PACE: a specialised service for young people at risk of psychotic disorders

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ABSTRACT

- 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.
- Identifying the schizophrenia prodrome is difficult, however, because of its non-specific symptoms and the wide symptom variability between individuals.
- Over the past 15 years, we have investigated the schizophrenia prodrome and developed criteria for detecting people suspected of experiencing a prodromal phase (ie, they are thought to be at imminent risk of onset of a psychotic disorder). About 35% of those meeting our criteria have developed a psychotic disorder within 12 months.
- We have established a clinical service, the PACE (Personal Assessment and Crisis Evaluation) Clinic, for people with suspected incipient psychosis, and trialled interventions aimed at preventing or delaying the onset of psychotic disorders.
- Our 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.

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It is well known that frank psychotic symptoms characteristic of schizophrenia and related disorders are preceded by a prodromal, or forerunner, phase.[1] Although the way prodromal phases manifest varies between patients, certain symptoms and signs frequently described include depressed mood, anxiety, irritability, fatigue, sleep disturbance, social withdrawal, and deterioration in the ability to perform a social role. Self-damaging behaviours, such as self-injury, drug overdose, and substance misuse have also been described. Closer to the onset of full-blown psychotic symptoms, attenuated (or subthreshold) psychotic symptoms tend to occur.[2] Examples include mild suspiciousness and subthreshold transitory auditory hallucinations, such as hearing a murmuring sound that is not a fully formed voice.

The fact that most people who develop psychotic disorders experience a prodrome raises the question: can we detect this early phase and provide intervention? Clearly, if the prodrome can be recognised prospectively and treatment provided at this stage, then disability may be minimised, some recovery may occur before symptoms and poor functioning become entrenched, and it may be possible to prevent, delay or ameliorate the onset of a diagnosable psychotic disorder.

Three things emerge from our knowledge of prodromal symptoms. First, many of them are non-specific; that is, they occur frequently in the prodromes and threshold syndromes of non-psychotic disorders, such as major depression.[3] Second, a number of psychiatric symptoms and considerable disability occur during this prodromal phase.[4,5] Third, those symptoms that seem to be most easily detectable and possibly predictive of psychotic disorders, the attenuated psychotic symptoms,[6] may be targets for early detection and possible intervention.

Although the idea of intervening during the prodromal phase is not new,[7,8] it has been the subject of renewed efforts in the past 10–15 years. An added impetus is that alterations in brain structure occur at some point in the transition from prodromal state to full-blown psychotic disorder.[9] This might herald the beginning of further neurobiological changes as the disorder progresses. It is still unclear exactly when these changes begin; whether they can be prevented, reversed or modified in some way with intervention; and whether there is a point at which irreversible brain damage has occurred and chronic psychotic disorder is inevitable. The possibility that these structural and, presumably, functional changes could be prevented, minimised or reversed makes the idea of prodromal intervention an even more tempting goal.

We review the more recent attempts to detect and intervene in the prodromal phase of psychotic disorders, but first consider what, if any, disadvantages prodromal intervention might entail.

Disadvantages of prodromal intervention

One of the main problems with attempting prodromal intervention is the possibility of "false positives"; that is, people who are identified as being possibly prodromal (at risk of developing a psychotic disorder in the near future), but who do not go on to develop the disorder. Those who are in fact not at risk of developing a psychotic disorder (the "true false positives") may be harmed by being labelled "prodromal" or at "high risk of psychosis" and may receive treatment unnecessarily.[10-14] Individuals who would have developed a psychotic disorder, but some alteration in their circumstances (eg, stress reduction or cessation of illicit drug use) prevented this from occurring have been termed "false false-positives".[4] Clearly, it is impossible to distinguish between these two groups phenotypically at either baseline or follow-up.

The non-specific nature of the most common prodromal features adds to the likelihood of detecting false positives. Indeed, the term "prodrome" should only be used once the full-blown syndrome has developed.[2] Prior to diagnosis with a psychotic disorder, the prodrome should be thought of as a risk factor for psychosis, not as a disease entity (ie, the presence of the syndrome implies that the affected person is at that time more likely to develop psychosis in the near future than someone without the syndrome). However, if the symptoms resolve, then this degree of increased risk may remit as well. In an attempt to deal with these issues, we have coined a new term — the "ultra high risk" (UHR)[4,5] state. We have developed UHR criteria that attempt to identify individuals with a strong likelihood of developing a psychotic disorder in the near future (eg, within 12 months).

