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Evaluating and Treating the Prodromal Stage of Schizophrenia

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Abstract

Identification of a person in the prodromal stage of schizophrenia, before the onset of the first episode of psychosis, provides an opportunity for early, potentially preventative, interventions. Recent attempts to develop “at risk” or “prodromal syndrome” diagnostic criteria have proved to be successful at identifying individuals at high risk for psychosis. Preliminary investigations find that pharmacologic and psychotherapeutic interventions may reduce the risk of psychosis in “at risk” individuals, but until more is known, current treatment guidelines recommend close monitoring, therapeutic interventions that address identified problems, including supportive or cognitive therapies to reduce the functional consequences of the presenting symptoms, family interventions to reduce family distress and improve coping, and intervention with schools to decrease likelihood of school failure. Pharmacologic intervention targeting the prodromal symptoms is not recommended, given the uncertain riskbenefit ratio.

Introduction

The onset of schizophrenia is defined as the onset of psychosis occurring in late adolescence or early adulthood for approximately 70% of affected individuals [1]. Frank psychosis is heralded by a prodromal stage for most patients (approximately 80%), with the time from the onset of the first prodromal symptom to frank psychosis on average of approximately 3 years—ranging from a few days to a decade or longer [2–4,5•].

Individuals with schizophrenia describe the prodrome to include gradually worsening visual, auditory, olfactory, or tactile misperceptions, suspiciousness, referential thinking, odd ideas, distractibility and other subjective cognitive deficits, dysphoric mood, mood lability, and sleep disturbance. [2,6,7]. The prodromal symptoms may lead to disruptive or impulsive behaviors, aggression, or suicidality, and often may impair function socially and vocationally. Approximately 70% to 75% of individuals who develop schizophrenia report a decline in school function and social withdrawal as prodromal symptoms emerge and worsen [2,6]. Longitudinal studies find that individuals who later went on to develop schizophrenia performed at approximately the level of or slightly lower than their peers in grade school and middle school; however, by high school, performance significantly declined and was well below average [8••,9]. As many as 15% to 20% of individuals with schizophrenia report self-har behaviors during the prodrome or at onset of psychosis [2,6].

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Despite the development of subjectively distressing and objectively dysfunctional symptoms, it is likely that many individuals do not seek help from health care providers for the prodromal symptoms. For example, a recent retrospective study of 86 individuals at first treatment for schizophrenia found that 62% made no attempts to receive help before developing psychosis [10]. Approximately one third of patients sought help from a family physician, another one third sought help from a mental health care professional, approximately 16% from a school teacher or counselor, and the remaining from clergy, friends, or emergency services. A wide variety of prodromal symptoms, with the most common being dysphoric moods (30.4%), attenuated positive symptoms (17.8%), and functional decline (19.2%), prompted individuals to seek help. Serious behavioral disturbances, including aggression (1.2%) and suicidality (4.8%), occurred in a minority of patients.

There are at least two reasons prompting efforts to identify individuals in the prodromal stage of illness, before the development of psychosis. First, prodromal identification offers the opportunity for preventative interventions, potentially avoiding the trauma, dangerous behaviors, hospitalization and other costly emergency interventions, and stigma associated with psychosis. Second, the prodromal stage involves potentially distressing and functionally disabling symptoms that may themselves be targets of intervention.

Defining the Prodrome

Adolescence is a time of emotional, social, and intellectual change, and some of the symptoms retrospectively described by patients with schizophrenia may not appear pathologic but rather part of normal adolescent development. Perceptual abnormalities, ideas of reference, excessive suspiciousness, or other odd beliefs may transiently occur in 5% to 10% of the general population, although these symptoms typically do not impact function [11–13].

In addition to being part of normal “adolescent angst,” prodromal symptoms may be early warning signs of other mental illnesses, including other psychotic disorders, such as bipolar disorder or substance-induced psychosis, an anxiety disorder, a mood disorder, or a personality disorder. The nonspecific nature of prodromal symptoms has led researchers to refer to prodromal symptoms as “high risk” or “basic” symptoms, because individuals experiencing these symptoms may not necessarily develop a psychotic disorder. Additionally, it may be that psychotic disorders, including psychotic mood disorders, schizophrenia, schizophreniform, schizoaffective disorders, psychosis not otherwise specified, and brief psychotic disorders, will have similar clinical presentation in the prodromal stage.

