EDITORIAL

"Early detection and prevention of schizophrenia"

Shyamanta Das
Assistant Professor, Department of Psychiatry, Fakhruddin Ali Ahmed Medical College Hospital, Barpeta, Assam, India

Abstract

The "entrenched level of disability" often associated with schizophrenia often occurs prior to the initial psychotic episode, during the prodromal period. The phenotype of psychotic symptoms extends to subclinical features in the general population. The traditional medical model assumes a categorical view of the schizophrenia syndrome and its core symptoms, in which differences between psychotic symptoms and their normal counterparts are considered to be qualitative. An alternative, dimensional approach assumes that schizophrenia is not a discrete illness entity, but that psychotic symptoms differ in quantitative ways from normal experiences and behaviours. The causes of and pathways to clinical psychotic disorder can be studied long before the disorder becomes clinically relevant. Delusional or hallucinatory experiences are much more frequent in subjects from the general population than the prevalence of cases of psychotic disorders, thereby suggesting the existence of a symptomatic continuum between subjects from the general population and clinical cases of psychosis. The ultra-high risk or prodromal state is an undifferentiated mix of clinical features, which may include subthreshold or even intermittent suprathreshold psychotic symptoms. Psychological and psychosocial interventions, either alone or in combination with pharmacotherapy, may be effective in at least delaying, if not preventing, the onset of a psychotic disorder. Some highly significant predictors of psychosis were found. It may be justifiable to target these individuals for intensive monitoring of mental state and even low-dose neuroleptic medication or other biological and psychosocial treatments depending on clinical condition. All this adds up to an approach that is called the 'clinical staging model.' That is, less-differentiated, early phases of psychiatric disorders benefit from broad-spectrum, simpler treatments. Subthreshold disorders – syndromes that do not meet the threshold for formal diagnostic entities – are associated with suffering, impairment, and disability; yet they are not classified by psychiatry's formal diagnostic systems. The field of schizophrenia research is alive with interest in the clues that early detection and treatment may hold for prevention of this disorder.

Das S. "Early detection and prevention of schizophrenia." Dysphrenia. 2012;3:107-11.
Keywords: Prodrome. Psychosis. Subthreshold. Intervention. Prediction.
Correspondence: shyamanta_das@rediffmail.com

The theme of the midterm continuing medical education (CME) of the Indian Psychiatric Society, Assam State Branch held in Guwahati on 2 June 2012 was "Early detection and prevention of schizophrenia."

While the primary prevention of schizophrenia on a population level may remain a somewhat distant goal, early detection and intervention strategies are promising in terms of the secondary prevention of schizophrenia and related psychotic disorders.[1] Interest in this area was stimulated in part by the 1994 Institute of Medicine (IOM) report entitled "Reducing risks for mental disorders: frontiers for preventive intervention research."[2] The "entrenched level of disability" often associated with schizophrenia (e.g. social withdrawal, dropping out of school, substance use, and other social collateral damage) often occurs prior to the initial psychotic episode, during the prodromal period.[3] However, a significant portion of patients who have the same clinical phenotype as the prodrome do not go on to develop a psychotic illness.[1] Symptoms may resolve or patients may develop another illness, such as major depression.[1] Thus, for researchers attempting to identify potentially prodromal adolescents and young adults for prospective research, these individuals would be considered false positives.[3] McGorry[3] also described a "false false positive" concept in which patients receive treatment or other protective factors during the prodrome that avert a psychotic episode, thus creating the appearance that the patient had been false positive for the prodrome, but actually the illness had been delayed or prevented. Also of relevance is the recent work suggesting that the phenotype of psychotic symptoms extends to subclinical features in the general population.[3] For example, up to nearly 20% of individuals in the general population endorse some level of minor psychotic experiences.[4-6]

Schizophrenia is a severe mental illness that affects one percent of the population.[4] The diagnosis is made according to current diagnostic systems of the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)[7] and the tenth revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10)[8] on the basis of characteristic 'positive' and 'negative' symptoms.[4] The traditional medical

model assumes a categorical view of the schizophrenia syndrome and its core symptoms, in which differences between psychotic symptoms and their normal counterparts are considered to be qualitative.[4] An alternative, dimensional approach assumes that schizophrenia is not a discrete illness entity, but that psychotic symptoms differ in quantitative ways from normal experiences and behaviours.[4]

