The schizophrenia prodrome: promise for prevention

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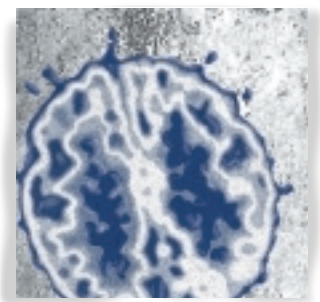

Converging theoretical, psychopharmacological, and neurodevelopmental advances have led to increasing interest in preventive intervention in schizophrenia. In particular, evidence suggests that early treatment is associated with a better prognosis. Furthermore, based on the reported reduction in severe side effects, the new novel antipsychotics potentially provide the tools for early intervention. Nevertheless, initiation of intervention during the prodrome has become controversial because of such unresolved issues as: (i) how to accurately identify susceptible individuals who are in true need of preventive intervention; (ii) at what developmental point in the prodrome medication should be initiated; (iii) how long medication should be continued; and (iv) what medication is optimal for each phase of the prodrome. By adopting a naturalistic, prospective research strategy, the Recognition and Prevention (RAP) program now underway in New York has been designed to address these and other important questions involved in prodromal research and treatment.

Keywords: *early identification; intervention; predictor; prevention; prodrome; risk factor; Recognition and Prevention (RAP) program; schizophrenia*

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Interest in the prodromal stage of schizophrenia has escalated dramatically over the past decade, as evidence has increased suggesting that the prevention of schizophrenia might be possible with early pharmaco-therapeutic intervention. The prodrome is considered to be the stage of schizophrenia that begins with the first changes in behavior and lasts up until the onset of psychosis.[1-3] As defined at present, the prodromal period is highly variable and can last from weeks to years, although typically it persists for at least a year.[1,4] Momentum for the shift in initiating treatment during the prodrome, rather than after the actual onset of psychosis, has been provided by the convergence of several developments, including: (i) increasing support for schizophrenia as a neurodevelopmental disorder; (ii) emerging evidence that early treatment improves outcome; and (iii) the introduction of novel antipsychotic medication, potentially providing the tools for preventive intervention. Yet, despite the growing optimism about prevention, little is understood about the basic characteristics of this phase of the illness. For example, little, if any, previous research has focused on whether the prodrome is a single clinical entity or, as in the case of full-blown schizophrenia, it is likely to be heterogeneous. In addition, given that adolescents make up a substantial proportion of the prodromal population, virtually no information is available about the developmental course of the prodrome. Of particular importance, long-term prospective research evaluating the predictive accuracy of prodromal risk factors is only now becoming of widespread interest—suggesting that it may not yet be the time to initiate large-scale clinical trials concerned with prevention. In this article, an overview of the currently available data about the schizophrenia prodrome will be presented, followed by a discussion of the major questions still to be answered and a brief description of a relatively new project ongoing at Hillside Hospital in New York—the Recognition and Prevention (RAP) program—

designed to provide substantial groundwork for future prevention trials.

Theory and background

Neurodevelopmental model of schizophrenia

A neurodevelopmental view of schizophrenia has provided the primary conceptual underpinnings of the movement toward early intervention and prevention. According to this approach, schizophrenia results from a basic biological error that occurs very early (probably prenatally), often involves a genetic component, and leads to a combination of structural, functional, and/or biochemical abnormalities in the developing brain. These abnormalities, in turn, result in a biological susceptibility to illness that may or may not be triggered by later, poorly understood, stressors. Since schizophrenia is typically not expressed clinically until late adolescence–early adulthood, a considerable developmental time period is thus available during which preventive treatment can be initiated.

One key to intervention is the ability to accurately identify who is susceptible to later illness and should thus receive early treatment. This requires the identification of accurate risk factors or "predictors" that are not yet available on an individual level. However, rapid progress is being made in establishing categories of risk factors. Traditional genetic high-risk research has indicated that, although clinically dormant, the biological susceptibility to schizophrenia is expressed in subtle neurocognitive deficits that can be detected throughout childhood and adolescence (see reference 5 for a more detailed discussion). In addition, it is now thought that somewhat later in the illness process, but still prior to the onset of psychosis, subclinical behavioral disturbances can also be identified that may predict later schizophrenia.[6] Thus, from a neurodevelopmental perspective, the unfolding of the clinical illness is a long-term process, with the identification of at least two classes of predictors (ie, neurocognitive and prodromal) possible in the near future, suggesting that preventive intervention may indeed be attainable.