Despite the nonspecificity of prodromal symptoms, there have been successful preliminary attempts to develop prodromal diagnostic criteria. The “ultra–high-risk” criteria include three categories—attenuated positive symptoms, brief limited intermittent psychotic symptoms, or functional decline in a person at risk for psychosis (because of meeting criteria for schizotypal personality disorder or to having a first-degree relative with a psychotic disorder) [14]. The “ultra–high-risk” criteria have been modified in the Criteria of

Prodromal Syndromes (COPS) [15]. Modifications include anchoring the actual attenuated positive symptoms to the Scale of Prodromal Symptoms (SOPS), and requiring a recent onset or worsening of symptoms (Table 1). A third set of criteria is used by a German early recognition clinic; FETZ (FruhErkennungs und TherapieZentrum fur Psychische Krisen) is based on Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised prodromal criteria and a subset of "basic symptoms" (discussed later) [16]. Subjects must experience at least two of the following symptoms to meet FETZ criteria for prodromal syndrome: social withdrawal or isolation, marked impairment in role function, odd beliefs or magical thinking, ideas of reference, perseverance of thought, thought interference, perceptual abnormalities, impaired ability to interact socially, and increased emotional reactivity in response to every day events.

In addition to the prodromal syndrome diagnostic criteria, there are three rating scales specifically designed to evaluate presence and severity of prodromal symptoms. The Comprehensive Assessment of At-Risk Mental State (CAARMS) evaluates seven areas, including the following: 1) attenuated positive symptoms (thought content, perceptual abnormalities, and disorganized speech); 2) subjective and objective cognitive change; 3) subjective and objective blunting or inappropriate affect; 4) negative symptoms (alogia, avolition, and anhedonia); 5) behavioral change (social isolation, impaired role function, disorganized or odd behaviors, and aggression or dangerous behaviors); 6) motor changes (subjective changes in bodily sensations, autonomic function, motor function, and object changes in motor function); and 7) general psychopathology (mania, depression, suicidality, mood lability, anxiety, obsessive-compulsive disorder, dissociative symptoms, and impaired tolerance to normal stress) [17,18]. The SOPS evaluates 19 symptoms, including five attenuated positive symptoms (Table 1), six negative symptoms (social isolation, avolition, decreased expression of emotion, experience of emotion, ideational richness, and role functioning), four disorganization symptoms (odd appearance, bizarre thinking, poor focus/attention, and poor hygiene), and three general symptoms (sleep disturbance, dysphoric mood, motor disturbance, and decreased stress tolerance) [19]. The Schizophrenia Prediction Instrument adult version is a modification of the Bonn Scale for the Assessment of Basic Symptoms [5•,20,21]. The Schizophrenia Prediction Instrument rates 40 "basic symptoms" in six categories: overstrain, emotional deficits, cognitive impairments, cognitive disturbances, perception and motor disturbances, and body perception disturbances.

Psychosis liability estimates vary from 10% to 70%, depending on the length of follow-up and the criteria used to categorize the subject as prodromal. The largest study has observed 104 individuals meeting "ultra–high-risk" criteria. By 6 months, 29 subjects had developed psychosis (Kaplan- Maier risk estimate 27%), and by 12 months, 36 subjects had progressed to psychosis (Kaplan-Maier risk estimate 35%) [22•]. Additional subjects have developed psychosis after 12- month follow-up, and so the ultimate risk of psychosis is not yet known. A second research group using the "ultra–highrisk" criteria found that three of 23 patients (13%) developed psychosis after 6 months of follow-up [23]. Using the COPS criteria, seven of 13 (54%) subjects in one cohort, four of eight (50%) subjects in second cohort, and 12 of 27 (44%) subjects in a third cohort developed psychosis after 1 year [19,24,25]. Based on the presence of at least one "basic symptom," 77 of 110 (70%) individuals developed schizophrenia after an average follow-up period of 9.6 years [5•]. Finally, based on the

FETZ criteria, five of 51 subjects (10%) developed psychosis after 15 months of follow-up [16].

With risk prediction there is concern about false-positive and false-negative results. The predictive accuracy may be quantified by the specificity (*eg*, to correctly identify who *will not* become ill of all of those who *do not* eventually become ill) and sensitivity (to correctly identify who *will* become ill from all those who eventually become ill) of the criteria. A set of criteria with low sensitivity will miss many people who are indeed at risk. Of perhaps more concern with criteria used to identify a person as at risk for a psychotic disorder is the specificity, because falsely identifying someone as "at risk" may lead to undue worry and concern, may be potentially stigmatizing, and may result in inappropriate treatment. The success of risk prediction is always limited by the underlying rate of illness. Because schizophrenia is relatively rare, with an estimated lifetime risk of one per 100, even criteria with high specificity (close to 100%) will have many more false-positive results than true-positive results (Tables 2–4) [26].

