severe attenuated positive symptoms. Thus, future work in this area should include further controlled intervention trials with large sample sizes to confirm and extend current findings. Second, as we obtain further confirmation on the various models of risk architecture that have been proposed, these need to be used to inform the choice of treatment or to design alternative treatments.

**NEXT STEPS**

As described above, the next steps for research are clear. The first is improved prediction models specifically including biomarkers. Such prediction models will aid our understanding of the development of schizophrenia but will also require translation so that they are clinically useful. The second is further work in testing treatments for this population. In addition to improved methodology in clinical trials, treatments that are based on established risk factors, that may be personalized, and that are specifically designed for this population need to be developed and tested. We need to differentiate between developing and testing treatments that are addressing current problems of this young population and studies that are testing treatments designed for selective prevention. This includes innovative treatments such as omega-3 fatty acids that are not necessarily effective once a disorder is established but that may work in a manner that forestalls the onset of illness.

This area clearly is most relevant for schizophrenia research, but there are important
connections to other areas. First, we have seen that although a proportion of those at CHR do go on to develop psychosis, a large proportion do not; however, they do not necessarily experience a remission of symptoms or improvement in functioning (Addington et al. 2011a). This opens the question of whether these young people are at risk for other disorders, and perhaps we need to consider some of this work in conjunction with recent advances in studying youth mental health and risk for mental health problems in general (McGorry et al. 2011). Second, a wealth of studies that have explored the existence of psychotic-like experiences in the general population has implications for CHR research as well as schizophrenia research. It will serve this area well to maintain links to these other developing focuses of research.

**DISCLOSURE STATEMENT**

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

**LITERATURE CITED**


Figure 1
Clinical course of psychosis prodrome. Adapted from Lewis & Lieberman (2000).
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