Recent work suggested that psychosis might be expressed at subclinical levels.[5] However, the determinants of subclinical psychotic symptoms, the degree of continuity over the life span, and the impact on functioning remain unclear. [5] Thus Rössler et al.[5] analysed the prevalence, determinants, patterns and impact of subclinical psychotic symptoms in a community cohort over a 20-year period. The Zurich Study - a longitudinal community study - started in 1979 with a sample of 591 participants aged 20/21 years.[5] Follow-up interviews were conducted at age 23, 28, 30, 35 and 41.[5] Symptoms were assessed with a semi-structured interview and the symptom checklist 90-revised (SCL90-R). [5] In the analysis where items of the SCL90-R symptom dimensions "paranoid ideation" and "psychoticism" were examined, two distinct symptom dimensions of subclinical psychosis became evident, one representing schizophrenia nuclear symptoms, the other representing schizotypal signs. [5] Cannabis use in adolescence was associated specifically with schizophrenia nuclear symptoms, whereas childhood adversity as well as chronic physical or mental disorders in parents contributed to schizotypal signs.[5] Individuals with a persistently high level of either of the two identified symptom dimensions over 20 years experienced significant deficiencies in social achievement and functioning.[5] Expression of psychotic symptoms in populations is continuous and characterised by differing levels of severity and persistence.[5] A small group of individuals displays persistence of subclinical psychotic symptoms over a period of 20 years.[5] The causes of and pathways to clinical psychotic disorder can be studied long before the disorder becomes clinically relevant.[5]

A growing body of evidence suggests that delusional or hallucinatory experiences are much more frequent in subjects from the general population than the prevalence of cases of psychotic disorders, thereby suggesting the existence of a symptomatic continuum between subjects from the general population and clinical cases of psychosis.[6] Exploring the risk factors modulating the expression of psychosis-like signs in non-clinical populations may better contribute to elucidate the aetiology of psychosis than research restricted to subjects at the endpoint of the distribution of the psychotic dimension.[6]

The ultra-high risk or prodromal state is an undifferentiated mix of clinical features, which may include subthreshold or even intermittent suprathreshold psychotic symptoms.[1] McGorry and his collaborators, particularly Yung, Medical Director of the Personal Assessment and Crisis Evaluation (PACE) Program in Melbourne, Australia[9], defined three types of syndromes to more fully classify the ultra-high-risk state.[10,11] A number of prodromal research programs around the world have demonstrated that the criteria for these three syndromal states predict conversion to psychosis in approximately 20% to 50% of individuals meeting the research criteria.[1]

Intervention in the prodromal phase of schizophrenia and related psychotic disorders may prevent or delay the onset of these disorders, or reduce the severity of the psychosis. [9] Identifying the schizophrenia prodrome is difficult, however, because of its non-specific symptoms and the wide symptom variability between individuals.[9] Over the past 15 years, Yung et al.[9] have investigated the schizophrenia prodrome and developed criteria for detecting people suspected of experiencing a prodromal phase (i.e. they are thought to be at imminent risk of onset of a psychotic disorder). About 35% of those meeting their criteria have developed a psychotic disorder within 12 months.[9] They have established a clinical service, the PACE Clinic, for people with suspected incipient psychosis, and trialled interventions aimed at preventing or delaying the onset of psychotic disorders. Their results and studies in other countries seem to indicate that psychological and psychosocial interventions, either alone or in combination with pharmacotherapy, may be effective in at least delaying, if not preventing, the onset of a psychotic disorder.

Intervention in the prodromal phase of schizophrenia and related psychoses may result in attenuation, delay or even prevention of the onset of psychosis in some individuals.[10] However, a prodrome is difficult to recognise prospectively because of its nonspecific symptoms.[10] Yung et al.[10] set out to recruit and follow up subjects at high risk of transition to psychosis with the aim of examining the predictive power for psychosis onset of certain mental state and illness variables. Symptomatic individuals with either a family history of psychotic disorder, schizotypal personality disorder, subthreshold psychotic symptoms or brief transient psychotic symptoms were assessed and followed up monthly for 12 months or until psychosis onset. [10] Twenty of 49 subjects (40.8%) developed a psychotic disorder within 12 months.[10] Some highly significant predictors of psychosis were found: long duration of prodromal symptoms, poor functioning at intake, low-grade psychotic symptoms, depression and disorganisation.[10] Combining some predictive variables yielded a strategy for psychosis prediction with good sensitivity (86%), specificity (91%) positive predictive value (80%) and negative predictive value (94%) within six months.[10] This study illustrates that it is possible to recruit and follow up individuals at ultra high risk of developing psychosis within a relatively brief follow-up period. Despite low numbers some highly significant predictors of psychosis were found.[10] The findings support the development of more specific preventive strategies targeting the prodromal phase for some individuals at ultra high risk of schizophrenia.[10]