There is preliminary evidence regarding the sensitivity and specificity of prodromal syndrome diagnostics. Based on one small study, the 1-year COPS sensitivity was estimated as 100% (95% confidence interval [CI] 59% to 100%), and specificity as 73% (95% CI 50% to 89%) [19]. Based on the presence of at least one basic symptom, the diagnostic sensitivity was 98% and specificity was 59% to predict risk of schizophrenia over an average 9-year period [5•].

Strategies are needed to determine specific risk for psychosis, because as many as one third of individuals who meet prodromal syndrome criteria based on the COPS or ultra–high-risk criteria appear to be at risk for a major psychiatric disorder other than a psychotic disorder. In a cohort of 49 individuals meeting ultra–high-risk criteria, the most common outcome was a psychotic disorder (41%), including schizophrenia (27%), schizoaffective disorder (2%), bipolar disorder with psychotic features (2%), major depression with psychotic features (4%), brief psychotic disorder (2%), and psychotic disorder not otherwise specified (4%). However, another 31% met criteria for another Axis I disorder—mostly major depression and anxiety disorders. Only a minority of subjects (25%) did not meet diagnostic criteria for a mental disorder during the 1-year follow-up period [27].

Improving Risk Prediction?

Efforts are underway to better predict risk of psychosis in individuals experiencing prodromal symptoms. The goal is to increase the specificity (*eg*, decrease the proportion of "false-positive results") of psychosis prediction by examining clinical and biologic risk markers in individuals who meet prodromal risk diagnostic criteria. This strategy is likely to reduce the proportion of false-positive results when the criteria are applied to groups of individuals with a higher risk of a disorder.

Preliminary results indicate that this strategy may prove to be successful. For example, within individuals who meet ultra–high-risk criteria for prodromal syndrome, those that had longer duration of symptoms (>5 years), worse global function (Global Assessment of Function score <40), family history and attenuated positive symptoms, or subjective

attentional deficits (Scale for the Assessment of Negative Symptoms attention >2) were more likely to develop psychosis within 1 year than those without these clinical features [22•]. The sensitivity and specificity of the individual criteria varied (sensitivity 8% to 31%; specificity 93% to 100%). A regression model requiring at least one of the four criteria resulted in the sensitivity within this high risk group of 60% and specificity of 93%. These criteria were quite successful at identifying who would not become ill (*eg*, high specificity). A two-stage screening process is likely to lead to identification of a group of individuals with very high-risk of psychosis (Table 4). Minimizing the number of false-positive results will be especially important for preventative interventions to avoid exposing individuals who will not benefit from the risks of the intervention.

Longitudinal studies of the offspring of individuals with schizophrenia indicate other potential clinical characteristics that may improve prodromal state risk prediction. These studies consistently find that impairments in attention, verbal memory, executive function, motor skills social function, and school function in childhood predict subsequent risk of schizophrenia [28•]. Several studies have found intelligence quotient or performance on standardized tests of academic performance to decline during adolescence before the emergence of frank psychosis [8••,9,29•,30].

There is preliminary evidence that neurocognitive function may prove to be a useful secondary risk predictor in individuals with prodromal symptoms. Studies find neurocognitive function impaired in individuals with prodromal symptoms compared with healthy individuals [16,31]. One preliminary study suggests that poor performance on tests of spatial working memory is associated with risk of psychosis in individuals with prodromal symptoms [32].

Finally, there is evidence that individuals at highest risk of psychosis may show other deficits found in individuals at their first episode of schizophrenia. For example, one study has found that impairments in olfactory identification ability are associated with risk of psychosis in individuals meeting ultra–high-risk [33]. A second study in an overlapping group of individuals meeting ultra–high-risk criteria also found that those individuals who developed psychosis had lower right medial temporal, lateral temporal, and inferior frontal cortical volumes than those who did not develop psychosis [34•].

As with cardiovascular disease and diabetes risk prediction, it is likely that psychosis risk prediction will involve sequential screening strategies. The hope is to improve diagnostic sensitivity and specificity to target those individuals at highest risk.

Early Identification and Intervention

There is emerging consensus that the emergence of subclinical, attenuated positive symptoms may indicate an “at-risk” state for a psychotic disorder. The various rating scales and diagnostic criteria continue require further study before these will be ready for general clinical use. However, clinicians may be faced with a distressed patient who reports onset of attenuated positive symptoms and functional decline, in addition to many other disturbances in mood and behavior. The symptoms do not meet diagnostic criteria for a specific disorder;

however, the dysfunctional and distressing nature of the symptoms warrants intervention. It may be prudent to consider this patient as “at risk.”