Identification of the ultra high risk population

Due to the non-specific nature of prodromal symptoms, there are problems using these features alone to identify people thought to

be at imminent risk of onset of psychotic disorder. Even psychotic-like experiences (attenuated or subthreshold psychotic symptoms) have been found to occur commonly in the general population, especially among adolescents and young adults.[15-18] Using symptoms alone would result in a high false-positive rate. Thus, some added criteria were needed to focus on those most likely to be in the prodromal phase of a psychotic disorder.[19] We added the risk factor of age, as the age of highest incidence of psychotic disorder is adolescence and young adulthood.[20] Clinical need for care was another factor. Thus, the young person must be seeking help, or be identified by someone, such as a parent or teacher, as needing help. This requirement reduces the chance that a well person who happens to have psychotic-like experiences, but who is otherwise functioning adequately and is not distressed, will be unnecessarily treated for imminent psychosis.[21]

We hypothesised that individuals with these multiple risk factors for psychosis would have a high likelihood of developing a psychotic disorder within a short time period. To test this theory, specific operationalised UHR criteria were developed to identify a young person at risk for psychotic disorder.

The UHR criteria require that a person is aged between 14 and 25 years, is referred for health care to a psychiatric service, and meets the criteria for one or more of the following groups:

- *Attenuated psychotic symptoms group:* patients have experienced subthreshold, attenuated positive psychotic symptoms during the past year;
- *Brief limited intermittent psychotic symptoms group:* patients have experienced episodes of frank psychotic symptoms that have not lasted longer than a week and have spontaneously abated; or
- *Trait and state risk factor group:* patients have schizotypal personality disorder or have a first-degree relative with a psychotic disorder and have experienced a significant decrease in functioning during the previous year.

These criteria are described in more detail elsewhere.[4,5] To further reduce the risk that well functioning individuals will be identified, since 2006 we have also required that all patients show a significant deterioration in social or occupational functioning.[21]

Validation of the UHR criteria

To test our model, we established a specialised service for the UHR group — the PACE (Personal Assessment and Crisis Evaluation) Clinic — in Melbourne in 1994. This service was the first clinical and research clinic in the world for individuals considered to have incipient psychosis.[2]

Using the UHR criteria, we found a rate of transition to psychosis within 12 months of about 35%,[4,5] a rate several thousand-fold greater than the expected incidence rate for first-episode psychosis in the general population. This occurred despite the provision of case management and antidepressant medication if required. The primary diagnostic outcome of the group who developed psychosis was schizophrenia (65%). The UHR criteria used in PACE have been adopted by a number of other centres around the world.[22-24]

The PACE clinical service

Detection of cases

The PACE service receives referrals of young people seeking help from agencies such as general practitioners, school and university counselling services, community health services and other support agencies for young people, including drug and alcohol services.[25]

Treatment of people referred to the PACE Clinic

Initially, a case-management model was provided, based around the presenting problems. The added focus of risk and attempted prevention of psychotic disorder was discussed with the patient, but no antipsychotic medication was prescribed.[2,24] We wanted to determine the "natural history" of the UHR syndromes and to examine the false-positive rate. Subsequently, cognitive behaviour therapy and antipsychotic medication were trialled at PACE (see the **Specific treatment** section, below). Case management is provided for those individuals who do not consent to trial involvement.

Providing information about risk of psychosis

Communicating with individuals about their UHR status needs to be done sensitively. The fact that being at risk of a psychotic disorder does not mean that a disorder will invariably follow must be emphasised to patients and their families. Additionally, there is a high degree of pessimism about the outcome attached to a diagnosis of schizophrenia. Providing information about psychotic disorders and the high likelihood of recovery with early treatment is therefore important.[26]

The potential for labelling and stigma should also be discussed with patients.[11,27] Stigmatisation could lead to difficulties obtaining health or life insurance and employment, as well as changes in the way family and friends interact with the person.[28] Confidentiality needs to be assured. Self-stigmatisation could lead to reduced self-esteem, dysphoria, alterations in life goals, and avoiding the normal challenges of maturation, such as dating, moving away from the parental home, and pursuing further education.[28]