The identification of individuals at high risk of developing a psychotic disorder has long been a goal of clinicians because it is thought that early treatment of this group may prevent onset of the disorder.[11] However, little is known of predictive factors of psychosis, even within a high risk group.[11] Yung et al.[11] followed up 104 young people thought to be at ultra high risk for schizophrenia and other psychotic disorders by virtue of having a family history of psychotic disorder combined with some functional decline or the presence of subthreshold or self-limiting psychotic

symptoms. All subjects were therefore symptomatic, but not psychotic, at intake.[11] Thirty-six subjects (34.6%) developed frank psychotic symptoms within 12 months.[11] Measures of symptom duration, functioning, disability and psychopathology were made at intake, six and 12 months.[11] Poor functioning, long duration of symptoms, high levels of depression and reduced attention were all predictors of psychosis.[11] A combination of family history of psychosis, a recent significant decrease in functioning and recent experience of subthreshold psychotic symptoms was also predictive of psychosis.[11] Combining highly predictive variables yielded a method of psychosis prediction at 12 months with good positive predictive value (80.8%), negative predictive value (81.8%) and specificity (92.6%) and moderate sensitivity (60.0%).[11] Within symptomatic high risk group, therefore, it appears possible to identify those individuals who are at particularly high risk of developing a psychotic disorder such as schizophrenia.[11] Given the very high positive predictive value and low false positive rate with this two-step process, it may be justifiable to target these individuals for intensive monitoring of mental state and even low-dose neuroleptic medication or other biological and psychosocial treatments depending on clinical condition.[11] This indicated prevention approach could be further developed and preventive strategies in the psychoses refined.[11]

A sentinel series of randomised controlled trials that include studies from Australia,[12] the United Kingdom,[13] North America,[14] and Austria[15] have given preliminary evidence for the possibility of reducing the risk of conversion from the ultra high risk or prodromal state to frank psychosis.[1]

Most disability produced by psychotic illnesses, especially schizophrenia, develops during the prepsychotic period, creating a case for intervention during this period.[12] However, only recently has it been possible to engage people in treatment during this phase.[12] A randomised controlled trial[12] compared two interventions in 59 patients at incipient risk of progression to first-episode psychosis. McGorry et al.[12] termed this group ultra high risk to emphasise the enhanced risk versus conventional genetic high risk studies. Needs-based intervention was compared with specific preventive intervention comprising low-dose risperidone therapy (mean dosage, 1.3 mg/d) and cognitive behaviour therapy.[12] Treatment was provided for six months, after which all patients were offered ongoing needs-based intervention.[12] Assessments were performed at baseline, six months, and 12 months.[12] By the end of treatment, ten of 28 people who received needs-based intervention progressed to first-episode psychosis versus three of 31 from the specific preventive intervention group (P=.03).[12] After six-month follow-up, another three people in the specific preventive intervention group became psychotic, and with intention-to-treat analysis, the difference was no longer significant (P=.24).[12] However, for risperidone therapy-adherent patients in the specific preventive intervention group, protection against progression extended for six months after cessation of risperidone use.[12] More specific pharmacotherapy and psychotherapy reduces the risk of early transition to psychosis in young people at ultra high risk, although their relative contributions could not be determined.[12] This represents at least delay in onset (prevalence reduction), and possibly some reduction in incidence.[12]

Advances in the ability to identify people at high risk of developing psychosis have generated interest in the possibility of preventing psychosis.[13] Morrison et al.[13] evaluated the efficacy of cognitive therapy for the prevention of transition to psychosis. A randomised controlled trial[13] compared cognitive therapy with treatment as usual in 58 patients at ultra high risk of developing a first episode of psychosis. Therapy was provided over six months, and all patients were monitored on a monthly basis for 12 months.[13] Logistic regression demonstrated that cognitive therapy significantly reduced the likelihood of making progression to psychosis as defined on the Positive and Negative Syndrome Scale over 12 months.[13] In addition, it significantly reduced the likelihood of being prescribed antipsychotic medication and of meeting criteria for a DSM-IV diagnosis of a psychotic disorder.[13] Analysis of covariance showed that the intervention also significantly improved positive symptoms of psychosis in this population over the 12-month period.[13] Cognitive therapy appears to be an acceptable and efficacious intervention for people at high risk of developing psychosis.[13]