Identification as “at risk” is an intervention that involves risks as well as benefits. The sizable proportion of individuals identified as “at risk” using current diagnostic criteria that do not, in fact, develop a psychotic disorder may become anxious or risk stigmatization from the association with schizophrenia or psychosis risk. The risk of undue anxiety and stigmatization may be mitigated by emphasizing the nonspecificity of these symptoms to the patient, family, and involved others, and avoiding use of terms (*eg*, prodromal symptoms) that imply that a person is actually in the early stages of a psychotic disorder. For example, McGorry *et al*. [35] suggest the term *at-risk mental state* to convey the potential but not certain risk of a psychotic disorder.

Although there is little systematic study, early identification offers the hope that functional decline may be addressed. For example, individuals with prodromal symptoms may present with a decline in academic performance, and intervention to adjust academic demands or provide extra help could increase the likelihood of staying in school and of graduation. In addition, psychotherapy could conceivably reduce distress over specific symptoms, or improve coping with prodromal symptoms. Enhanced symptom monitoring may lead to prompt identification of a treatable Axis I disorder. This is especially important with schizophrenia spectrum psychotic disorders, in which delays in treatment are associated with decreased likelihood of symptom remission [36]. Early identification and prompt treatment of a psychotic disorder could potentially decrease likelihood of hospitalization, risk of aggressive or suicidal behaviors, and risk of behaviors that may be embarrassing or criminal. In addition, because prodromal symptoms are relatively nonspecific, there is a risk of misdiagnosis and inappropriate treatment. For example, psychostimulants may be prescribed for the deficits in attention and distractibility that are common in the prodrome, risking precipitation of psychosis [37]. Thus, identification as *at-risk mental state* may reduce the risk of premature diagnosis and inappropriate treatment.

There have been two clinical trials that have examined the impact of antipsychotic treatment in individuals with prodromal symptoms. The most methodologically rigorous is a 12-month multicenter, randomized, double-blind clinical trial comparing olanzapine (5 to 15 mg per day) with placebo in 60 subjects who met COPS criteria (Table 1) [38,39]. The study also included a 1-year post-treatment follow-up period. Preliminary data are available from this trial [40]. The mean age of the study subjects was 17.7 years and 65% were males. In the olanzapine treated subjects, five of 31 (16%) compared with 11 of 29 (38%) of the placebo-treated subjects developed psychosis in the active treatment phase of the study (McGlashan, Personal communication). Olanzapine treatment also was associated with significant reductions in the severity of the “positive” prodromal symptoms (perceptual abnormalities, suspiciousness, unusual thought content, and grandiosity; P=0.002) [41••]. Prodromal symptom severity significantly increased with active medication withdrawal in the olanzapine-treated subjects. The olanzapine-treated subjects gained, on average, 8.8 kg compared with 0.3 kg in placebo- treated subjects.

The second trial was a 6-month randomized, open-label comparison of risperidone (mean dose 1.3 mg per day) and cognitive-behavioral therapy compared with “needs based intervention” in 59 subjects who met “ultra–high-risk” criteria for prodromal state [42••]. The study also included a 6- month post-treatment follow-up period. The mean age of the study subjects was 20 years (range 14 to 28 years) and 58% were male patients. In the risperidone plus cognitive-behavioral therapy–treated subjects, three of 31 (10%), compared with 10 of 28 (36%) of the “needs-based” group, developed psychosis in the active treatment phase of the study (P=0.03). At the end of the 6-month follow-up treatment period, three additional subjects, all from the specific intervention group, developed psychosis. In the specific intervention group, 14 subjects were fully compliant and 17 were partially compliant. Only one (7%) of the fully compliant subjects developed psychosis by the end of 1 year compared with five (29%) of the partially compliant subjects. It is not known whether the antipsychotic, the therapy, or a combination of the two were effective in reducing psychosis risk. Antidepressant use was not associated with psychosis risk. Unfortunately, adverse effects were not reported, making evaluation of the risk-benefit ratio difficult. However, clinical trials using risperidone in psychotic adolescents suggest that risperidone treatment is likely to be associated with weight gain, as well as neurologic and other side effects [43].

Psychotherapeutic interventions may be effective at reducing risk of psychosis individuals experiencing prodromal symptoms. Theoretically, psychotherapeutic interventions may impact psychosis by reducing the impact of stressful events, including the stress of the emerging symptoms. Preliminary data from an ongoing randomized trial of cognitive therapy in 58 individuals meeting “ultra–high-risk” criteria found that risk of developing psychosis and of antipsychotic treatment was significantly less in treated compared with untreated subjects [23]. Psychotherapeutic intervention is an attractive preventative strategy, because of the presumed minimal side effects associated with this treatment.

Conclusions

Available studies support the notion that pharmacologic and nonpharmacologic interventions may reduce the risk of psychosis in individuals experiencing prodromal symptoms; however, the relative risks and benefits have not yet been systematically investigated. The major obstacle to develop and systematically test preventative intervention strategies is the need for criteria with greater specificity to minimize the exposure of individuals not truly at risk to the risks of treatment.