Specific treatment aimed at preventing or delaying the onset of psychotic disorders

The first clinical trial in the UHR group was conducted at the PACE Clinic from 1996 to 2000.[29] In this trial, the effect of combined cognitive behaviour therapy plus low-dose antipsychotic medication, risperidone (treatment group; $n = 31$) was compared with supportive therapy (control group; $n = 28$). At the end of the 6-month treatment phase, significantly more subjects in the control group than in the treatment group had developed psychosis ($P = 0.026$). This difference was no longer significant at the end of a 6-month follow-up period after the treatment ($P = 0.16$), although it did remain significant for those members of the treatment group who adhered to the medication regimen. This result suggests that it is possible to delay the onset of a psychotic disorder. Both groups experienced an amelioration of global psychiatric symptoms and improved functioning over the treatment and follow-up phases compared with levels at entry to the study.

A further, longer double-blind randomised controlled trial undertaken in the United States compared olanzapine and placebo.[30] This study found that more participants in the control group than in the treatment group became psychotic within 1 year (37.9% v 16.1%), a difference which approached significance. A trial conducted in the United Kingdom comparing cognitive therapy with monitoring found a significant effect of treatment in reducing transition rate.[31] These results 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. Further research is required to resolve which elements of an intervention are essential at this time point and for how long they need to be applied.

Ongoing evaluation of the UHR criteria and future directions

Some have suggested that the UHR and similar prodromal criteria could be applied widely, even within schools, to identify young people with emerging psychotic disorders.[32] However, one problem with this is that the base rate of psychotic disorders in unselected populations will be much lower than in a help-seeking cohort identified as "possibly prodromal".[33] Even in other clinical populations, the UHR criteria cannot be expected to be as strongly predictive of future psychotic disorder as in the PACE sample,[21] as the individuals referred to PACE are considered to be prodromal by their referrers.

Similarly, any changes in referral pattern to the UHR services may affect transition rate. That is, the rate of developing a psychotic disorder would be expected to decrease as young people were referred earlier in their course of illness, and referral sources expanded to include community sources other than mental health clinics.[21,34]

Thus, ongoing evaluation of the criteria is needed. Lower transition rates due to sampling effects or earlier referral suggest the need for more benign treatments early on and a period of observation, monitoring and treatment of existing problems. Evidence of deterioration and worsening of subthreshold psychotic symptoms could lead to more specific treatment, involving perhaps cognitive therapy in the first instance, or antipsychotic drugs if rapid worsening occurs. This type of service is consistent with the clinical staging model in psychiatry,[35] which emphasises that less differentiated early phases of mental illnesses may benefit from broad-spectrum simpler treatments. This could enable young people to receive the help they need in a timely manner, with the potential for less suffering and improved outcomes.