McGlashan et al.[14] assessed the efficacy of olanzapine in delaying or preventing conversion to psychosis and reducing symptoms in people with prodromal symptoms of schizophrenia. This randomised trial[14] occurred at four North American clinics in the Prevention Through Risk Identification, Management, and Education project. Outpatients received olanzapine (5-15 mg/day, N=31) or placebo (N=29) during a one-year double-blind treatment period and no treatment during a one-year follow-up period.[14] Efficacy measures included the conversion-to-psychosis rate and Scale of Prodromal Symptoms scores.[14] During the treatment year, 16.1% of olanzapine patients and 37.9% of placebo patients experienced a conversion to psychosis, a nearly significant difference.[14] The hazard of conversion among placebo patients was about 2.5 times that among olanzapine-treated patients, which also approached significance.[14] In the follow-up year, the conversion rate did not differ significantly between groups.[14] During treatment, the mean score for prodromal positive symptoms improved more in the olanzapine group than in the placebo group, and the mixed-model repeated-measures least-squares mean score showed significantly greater improvement between weeks eight and 28 with olanzapine.[14] The olanzapine patients gained significantly more weight (mean=8.79 kg, standard deviation [SD]=9.05, versus mean=0.30 kg, SD=4.24).[14] A significant treatment difference in the conversion-to-psychosis rate was not demonstrated.[14] However, these results may be influenced by low power.[14] The nearly significant differences suggest that olanzapine might reduce the conversion rate and delay onset of psychosis.[14] Olanzapine was efficacious for positive prodromal symptoms but induced weight gain.[14] Further treatment research in this phase of illness is warranted.[14]

The use of antipsychotic medication for the prevention of psychotic disorders is controversial.[15] Long-chain omega-3 (omega-3) polyunsaturated fatty acids (PUFAs) may

be beneficial in a range of psychiatric conditions, including schizophrenia.[15] Given that omega-3 PUFAs are generally beneficial to health and without clinically relevant adverse effects, their preventive use in psychosis merits investigation.[15] Objective of Amminger et al.[15] was to determine whether omega-3 PUFAs reduce the rate of progression to first-episode psychotic disorder in adolescents and young adults aged 13 to 25 years with subthreshold psychosis. Design was randomised, double-blind, placebo-controlled trial conducted between 2004 and 2007.[15] Setting was psychosis detection unit of a large public hospital in Vienna, Austria.[15] Participants were eighty-one individuals at ultra high risk of psychotic disorder.[15] A 12-week intervention period of 1.2-g/d omega-3 PUFA or placebo was followed by a 40-week monitoring period; the total study period was 12 months.[15] The primary outcome measure was transition to psychotic disorder.[15] Secondary outcomes included symptomatic and functional changes.[15] The ratio of omega-6 to omega-3 fatty acids in erythrocytes was used to index pretreatment versus posttreatment fatty acid composition.[15] Seventy-six of 81 participants (93.8%) completed the intervention.[15] By study's end (12 months), two of 41 individuals (4.9%) in the omega-3 group and 11 of 40 (27.5%) in the placebo group had transitioned to psychotic disorder (P=.007).[15] The difference between the groups in the cumulative risk of progression to full-threshold psychosis was 22.6% (95% confidence interval, 4.8-40.4).[15] Omega-3 PUFAs also significantly reduced positive symptoms (P=.01), negative symptoms (P=.02), and general symptoms (P=.01) and improved functioning (P=.002) compared with placebo.[15] The incidence of adverse effects did not differ between the treatment groups.[15] Long-chain omega-3 PUFAs reduce the risk of progression to psychotic disorder and may offer a safe and efficacious strategy for indicated prevention in young people with subthreshold psychotic states.[15]

All this adds up to an approach that is called the 'clinical staging model.'[3] That is, less-differentiated, early phases of psychiatric disorders benefit from broad-spectrum, simpler treatments.[1] As clear target syndromes emerge, more specific interventions can be used.[1] Because the evidence is still accumulating, clinical practice guidelines for youth who appear to be in a prodromal state are fairly conservative, and include tenets like engaging in youth-friendly services, carefully monitoring symptoms, and treating comorbidity.[16] Antipsychotics are generally not recommended unless frank psychotic symptoms emerge.[1]