Until more is known, current treatment guidelines recommend close monitoring for development of diagnosable disorders, dangerous behaviors, distress, and functional decline [44]. Therapeutic interventions should address identified problems, including supportive or cognitive therapies to reduce the functional consequences of the presenting symptoms, family interventions to reduce family distress and improve coping, and intervention with schools to decrease likelihood of school failure. The patient and family may benefit from education about the symptoms of mood or psychotic disorders, and from the development of a plan of action should symptoms worsen, or suicidal or aggressive ideation or behaviors occur. Pharmacologic intervention targeting the prodromal symptoms is *not recommended*,

given the uncertain risk-benefit ratio. Clinicians should recognize the potential side effects of medication treatment, and the risk of unnecessarily exposing individuals who are not in the early stages of psychotic disorder to the risks of antipsychotic medication. If the patient develops a diagnosable disorder, such as a psychotic or mood disorder, detection and intervention should occur promptly.

Secondary prevention of schizophrenia and other psychotic disorders is a conceivable goal within the decade. In addition to antipsychotic drugs, a variety of neuroprotective pharmacologic agents, such as antioxidant drugs that target *N*-methyl-D-aspartate glutamate receptors or gamma-aminobutyric acid receptors deserve investigation as potential preventative pharmacologic treatment strategies. Until effective specific interventions are developed, close monitoring of high-risk individuals and symptom-based intervention is likely to minimize the trauma associated with a first psychotic episode, minimize disability, and improve outcomes.

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References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

• Of importance

•• Of major importance

1. Hafner H, an der Heiden W. Epidemiology of schizophrenia. Can J Psychiatry. 1997; 42:139–151. [PubMed: 9067063]
2. Yung AR, McGorry PD. The initial prodrome in psychosis: descriptive and qualitative aspects. Aust N Z J Psychiatry. 1996; 30:587–599. [PubMed: 8902166]
3. Yung AR, McGorry PD. The prodromal phase of first-episode psychosis: past and current conceptualizations. Schizophr Bull. 1996; 22:353–370. [PubMed: 8782291]
4. Gross G. The onset of schizophrenia. Schizophr Res. 1997; 28:187–198. [PubMed: 9468353]
5•. Klosterkotter J, Hellmich M, Steinmeyer EM, Schultze-Lutter F. Diagnosing schizophrenia in the initial prodromal phase. Arch Gen Psychiatry. 2001; 58:158–164. [PubMed: 11177117] [Of importanceThis article describes the results of a 9-year prospective study examining psychosis risk prediction with the Bonn Scale for the Assessment of Basic Symptoms in 160 individuals seeking help. The study reports good sensitivity and specificity for individual symptoms, and also for a risk prediction scale based on the most predictive symptoms.]
6. Tan HY, Ang YG. First-episode psychosis in the military: a comparative study of prodromal symptoms. Aust N Z J Psychiatry. 2001; 35:512–519. [PubMed: 11531734]
7. Perkins DO, Leserman J, Jarskog LF, et al. Characterizing and dating the onset of symptoms in psychotic illness: the Symptom Onset in Schizophrenia (SOS) inventory. Schizophr Res. 2000; 44:1–10. [PubMed: 10867307]
8••. Fuller R, Nopoulos P, Arndt S, et al. Longitudinal assessment of premorbid cognitive functioning in patients with schizophrenia through examination of standardized scholastic test performance. Am J Psychiatry. 2002; 159:1183–1189. [PubMed: 12091197] [Of major importanceThis study is one of the first “retrospective prospective” longitudinal studies of academic performance in grades 4, 8, and 11. Individuals who subsequently developed schizophrenia performed slightly worse than average in grades 4 and 8, but had a significant decline in function by grade 11. The

findings of this study suggest that there may be subtle premorbid impairments in cognition. The emergence of further cognitive dysfunction as an early symptom of schizophrenia highlights the potential importance of early identification and treatment to impact function and recovery.]