Benefits of early treatment

From a treatment perspective, recent research has independently provided a compelling justification for pre-illness intervention. A number of studies have now suggested that the earlier medication begins after the onset of psychosis, the better the outcome.[4,6-11] It therefore follows that intervention initiated prior to onset will be better still.

The notion that the longer psychosis remains untreated, the poorer the prognosis, is typically referred to as the duration of untreated psychosis (DUP) effect. McGlashan[6,12,13] has argued that the DUP effect, in itself, justifies prodromal intervention in spite of the possibility of false-positive identifications. However, the importance of the DUP has been increasingly challenged by several more recent studies,[14-16] in which no association between the DUP and outcome is reported. Furthermore, several researchers have raised questions about the direction of causality, maintaining that, even if there is a correlation between the DUP and prognosis, this may simply reflect a third factor, most likely severity of illness.[17]

Introduction of novel antipsychotic medications

Until recently, intervention could not be attempted, regardless of whether stable risk factors could be identified. This was because standard neuroleptics, the most effective pharmacological treatment available, were associated with quite severe side effects (eg, tardive dyskinesia and other types of movement disorders). Given the likelihood of involving a relatively high rate of false-positive identifications, pre-illness intervention was not considered either feasible or ethical. However, the emergence of the new novel antipsychotics has changed this situation and has provided the tools for preventive intervention. Given the reduced side effects of the novel antipsychotics currently available,[18-20] intervening early in the illness process, before psychosis sets in, has been increasingly regarded as ethically acceptable.

Characterizing the prodrome

The early studies of the prodromal stage of schizophrenia, conducted primarily in Germany, were typically retrospective and involved the recollection of the signs and symptoms preceding onset by patients in the early stages of illness and their family members.[21-23] The initial prodromal clinical assessment that emerged, the Bonn Scale for the Assessment of Basic Symptoms (BSABS),[22,24,25] has had a major influence on the development of several subsequent measures, including: (i) the Instrument for the Retrospective Assessment of the Onset of Schizophrenia (IROAS), developed by Hafner and colleagues[26-29];

(ii) the Multidimensional Assessment of the Psychotic Prodrome (MAPP) used in the Personal Assessment and Crisis Evaluation (PACE) clinic assessments[30]; and, in turn, (iii) the Structured Interview for Prodromal Symptoms (SIPS) and Scale of Prodromal Symptoms (SOPS) developed by McGlashan and colleagues.[31]

With the exception of the BSABS,[25] research concerned with the prospective validity of prodromal assessments, especially those developed in the United States, has just begun.[30-34] As a result, prodromal diagnostic criteria are in the process of evolving. In terms of the definitions most widely used at present, much of the groundbreaking work has been carried out by McGorry and colleagues in Australia.[30,32-34] Based on a series of creative early studies, they have developed a highly influential set of criteria for identifying prodromal individuals. Their system consists of three separate categories of selection criteria.[35] Category 1 requires at least one of the following attenuated (ie, subthreshold) positive symptoms: ideas of reference, odd beliefs, or magical thinking; perceptual disturbance; odd thinking and speech; paranoid ideation; and odd behavior or appearance. Category 2 consists of individuals who have experienced transient psychotic symptoms that have spontaneously resolved within 1 week. Category 3 combines genetic risk (ie, being the first-degree relative of an individual with a diagnosis of schizophrenia) with state change in functioning (must have undergone a substantial decline in the previous year). These categories have also been integrated into the SIPS and SOPS developed by McGlashan and colleagues.[31]

Unanswered questions

Heterogeneity and false-positive identifications

The prodrome is typically considered to be a unitary clinical entity. This appears to be overly simplistic from a number of perspectives. First, in the McGorry/McGlashan criteria described above, there is no evidence to indicate that the three categories presented involve a common etiology. In fact, there is no reason to think that the prodrome is etiologically less heterogeneous than the full illness. Second, it should be noted that most of the criteria discussed above are derived from positive symptoms; the focus on attenuated positive symptoms may be both overly restrictive and lead to an unacceptably high false-positive rate.

