

The prodromal stage of psychotic illness: Observation, detection or intervention?

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Accurate identification of individuals in the earliest symptomatic stages of psychosis offers perhaps the best hope for more effective treatment strategies. Recently, research clinics have been set up to identify and possibly treat individuals who are seen as being at high risk of a psychotic disorder. However, there have been concerns about beginning treatment at this stage. We need to address these concerns so that individuals who are at risk of psychosis come to no harm, yet the development of potential interventions is not delayed. This article briefly reviews some of the newer developments and concerns in this area of psychosis research.

L'identification exacte des personnes qui en sont aux premiers stades des symptômes de psychose offre peut-être le meilleur espoir d'élaborer des stratégies de traitement plus efficaces. On a créé récemment des cliniques de recherche pour repérer et, peut-être, traiter des personnes considérées comme à risque élevé de troubles psychotiques. Le début du traitement à ce stade soulève toutefois des préoccupations. Il faut y donner suite de telle façon que les personnes à risque de psychose ne subissent pas de préjudice, sans toutefois retarder la mise au point d'interventions possibles. Cet article passe brièvement en revue des préoccupations et des événements récents dans ce domaine de la recherche sur la psychose.

Introduction

The primary reason for early detection and intervention in schizophrenia psychoses is that existing treatments for these severe and chronic illnesses tend to be palliative. Throughout the world, there are "early intervention" or "first-episode" programs. Many are well-established,^{1,2} but others are just being developed.²

Canada is taking a leading role, with initiatives in most provinces; several programs are gaining international repute.^{2,3} Generally, these programs are for individuals who are experiencing their first episode of a psychotic illness. The goal is to offer optimal treatment right at the beginning of the psychosis. Thus, new patients tend to be in the first few weeks or months of their illness. However, many individuals seen in first-episode

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programs have been sick for weeks, months or even years but are presenting for treatment for the first time. Thus, another goal of first-episode work is to reduce the duration of untreated psychosis and have people receive optimal treatment as soon as possible. This early-intervention work is well described elsewhere.⁴⁻⁶

Accurate identification of individuals in the earliest symptomatic stages of schizophrenia psychoses offers perhaps the best hope for the development of more effective treatment strategies. Recently, research clinics have been set up to identify and possibly treat individuals who are seen as being at high risk of a psychotic disorder. However, there have been concerns about beginning treatment at this stage. We need to address these concerns and issues so that individuals at risk of psychosis come to no harm, yet the development of potential interventions is not delayed. Many of these issues have been addressed in specialized journals and at research meetings focused on early intervention.

This article briefly reviews some of the newer developments and concerns in early-psychosis research to update clinicians in psychiatry and psychology as to the state of the art in identifying high-risk patients and the effects of early intervention in the prodromal phase of a psychotic illness.

The prodrome

The prodrome is a retrospective concept: until there is an established psychotic illness, it cannot be defined.⁷ In psychotic illnesses the prodrome refers to the period characterized by mental state features that represent a change from a person's premorbid functioning^{8,9} up until the onset of frank psychotic features. If the prodrome is the beginning stage of schizophrenia, psychosis will inevitably follow in the absence of intervention. Alternatively, if the prodrome is a risk factor, then only a proportion of individuals will progress to a psychotic episode, which implies that psychosis is not inevitable, but a heightened vulnerability.¹⁰

Approximately 80%–90% of patients with schizophrenia report a variety of symptoms, including changes in perception, beliefs, cognition, mood, affect and behaviour, before becoming psychotic; in the other 10%–20%, psychotic symptoms develop precipitously, without a significant prodromal period.¹¹ Nonspecific symptoms and negative symptoms usually develop first, and then attenuated positive symptoms appear. Although most

cases of schizophrenia have a prodromal period, it is less clear how often a psychotic illness develops in patients who experience prodromal symptoms. Thus, it is important to consider who may be at risk.