9. Ang YG, Tan HY. Academic deterioration prior to first episode schizophrenia in young Singaporean males. Psychiatry Res. 2004; 121:303–307. [PubMed: 14675749]
10. Addington J, van Mastrigt S, Hutchinson J, Addington D. Pathways to care: help seeking behaviour in first episode psychosis. Acta Psychiatr Scand. 2002; 106:358–364. [PubMed: 12366470]
11. McGorry PD, McFarlane C, Patton GC, et al. The prevalence of prodromal features of schizophrenia in adolescence: a preliminary survey. Acta Psychiatr Scand. 1995; 92:241–249. [PubMed: 8848947]
12. Tien AY. Distributions of hallucinations in the population. Soc Psychiatry Psychiatr Epidemiol. 1991; 26:287–292. [PubMed: 1792560]
13. van Os J. Is there a continuum of psychotic experiences in the general population? Epidemiol Psichiatr Soc. 2003; 12:242–252. [PubMed: 14968483]
14. Phillips LJ, Yung AR, McGorry PD. Identification of young people at risk of psychosis: validation of Personal Assessment and Crisis Evaluation Clinic intake criteria. Aust N Z J Psychiatry. 2000; 34(suppl):S164–169. [PubMed: 11129303]
15. Miller TJ, McGlashan TH, Rosen JL, et al. Prodromal assessment with the structured interview for prodromal syndromes and the scale of prodromal symptoms: predictive validity, interrater reliability, and training to reliability. Schizophr Bull. 2003; 29:703–715. [PubMed: 14989408]
16. Hambrecht M, Lammertink M, Klosterkotter J, et al. Subjective and objective neuropsychological abnormalities in a psychosis prodrome clinic. Br J Psychiatry Suppl. 2002; 43:S30–S37. [PubMed: 12271798]
17. Yung AR, McGorry PD, McFarlane CA, et al. Monitoring and care of young people at incipient risk of psychosis. Schizophr Bull. 1996; 22:283–303. [PubMed: 8782287]
18. Yung, AR.; Phillips, LJ.; McGorry, P., et al. The Comprehensive Assessment of At-risk Mental States (CAARMS). Victoria, Australia: University of Melbourne; 2000.
19. Miller TJ, McGlashan TH, Rosen JL, et al. Prospective diagnosis of the initial prodrome for schizophrenia based on the Structured Interview for Prodromal Syndromes: preliminary evidence of interrater reliability and predictive validity. Am J Psychiatry. 2002; 159:863–865. [PubMed: 11986145]
20. Gross, G.; Huber, G.; Klosterkotter, J.; Linz, M. Bonn Scale for the Assessment of Basic Symptoms. New York: Springer-Verlag; 1987.
21. Ruhrmann S, Schultze-Lutter F, Klosterkotter J. Early detection and intervention in the initial prodromal phase of schizophrenia. Pharmacopsychiatry. 2003; 36(suppl):S162–S167. [PubMed: 14677074]
22•. Yung AR, Phillips LJ, Yuen HP, McGorry PD. Risk factors for psychosis in an ultra high-risk group: psychopathology and clinical features. Schizophr Res. 2004; 67:131–142. [PubMed: 14984872] [Of importanceThis is one of the first attempts to use sequential screening strategies (*eg*, a “close in” approach) to enhance specificity (and thereby reduce false-positive results) of psychosis risk prediction.]
23. Morrison AP, French SA, Walford L, et al. A randomized controlled trial of cognitive therapy for the prevention of psychosis in people at ultra-high risk. Schizophr Res. 2004; 67:7.
24. Woods SW, Miller TJ, McGlashan TH. The prodromal patient: both symptomatic and at risk. CNS Spectrums. 2001; 6:223–232. [PubMed: 16951657]
25. Haak DC, Perkins DO, Graham KA, et al. Risk of psychosis in individuals experiencing prodromal symptoms. Schizophr Res. 2004; 67:33.
26. Perkins DO. Markers for schizophrenia. Am J Psychiatry. 2000; 157:1527. [PubMed: 10964884]
27. Yung AR, Phillips LJ, Yuen HP, et al. Psychosis prediction: 12- month follow up of a high-risk (“prodromal”) group. Schizophr Res. 2003; 60:21–32. [PubMed: 12505135]
28•. Niemi LT, Suvisaari JM, Tuulio-Henriksson A, Lonnqvist JK. Childhood developmental abnormalities in schizophrenia: evidence from high-risk studies. Schizophr Res. 2003; 60:239–

258. [PubMed: 12591587] [Of importanceThis article comprehensively reviews the premorbid risk prediction literature.]

29•. Cosway R, Byrne M, Clafferty R, et al. Neuropsychological change in young people at high risk for schizophrenia: results from the first two neuropsychological assessments of the Edinburgh High Risk Study. Psychol Med. 2000; 30:1111–1121. [PubMed: 12027047] [Of importanceAn early report from the Edinburgh High-Risk Study, after the offspring of individuals with schizophrenia from adolescents, before the onset of psychosis, through the age of risk. The Edinburgh High-Risk Study potentially will further our understanding of the progressive symptomatic and neuropathologic processes underlying the development of psychosis.]