Competing interests

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References

1 Yung AR, McGorry PD. The prodromal phase of first-episode psychosis: past and current conceptualizations. *Schizophr Bull* 1996; 22: 353-370.
2 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.
3 Hafner H, Maurer K, Trendler G, et al. Schizophrenia and depression: challenging the paradigm of two separate diseases — a controlled study of schizophrenia, depression and healthy controls. *Schizophr Res* 2005; 77: 11-24.
4 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.
5 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.
6 Poulton R, Caspi A, Moffitt TE, et al. Children's self-reported psychotic symptoms and adult schizophreniform disorder: a 15-year longitudinal study. *Arch Gen Psychiatry* 2000; 57: 1053-1058.
7 Meares A. The diagnosis of prepsychotic schizophrenia. *Lancet* 1959; 1: 55-58.
8 Sullivan HS. The onset of schizophrenia. 1927. *Am J Psychiatry* 1994; 151 (6 Suppl): 134-139.
9 Pantelis C, Velakoulis D, McGorry P, et al. Neuroanatomical abnormalities before and after onset of psychosis: a cross-sectional and longitudinal MRI comparison. *Lancet* 2003; 361: 281-288.
10 Corcoran C, Malaspina D, Hercher L. Prodromal interventions for schizophrenia vulnerability: the risks of being "at risk". *Schizophr Res* 2005; 73: 173-184.
11 Cornblatt BA, Lencz T, Kane JM. Treatment of the schizophrenia prodome: is it presently ethical? *Schizophr Res* 2001; 51: 31-38.
12 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.
13 Yung AR, McGorry PD. Is pre-psychotic intervention realistic in schizophrenia and related disorders? *Aust N Z J Psychiatry* 1997; 31: 799-805.
14 Bentall RP, Morrison AP. More harm than good: the case against using antipsychotic drugs to prevent severe mental illness. *J Ment Health* 2002; 11: 351-356.
15 Tien AY. Distributions of hallucinations in the population. *Soc Psychiatry Psychiatr Epidemiol* 1991; 26: 287-292.
16 van Os J, Hanssen M, Bijl RV, Vollebergh W. Prevalence of psychotic disorder and community level of psychotic symptoms: an urban–rural comparison. *Arch Gen Psychiatry* 2001; 58: 663-668.
17 Verdoux H, van Os J. Psychotic symptoms in non-clinical populations and the continuum of psychosis. *Schizophr Res* 2002; 54: 59-65.
18 Johns LC, Cannon M, Singleton N, et al. Prevalence and correlates of self-reported psychotic symptoms in the British population. *Br J Psychiatry* 2004; 185: 298-305.
19 Bell RQ. Multiple-risk cohorts and segmenting risk as solutions to the problem of false positives in risk for the major psychoses. *Psychiatry* 1992; 55: 370-381.
20 Häfner H, Maurer K, Löffler W, Riecher-Rössler A. The influence of age and sex on the onset and early course of schizophrenia. *Br J Psychiatry* 1993; 162: 80-86.
21 Yung AR, Stanford C, Cosgrave E, et al. Testing the ultra high risk (prodromal) criteria for the prediction of psychosis in a clinical sample of young people. *Schizophr Res* 2006; 84: 57-66.
22 Haroun N, Dunn L, Haroun A, Cadenhead K. Risk and protection in prodromal schizophrenia: ethical implications for clinical practice and future research. *Schizophr Bull* 2006; 32: 166-178.

23 Olsen KA, Rosenbaum B. Prospective investigations of the prodromal state of schizophrenia: review of studies. *Acta Psychiatr Scand* 2006; 113: 247-272.
24 Yung AR, Phillips LJ, McGorry PD. Treating schizophrenia in the prodromal phase. London: Taylor and Francis, 2004.
25 Phillips LJ, Yung AR, Hearn N, et al. Preventive mental health care: accessing the target population. *Aust N Z J Psychiatry* 1999; 33: 912-917.
26 McGorry PD, Yung AR. Early intervention in psychosis: an overdue reform. *Aust N Z J Psychiatry* 2003; 37: 393-398.
27 McGlashan TH. Psychosis treatment before psychosis onset: ethical issues. *Schizophr Res* 2001; 51: 47-54.
28 Heinssen RK, Perkins DO, Appelbaum PS, Fenton WS. Informed consent in early psychosis research: National Institute of Mental Health Workshop, November 15, 2000. *Schizophr Bull* 2001; 27: 571-584.
29 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.
30 McGlashan TH, Zipursky RB, Perkins D, et al. Randomized, double-blind trial of olanzapine versus placebo in patients prodromally symptomatic for psychosis. *Am J Psychiatry* 2006; 163: 790-799.
31 Morrison AP, French P, Walford L, et al. Cognitive therapy for the prevention of psychosis in people at ultra-high risk: randomised controlled trial. *Br J Psychiatry* 2004; 185: 291-297.
32 Loewy RL, Bearden CE, Johnson JK, et al. The prodromal questionnaire (PQ): preliminary validation of a self-report screening measure for prodromal and psychotic syndromes. *Schizophr Res* 2005; 79: 117-125.
33 Yung AR. The schizophrenia prodrome: a high risk concept. *Schizophr Bull* 2003; 29: 859-865.
34 Yung AR, Yuen HP, Berger G, et al. Declining transition rate in ultra high risk (prodromal) services: dilution or reduction of risk? *Schizophr Bull* 2007; 33: 673-681.
35 McGorry PD, Hickie IB, Yung AR, et al. Clinical staging of psychiatric disorders: a heuristic framework for choosing earlier, safer and more effective interventions. *Aust N Z J Psychiatry* 2006; 40: 616-622.

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