High risk and ultra-high risk

High-risk groups, selected by family history, have long been identified in schizophrenia research,¹² and several prospective longitudinal studies are ongoing.¹³⁻¹⁵ High-risk groups consist of individuals who have a first-degree relative with schizophrenia, most often a parent or a sibling. In genetic high-risk studies, the risk of psychosis has been found to be relatively low, at approximately 10%–20%.¹²

If we are interested in prepsychotic intervention, we need to work with individuals whose risk of psychosis is much higher than 10%–20%. Recently a second high-risk group — the “ultra-high-risk group” — has been identified.^{7,16} In Melbourne, Australia, McGorry and colleagues developed a specialized clinical setting, the Personal Assistance and Crisis Evaluation (PACE) Clinic, to study and treat individuals who present for help and are concerned about symptoms that appear to be psychotic but may be subclinical or attenuated positive. The Melbourne group has defined criteria for 3 syndromes that they proposed may reflect an “ultra-high risk” for developing a psychotic disorder in the near future.¹⁶⁻¹⁸ Individuals considered to be at ultra-high risk fall into 1 of 3 groups according to the syndrome identified: attenuated positive symptom syndrome, brief intermittent psychotic syndrome or genetic risk and recent deterioration syndrome.⁷ Table 1 presents the criteria for these syndromes.

Detection: assessment of ultra-high-risk mental state

To promote accurate and valid assessment of ultra-high-risk individuals, specific scales are being developed. The first was the Bonn Scale for the Assessment of Basic Symptoms.²⁰ Basic symptoms are the early subtle changes in thinking, feeling and perception that are subjectively experienced. In one study of 160 subjects, after a mean follow-up period of 9.6 years schizophrenia had developed in 79 (49.4%); the presence of basic symptoms predicted schizophrenia with a probability of 70%.²¹

McGorry's group developed the Comprehensive

Assessment of At Risk Mental State (CAARMS),⁷ which incorporates 8 psychopathological dimensions and operationally defines ultra-high-risk criteria. The revised version, CAARMS II, constructed in 2000,²² has demonstrated good reliability and predictive validity.¹⁰ Using the Australian criteria, the Yale group led by McGlashan developed the Scale of Prodromal Symptoms (SOPS), embedded within the Structured Interview for Prodromal Syndromes (SIPS).²³⁻²⁵

Observation: conversion to psychosis

The risk of conversion to psychosis among unmedicated individuals with prodromal symptoms has been examined. At the PACE Clinic in Melbourne, in a sample of 49 the rate of transition to psychosis was 41% by 12 months and 50% by 24 months.^{16,18} McGlashan's group in their New Haven, Conn., prodromal clinic, studied the predictive value of their SOPS assessments with 22 help-seeking subjects. Seven of 11 subjects (rated as prodromal) converted to psychosis by 1 year, whereas none of the 11 (rated as nonprodromal) converted. This suggests a conversion rate of 64%.²⁴ Using the new criteria for ultra-high-risk mental status, the risk of converting to psychosis increases from 10%–20% in the genetically high-risk group to approximately 40%–60%.

Intervention: the first trials

After identification of a group at much higher risk of psychosis than those who are at genetic risk through observational studies, treatment trials were conducted. In a prospective, randomized, open-intervention trial at the PACE Clinic,¹⁰ 31 of 59 ultra-high-risk subjects were randomly allocated to receive a low dose of an-

tip psychotic and cognitive therapy; the other 28 were randomly allocated to receive supportive case management. In the first 6 months, the rates of transition to psychosis were 9.7% in the treatment group and 35.7% in the control group ($p = 0.026$). The investigators reported minimal side effects from medication. Those not making the transition to psychosis showed improvement in both symptoms and functioning.

The second randomized trial, probably one of the most scientific and rigorous to date, began in December 1999 at the PRIME (Prevention through Risk Identification, Management & Education) Research Clinic of McGlashan and colleagues.²³ This ongoing double-blind, parallel study of 60 outpatients meeting criteria for a prodromal state is intended to compare the efficacy of low-dose antipsychotic versus placebo therapy in preventing or delaying the onset of psychosis in such patients. There are now 3 additional sites — the University of North Carolina at Chapel Hill, the Centre for Addiction and Mental Health in Toronto and the University of Calgary — each with its own PRIME Research Clinic. The study will be completed in 2003.