Clinical high risk for schizophrenia, and more recently, bipolar disorder, in general, is equivalent to the previously described ultra high risk and prodromal states.[1] The marked increase in interest in these areas over the past decade relates to the fact that such research could lead us to more direct pathways to prevention.[1] Four domains that are most representative of the underlying vulnerability for psychosis include cognitive deficits; affective symptoms, especially depression; social isolation; and school failure, which also relates to inability to function in work after the school years.[1] Two particular areas that appear to predict conversion to psychosis are lower verbal learning[17] and social isolation.[18,19]

Research in the line of "Can early symptoms predict the course of schizophrenia?"[20] is relevant to early detection and intervention for schizophrenia by virtue of improved prediction. In terms of the impact of first-rank symptoms on recovery, those with first-rank symptoms were less likely to achieve remission.[20] In clinical samples, it has become clear that negative symptoms and general symptoms precede psychosis, and may precede the onset of other disorders.[20]

Subthreshold disorders – syndromes that do not meet the threshold for formal diagnostic entities – are associated with suffering, impairment, and disability; yet they are not classified by psychiatry's formal diagnostic systems. As such, subthreshold disorders are marginalised as atypical or "not otherwise specified."[21] Over the past decade, there has been increased interest in subthreshold psychiatric syndromes.[22] However, little is known about the natural history and course of subthreshold conditions.[1] For example, do they tend to be self-limiting, progressive, or persistent?[1] Furthermore, virtually nothing is known about the effects of treatments on subthreshold syndromes.[1] Multiple sources of data suggest that subthreshold conditions exist along a continuum with full syndromic disorders, and across many diagnostic categories.[1] Critics tend to focus on the field of psychiatry extending of the boundaries of what is considered a mental disorder, arguing that this is a medicalisation of normal human distress.[1] We don't have enough evidence yet to justify pre-onset pharmacologic treatments due to potential risks of side effects, but we do know that subthreshold conditions are in fact associated with impairment and require further research.[21]

The field of schizophrenia research is alive with interest in the clues that early detection and treatment may hold for prevention of this disorder.[23] Studies in this area include those that aim for early detection both after the onset of psychosis (during the first episode) and before the onset of psychosis (during the prodromal period).[1] The former are exemplified by studies aiming to reduce the duration of untreated psychosis (DUP).[24,25] The latter is exemplified by several controlled studies of interventions during the prodrome[12-15] and the recent work from the North American Prodrome Longitudinal Study (NAPLS) consortium.[18] "Close clinical monitoring, to see if potentially prodromal patients are indeed getting worse, is clinically indicated,"[23] even though much more research is needed on potential pharmacologic treatments during the prodromal period.[1]

The importance of early detection prior to psychosis (during the prodrome) was recognised as early as 1927 by Harry Stack Sullivan,[26] and the research field was launched largely by Yung and McGorry in Melbourne who defined three prodromal syndromes.[10,11]

Further reading

Das S. "Nutrition & Mental Health." Dysphrenia. 2012;3:1-3.

References

1. Compton MT. Advances in the early detection and prevention of schizophrenia. Medscape Psychiatry Ment Health [Internet]. 2008 [cited 2012 Apr 17]. Available from: http://www.google.co.in/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1

&ved=0CFEQFjAA&url=http%3A%2F%2Fwww.medscape.org%2Fviewarticle%2F575910&ei=YmnAT9SbDInTrQfM94DkCQ&usg=AFQjCNE7jt3AI36yd5cGIrGgCNURWGNG7A&sig2=TnVL_A5XPRkA676X4JGzxw

2. Mrazek PJ, Haggerty RJ, editors. Reducing risks for mental disorders: frontiers for preventive intervention research. Washington, DC: National Academy Press; 1994.

3. McGorry P. The prodromal or ultra-high risk stage of schizophrenia and related psychoses: a window for understanding and intervention. Programs and abstracts of the American Psychiatric Association 2008 Annual Meeting; May 3-8, 2008; Washington, DC.

4. Johns LC, van Os J. The continuity of psychotic experiences in the general population. Clin Psychol Rev. 2001;21:1125-41.

5. Rössler W, Riecher-Rössler A, Angst J, Murray R, Gamma A, Eich D, et al. Psychotic experiences in the general population: a twenty-year prospective community study. Schizophr Res. 2007;92:1-14.