30. Rabinowitz J, Reichenberg A, Weiser M, et al. Cognitive and behavioural functioning in men with schizophrenia both before and shortly after first admission to hospital: crosssectional analysis. Br J Psychiatry. 2000; 177:26–32. [PubMed: 10945084]

31. Hawkins KA, Addington J, Keefe RS, et al. Neuropsychological status of subjects at high risk for a first episode of psychosis. Schizophr Res. 2004; 67:115–122. [PubMed: 14984870]

32. Wood SJ, Pantelis C, Proffitt T, et al. Spatial working memory ability is a marker of risk-for-psychosis. Psychol Med. 2003; 33:1239–1247. [PubMed: 14580078]

33. Brewer WJ, Wood SJ, McGorry PD, et al. Impairment of olfactory identification ability in individuals at ultra-high risk for psychosis who later develop schizophrenia. Am J Psychiatry. 2003; 160:1790–1794. [PubMed: 14514492]

34•. Pantelis C, Velakoulis D, McGorry PD, et al. Neuroanatomical abnormalities before and after onset of psychosis: a cross sectional and longitudinal MRI comparison. Lancet. 2003; 361:281–288. [PubMed: 12559861] [Of importanceThis study reports the results of one of the first prospective neuroimaging studies of individuals before the development of psychosis.]

35. McGorry PD, Yung A, Phillips L. Ethics and early intervention in psychosis: keeping up the pace and staying in step. Schizophr Res. 2001; 51:17–29. [PubMed: 11479062]

36. Perkins, DO.; Lieberman, JA.; Gu, H., et al. Predictors of antipsychotic treatment response in patients with first-episode schizophrenia, schizoaffective, and schizophreniform disorders. Br J Psychiatry. 2004. in press

37. DelBello MP, Soutullo CA, Hendricks W, et al. Prior stimulant treatment in adolescents with bipolar disorder: association with age at onset. Bipolar Disord. 2001; 3:53–57. [PubMed: 11333062]

38. McGlashan TH, Zipursky RB, Perkins D, et al. The PRIME North America randomized double-blind clinical trial of olanzapine versus placebo in patients at risk of being prodromally symptomatic for psychosis, I: study rationale and design. Schizophr Res. 2003; 61:7–18. [PubMed: 12648731]

39. Miller TJ, Zipursky RB, Perkins D, et al. The PRIME North America randomized double-blind clinical trial of olanzapine versus placebo in patients at risk of being prodromally symptomatic for psychosis, II: baseline characteristics of the “prodromal” sample. Schizophr Res. 2003; 61:19–30. [PubMed: 12648732]

40. McGlashan TH, Zipurksy RB, Perkins DO, Addington J. Olanzapine for treatment of the schizophrenia prodrome: 2- year results of a randomized placebo-controlled study. Schizophr Res. 2004; 67:164.

41••. Woods SW, Breier A, Zipursky RB, et al. Randomized trial of olanzapine versus placebo in the symptomatic acute treatment of the schizophrenic prodrome. Biol Psychiatry. 2003; 54:453–464. [PubMed: 12915290] [Of major importanceThis study reports the results of a double-blind, placebo-controlled clinical trial of olanzapine in the treatment of prodromal symptoms. The study finds that prodromal symptoms significantly improve with olanzapine.]

42••. McGorry PD, Yung AR, Phillips LJ, et al. Randomized controlled trial of interventions designed to reduce the risk of progression to first-episode psychosis in a clinical sample with subthreshold symptoms. Arch Gen Psychiatry. 2002; 59:921–928. [PubMed: 12365879] [Of major importanceThis study reports the results of a clinical trial comparing psychotherapy plus risperidone with no specific treatment in individuals at high risk of psychosis caused by the presence of prodromal symptoms. The treatment was effective at reducing the risk of psychosis.]

43. Sikich L, Hamer RM, Bashford RA, et al. A pilot study of risperidone, olanzapine, and haloperidol in psychotic youth: a double-blind, randomized, 8-week trial. Neuropsychopharmacology. 2004; 29:133–145. [PubMed: 14583740]

44. Lehman AF, Lieberman JA, Dixon LB, et al. Practice guideline for the treatment of patients with schizophrenia: second edition. Am J Psychiatry. 2004; 161:1–56. [PubMed: 15000267]