Discussion

Some psychiatrists and clinical psychologists believe that trials such as the PRIME study are premature in their scientific rigour and favour an observational strategy.²⁷ Others support open randomized or randomized double-blind, placebo-controlled trials.^{16,23}

Several complex issues were addressed in a recent issue of *Schizophrenia Research* (issue 1, vol. 51, 2001). Trials have been controversial since they may include the administration of low doses of novel antipsychotic drugs to some people who are not psychotic. The con-

Table 1: Criteria for ultra-high risk syndromes of schizophrenic psychoses

Attenuated positive symptom syndrome

Within the past year, attenuated (subclinical positive) but not frankly psychotic symptoms have occurred.
Symptoms have occurred at least once a week in the past month.

Brief intermittent psychotic syndrome

Brief, time-limited, frankly psychotic experiences have occurred within the past 3 months.
The experiences do not meet DSM-IV¹⁹ criteria for psychotic disorders.
Symptoms occur for at least several (but not more than 60) minutes per day, up to 4 days per week.
Symptoms are not seriously disorganizing or dangerous.

Genetic risk and recent deterioration syndrome

Individual has either a schizotypal personality disorder or a first-degree relative with psychosis.
In the past year, function has been reduced by 30 points or more on the GAF scale for at least a month.

DSM-IV = *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*;¹⁹ GAF = Global Assessment of Functioning.

cerns are briefly reviewed here, and the reader is directed to other, more detailed discussions.^{10,23,26–31}

Are we treating sick or well people?

The individuals in the trials I have described were help-seeking, symptomatic and describing dysfunction.^{16,26} In the Melbourne sample, the prodromal groups were more disabled than a sample from their first-episode program; furthermore, most of the former developed a psychotic illness within 6 months.^{7,16} Thus, clinical populations are being studied.

What about false-positive subjects?

False-positive subjects are individuals who, despite symptoms, are not vulnerable to psychosis. They are competent and able to decide to participate in such a trial. Although they do not convert to psychosis, they present with enough disability, symptoms and distress that with current criteria they could not be differentiated from those who do convert. False-positive subjects have the opportunity to know better their own risk, and by being involved, they have the opportunity to participate in extensive evaluation and follow-along, which may help clarify their problem. Those who do not convert show improvement in both symptoms and functioning.¹⁰

What about drug side effects?

Current trials use novel antipsychotics because of the relatively low risk of side effects. In PACE, there was no evidence of any significant neuroleptic side effects that were not manageable by dose reduction.^{10,16} Undoubtedly further research is needed to determine if benefits outweigh the risks in many patients.

Is enrolment stigmatizing?

There is concern that if individuals are identified as being at high risk of psychosis they may be doomed to chronic illness and stigma. PACE and PRIME suggest that this is not the case.^{16,26} People with a 40% risk of psychosis have the right to know their risk. In our Calgary PRIME Research Clinic, individuals want clarification on their level of risk and are relieved to know that their symptoms signify a risk for a psychotic illness rather than “schizophrenia.” Counselling about the probability

and the uncertainty of prediction needs to be offered in a sensitive way.²³

How long should medication be continued?

The length of treatment that is required to prevent a first episode indefinitely has not been properly researched in relation to patients who have recovered from their first episode, let alone ultra-high-risk individuals.¹⁰ Therefore, outside of controlled trials, prepsychotic individuals should not be given antipsychotics.²³

Treatment research in the prodrome appears to be justified. The Melbourne group now has 7 years' experience in this area, but their results need replication in carefully designed and conducted clinical research.²³

Conclusion

The rate of conversion to psychosis for individuals with a genetic risk for schizophrenia is 10%–20%. For those who meet the ultra-high-risk criteria the rate is approximately 40%–60%. There are 2 potential benefits to therapeutic intervention for prodromal symptoms. First, by treating symptoms we can potentially reduce distress and disability. Second, we may reduce the risk of evolution to a more serious condition, such as acute psychosis. The first strategy is good clinical care; the second is unproven.

Although we have made an excellent beginning in this area, with the Melbourne trial suggesting that intervention significantly reduces the risk of conversion in a 6-month period, systematic prospective studies at the prodromal stage are lacking. Future work should include developing more sophisticated, well-defined, validated clinical criteria by which to identify those at risk, enhancing the prediction of psychosis, and determining the sensitivity, specificity and positive predictive value of these criteria. Prepsychotic intervention as a form of indicated prevention has great potential but at present is an issue for research rather than practice. Leaving it in the realm of research will allow time for appropriate, well-designed studies to explore the issues that are currently controversial. This will potentially allow our best hope to make an impact on schizophrenia.

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