6. Verdoux H, van Os J. Psychotic symptoms in non-clinical populations and the continuum of psychosis. Schizophr Res. 2002;54:59-65.

7. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4th ed. Washington, DC: American Psychiatric Association; 1994.

8. World Health Organization. International Statistical Classification of Diseases and Related Health Problems. 10th rev. Geneva: World Health Organization; 1992.

9. Yung AR, McGorry PD, Francey SM, Nelson B, Baker K, Phillips LJ, et al. PACE: a specialised service for young people at risk of psychotic disorders. Med J Aust. 2007;187:S43-6.

10. Yung AR, Phillips LJ, Yuen HP, Francey SM, McFarlane CA, Hallgren M, et al. Psychosis prediction: 12-month follow up of a high-risk ("prodromal") group. Schizophr Res. 2003;60:21-32.

11. 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;67:131-42.

12. McGorry PD, Yung AR, Phillips LJ, Yuen HP, Francey S, Cosgrave EM, 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;59:921-8.

13. Morrison AP, French P, Walford L, Lewis SW, Kilcommons A, Green J, et al. Cognitive therapy for the prevention of psychosis in people at ultra-high risk: randomised controlled trial. Br J Psychiatry. 2004;185:291-7.

14. McGlashan TH, Zipursky RB, Perkins D, Addington J, Miller T, Woods SW, et al. Randomized, double-blind trial of olanzapine versus placebo in patients prodromally symptomatic for psychosis. Am J Psychiatry. 2006;163:790-9.

15. Amminger GP, Schäfer MR, Papageorgiou K, Klier CM, Cotton SM, Harrigan SM, et al. Long-chain omega-3 fatty acids for indicated prevention of psychotic disorders: a randomized, placebo-controlled trial. Arch Gen Psychiatry. 2010;67:146-54.

16. International Early Psychosis Association Writing Group. International clinical practice guidelines for early psychosis. Br J Psychiatry Suppl. 2005;48:s120-4.

17. Lencz T, Smith CW, McLaughlin D, Auther A, Nakayama E, Hovey L, et al. Generalized and specific neurocognitive deficits in prodromal schizophrenia. Biol Psychiatry. 2006;59:863-71.

18. Cannon TD, Cadenhead K, Cornblatt B, Woods SW, Addington J, Walker E, et al. Prediction of psychosis in youth at high clinical risk: a multisite longitudinal study in North America. Arch Gen Psychiatry. 2008;65:28-37.

19. Cornblatt BA, Auther AM, Niendam T, Smith CW, Zinberg J, Bearden CE, et al. Preliminary findings for two new measures of social and role functioning in the prodromal phase of schizophrenia. Schizophr Bull. 2007;33:688-702.

20. Akbiyik DI. Can early symptoms predict the course of schizophrenia? Programs and abstracts of the American Psychiatric Association 2008 Annual Meeting; scientific and clinical report session 6; May 3-8, 2008; Washington, DC.

21. Okasha A. The emergence of subthreshold psychiatry. Programs and abstracts of the American Psychiatric Association 2008 Annual Meeting; International symposium; May 3-8, 2008; Washington, DC.

22. Rucci P, Gherardi S, Tansella M, Piccinelli M, Berardi D, Bisoffi G, et al. Subthreshold psychiatric disorders in primary care: prevalence and associated characteristics. J Affect Disord. 2003;76:171-81.

23. Beardslee WR. Recent advances in prevention science: implications for practice and DSM-V. Programs and abstracts of the American Psychiatric Association 2008 Annual Meeting; symposium 6; May 3-8, 2008; Washington, DC.

24. Larsen TK, Melle I, Auestad B, Friis S, Haahr U, Johannessen JO, et al. Early detection of first-episode psychosis: the effect on 1-year outcome. Schizophr Bull. 2006;32:758-64.

25. Melle I, Larsen TK, Haahr U, Friis S, Johannessen JO, Opjordsmoen S, et al. Reducing the duration of untreated first-episode psychosis: effects on clinical presentation. Arch Gen Psychiatry. 2004;61:143-50.

26. Heinssen RK, McGlashan TH. Advances in early detection, treatment, and prevention of psychosis: findings from the North American prodrome longitudinal study. Programs and abstracts of the American Psychiatric Association 2008 Annual Meeting; symposium 50; May 3-8, 2008; Washington, DC.