Table 1

Comparison of prodromal state diagnostic criteria

Ultra–high-risk	Criteria of Prodromal States (COPS)
Attenuated positive symptom criteria	Attenuated positive symptom criteria
The presence of one or more of the following symptoms: ideas of reference, odd beliefs or magical thinking, paranoid ideation, perceptual disturbance, and odd behavior and appearance of sufficient severity based on the Brief Psychiatric Rating Scale (a rating of 2 or 3 on suspiciousness or unusual thought content scale, 1 or 2 on the hallucinations scale, or 1 to 3 on conceptual disorganization scale) held with some conviction based on rating with the Comprehensive Assessment of Symptoms and History	The presence of one or more of the following symptoms: unusual thought content, suspiciousness, grandiose ideas, perceptual abnormalities, or disorganized communication of sufficient severity (2 to 5), based on the Scale of Prodromal Symptoms rating scale
At least one symptom must have been present at least 1 week and not longer than 5 years	At least one symptom must have begun or significantly worsened during the past year
At least one symptom must occur at a frequency of at least several times per week	At least one symptom must occur at a frequency of once per week
Brief limited intermittent psychotic symptoms (BLIP)	Brief intermittent psychotic symptoms
The presence of one or more of the following symptoms: ideas of reference, odd beliefs or magical thinking, paranoid ideation, perceptual disturbance, and odd behavior and appearance of sufficient severity based on the Brief Psychiatric Rating Scale (a rating of 4 or greater on suspiciousness or unusual thought content scale, 3 or greater on hallucinations scale, or 4 or greater on conceptual disorganization scale) held with strong conviction based on rating with the Comprehensive Assessment of Symptoms and History	The presence of one or more of the following symptoms: unusual thought content, suspiciousness, grandiose ideas, perceptual abnormalities, or disorganized communication at psychotic severity (6), based on the Scale of Prodromal Symptoms rating scale
The BLIP occurred in the past year	The symptom must have begun or significantly worsened in the past 3 months
The duration of the episode is less than 1 week and symptoms resolved spontaneously	The symptom must be present for several minutes a day at least once per month
Trait and state	Genetic risk and deterioration
Schizotypal personality disorder or a first-degree relative with a psychotic disorder	Schizotypal personality disorder or a first-degree relative with a psychotic disorder
Significant decrease in mental state or functioning for at least 1 month and not longer than 5 years (Global Assessment of Functioning of <30 points from premorbid level); the decrease in functioning occurred within the past year	At least a 30% drop in Global Assessment of Functioning score for at least 1 month in the past 12 months, and the current Global Assessment of Functioning is 90% less than the highest Global Assessment of Functioning in the past year

Table 2

Risk assessment

	Actual results		
Test prediction	**Develops psychosis**	**Does not develop psychosis**	**Total**
At risk for psychosis	14	294	308
Not at risk for psychosis	6	686	692
Total	20	980	1000

Assuming that two of every 100 individuals will ultimately develop schizophrenia or a psychotic mood disorder, this means that of a group of 1000, 20 individuals will develop a psychotic disorder and 980 will not. Assuming that the sensitivity of the at-risk criteria is 70%, this means that the criteria will correctly identify 12 but miss 6 individuals truly at risk. Assuming that the specificity is 60%, the test will correctly identify 686 as not at risk, but will misclassify 294 individuals as at risk, even though they are truly not at risk.

Table 3

Risk assessment

	Actual results		
Test prediction	**Develops psychosis**	**Does not develop psychosis**	**Total**
At risk for psychosis	120	240	360
Not at risk for psychosis	80	560	640
Total	200	800	1000

Applying the same criteria to a help-seeking clinical population at a higher risk of a psychotic disorder will reduce the proportion of false-positive results. Assuming that in a clinical help-seeking population that the risk of psychosis is much higher than the general population risk, for example, 20 of every 100 individuals will ultimately develop schizophrenia or a psychotic mood disorder. This means that of 1000 individuals, 200 will develop a psychotic disorder and 800 will not. Assuming that the sensitivity of the at-risk criteria is 60%, this means that the criteria will correctly identify 120 but miss 80 individuals truly at risk. Assuming that the specificity is 60%, the test will correctly identify 560 individuals as not at risk, but will misclassify 240 individuals as at risk, even though they are truly not at risk.

Table 4

Risk assessment

	Actual results		
Test prediction	**Develops psychosis**	**Does not develop psychosis**	**Total**
At risk for psychosis	72	17	89
Not at risk for psychosis	48	223	271
Total	120	240	360

Applying a second round of risk assessment to individuals identified in Table 2 may dramatically improve specificity, but at the expense of sensitivity. The risk criteria in Table 3 identified 360 individuals, 120 of whom are truly at risk and 240 of whom are false-positive. If the second set of risk criteria in this high-risk group has a sensitivity of 60%, then these criteria misclassify 48 additional individuals who develop psychosis as not at risk, and give an overall sensitivity for the two-stage screening process of 36%. If the specificity for the second set of criteria in this high-risk group is 93%, then the two-stage screening process will incorrectly classify only 17 individuals as at risk who truly are not at risk, giving an overall specificity of the two-stage screening process of 98%. Observe that the sensitivity and specificity of the second-stage risk criteria is likely to be very different if applied to a general population.