Although deriving prodromal criteria from positive symptoms provides considerable face-validity, the accuracy with which these indicators actually predict schizophrenia, or even psychosis, is unestablished. For example, McGorry et al[3] reported that approximately half of the 657 high-school students completing a self-report questionnaire met criteria for the prodromal phase of schizophrenia as defined by *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition (DSM-III-R)* attenuated positive symptoms. Similarly, positive schizophrenia-like personality features have also been found in clinically normal individuals as well as in patients with a variety of nonpsychotic disorders, such as adults with dyslexia.[36] Such findings raise questions about the rate of false positives resulting from a reliance on positive symptoms. The issue of false positives is particularly important for prevention trials involving pharmacotherapy. Although the side-effect profile of the new novel antipsychotics appears, at this time, to be less severe than that associated with traditional neuroleptics, there are nevertheless side effects, such as substantial weight gain, to consider. In addition, the impact of long-term treatment on adolescent neurological development has yet to be determined.

Negative symptoms

There is considerable evidence to suggest that attenuated negative symptoms, such as deficits in social functioning, are important characteristics of the prodromal phase of the illness.[25,26,37-39] Several genetics studies have demonstrated that social deficits and other negative symptoms are more characteristic of the relatives of patients with schizophrenia than are positive symptoms.[40-42] Furthermore, prospective birth cohort studies of schizophrenia have consistently detected social deficits very early in development, prior to the onset of positive symptoms.[43,44]

The omission of attenuated negative symptoms in the most recent prodromal assessments (eg, SIPS and SOPS)[31] parallels the reliance on positive symptoms for a diagnosis of Axis I schizophrenia. However, in so doing, major early features of the prodrome may be missed. It may be at the stage where nonspecific, attenuated negative symptoms begin to emerge that interventions not involving antipsychotic medications are most effective. Moreover, it is possible that a combination of attenuated negative/disorganized and attenuated positive symptoms will prove to be the most accurate way of defining the prodrome.

Medication issues: what kind to use, when, and for how long?

In keeping with the view of the prodrome as a single clinical entity, it has been assumed by most clinical researchers that antipsychotic medication should be the starting point for intervention trials. On the surface, this appears to be a logical extension of treatment for the full disorder. However, by definition, individuals considered to be prodromal do not display florid psychotic symptoms, the symptoms most improved by antipsychotic medication. As a result, other pharmacological interventions must be considered. For example, it is possible that medications decreasing stress may reduce the risk of clinical deterioration in susceptible individuals, at least in the early stages of the prodrome.

Moreover, in contrast with the absence of psychotic features, neurocognitive deficits have been consistently reported to characterize both premorbid[5,45-48] and prodromal[49,50] stages of schizophrenia. These data suggest that neurocognitive deficits should therefore be a primary medication target. However, a number of researchers have reported that standard neuroleptics have little, if any, positive effect on neurocognition in individuals with schizophrenia.[51,52] There is some preliminary evidence to suggest that novel antipsychotics are more effective in treating specific cognitive deficits.[53-56] However, this evidence is still relatively preliminary, and it does not appear that any one agent affects cognition in general. As a result, optimal treatment may involve an as-yet unidentified pharmacological agent that directly improves cognition across a wide range of functions.

Finally, a number of additional, related questions remain to be addressed before treatment with antipsychotics (or other pharmacological agents) can be generally supported. For example, no information is available to guide length of treatment in prodromal individuals. Even for individuals definitely diagnosed to have schizophrenia, it is unclear as to how long treatment with antipsychotic medication should continue.[11] This issue is particularly important when considering prolonged use of antipsychotics, since many patients may still be in their teens and not yet have completed their neurological development.

An additional interrelated concern involves the lack of solid information describing the developmental course of the prodromal phase. The prodromal stage of schizophrenia is a complex clinical construct in its own right. The extent to which there are stages of the prodrome that are common to most individuals (for example, as hypothesized by Cornblatt and colleagues (private communication), attenuated negative symptoms followed by attenuated positive symptoms) is unknown. Such information would contribute to an understanding of when treatment should be initiated and what type of treatment is most appropriate for each prodromal phase. In our research program at Hillside Hospital, we have proposed that a naturalistic prospective research strategy can help to clarify the major developmental and clinical characteristics of the prodrome and answer many of the unresolved issues discussed above.

The Hillside Recognition and Prevention (RAP) program

The Recognition and Prevention (RAP) program of Hillside Hospital of the North Shore–Long Island Jewish Health System in New York is designed to prospectively characterize the schizophrenia prodrome and evaluate a range of early interventions, including various psychosocial and psychopharmacological therapies. The program consists of the RAP clinic, which provides treatment for prodromal adolescents, and a number of related research projects. Since prevention involves both the accurate identification of vulnerable individuals and the administration of effective treatments, both are major foci of the program. In terms of selection, a major goal of the RAP program is to establish a predictor profile that will combine the most accurate neurocognitive and prodromal (behavioral) risk factors. With respect to treatment, our strategy is to first conduct a naturalistic study of treatment effects. To do this, we currently treat "prodromal" symptoms as they would be treated in the real world; in other words, treatment targets specific symptoms rather than attempting prevention. As a result, RAP clinic interventions do not necessarily involve antipsychotic medication. In fact, preliminary data collected from a recently completed 3-year pilot study involving 50 prodromal adolescents have suggested that antidepressants are as effective as antipsychotics in improving overall level of functioning in individuals free of overt psychotic symptoms.

By following a naturalistic prospective study design and treatment strategy for a minimum of 5 years, we

hope to pinpoint the therapies most appropriate for specific symptoms and developmental stages of the prodrome and to address many of the other questions raised in the discussion above. Our long-term goals are to establish a highly accurate system of early detection and to develop clinical trials on the basis of our naturalistic findings, and thus move increasingly closer to prevention. ❑

El pródromo esquizofrénico: una promesa para la prevención

Una convergencia de los progresos teóricos, psicofarmacológicos y del neurodesarrollo ha conducido a incrementar el interés en una intervención preventiva en la esquizofrenia. En particular, la evidencia sugiere que el tratamiento precoz está asociado con un mejor pronóstico. Además, de acuerdo con las publicaciones sobre la reducción de los efectos secundarios severos, los antipsicóticos más modernos potencialmente proveen las herramientas para una intervención precoz. Sin embargo, el comienzo de la intervención durante el pródromo ha llegado a ser controvertida debido a algunos aspectos no resueltos como: 1) ¿cómo identificar con precisión a aquellos individuos susceptibles que tienen una verdadera necesidad de una intervención preventiva?, 2) ¿en qué momento del desarrollo del pródromo se debe iniciar la medicación?, 3) ¿por cuánto tiempo debe mantenerse la medicación? y 4) ¿qué medicación es óptima para cada fase del pródromo? Mediante la adopción de una estrategia naturalística y de una investigación prospectiva, el Programa de Reconocimiento y Prevención (PRP) que actualmente se lleva a cabo en Nueva York, ha sido diseñado para aclarar éstas y otras preguntas que surgen en la investigación y el tratamiento del pródromo.

Le prodrome schizophrénique : une promesse pour la prévention

Les avancées convergentes tant sur le plan théorique, psychopharmacologique que du neurodéveloppement de la schizophrénie se sont traduites par un intérêt croissant pour la prévention de cette affection. En particulier, il semble acquis que le traitement précoce assure un meilleur pronostic. De plus, les nouveaux antipsychotiques de deuxième génération, du fait qu'ils sont caractérisés par une diminution avérée d'effets secondaires graves, pourraient constituer l'outil de cette prévention précoce. Néanmoins, une intervention pendant la phase prodromique demeure controversée en raison des questions suivantes toujours en suspens : (1) comment identifier avec exactitude les patients nécessitant effectivement une prévention ? (2) à quel stade de la phase prodromique le traitement doit-il être débuté ? (3) combien de temps le traitement doit-il être poursuivi ? et (4) quel est le traitement optimal pour chaque stade de la phase prodromique ? Adoptant une stratégie de recherche prospective et naturaliste, le programme " Recognition and Prevention " (Reconnaissance et Prévention) actuellement en cours à New York a été élaboré pour répondre à ces questions et à d'autres aussi importantes concernant la recherche et le traitement relatifs à la phase prodromique.

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