Overview of the First Annual Workshop on the Schizophrenia Prodrome

by Andrea M. Auther, Todd Lencz, Christopher W. Smith, Christopher R. Bowie, and Barbara A. Cornblatt

Abstract

The First Annual Workshop of the Schizophrenia Prodrome was held in New York City in April 2002. This workshop was organized to address many of the unique methodological issues and controversies facing researchers interested in early intervention and prevention. It brought together representatives of most of the prodromal research groups active at that time as well as a number of consultants. This report summarizes the five major topics discussed throughout the workshop: (1) vulnerability and risk factors, (2) developmental issues, (3) neuroimaging and cognition, (4) alternative prevention strategies, and (5) clinical trials. The outcome of this workshop included consensus on several research issues, recognition that continued discussion and research was needed on many others, the emergence of a spirit of collaboration and collegiality among participants, and the very enthusiastic generation of the articles that make up this special issue of the Schizophrenia Bulletin. Two additional results were the decision to hold similar workshops in the future and the formation of the International Prodromal Research Network to foster international multisite collaborations.

Keywords: Schizophrenia, prodrome, psychosis, workshop, prevention, risk factors, vulnerability.


Introduction

Interest in initiating treatment during the prodromal stage of schizophrenia, prior to the onset of psychosis, has been a focus of active research for less than a decade, but increasing numbers of researchers are joining the field and enthusiasm for the potential of early intervention is high. Nevertheless, the methodology critical to this field is still in its infancy, and considerable controversy abounds. Given the unique challenges of prodromal research, a small workshop was planned to bring together active prodromal researchers who, working with each other and a few highly qualified consultants, could address many of the most vexing methodological issues of the day. Recognizing the great potential of the prodromal field and this working-group approach, Janssen Pharmaceutica Products, L.P., awarded an educational grant to sponsor this meeting. Thus, the First Annual Workshop on the Schizophrenia Prodrome was held at the SoHo Grand Hotel in New York City on April 4 to 6, 2002. The workshop was organized by Barbara Cornblatt, working with Todd Lencz and other staff of the New York Recognition and Prevention (RAP) Program.

The workshop brought together representatives of the major prodromal programs throughout the world, including those in Australia, Germany, the United Kingdom, and the United States. In addition, experts in the areas of epidemiology, prevention, psychopharmacology, and child psychiatry contributed their expertise to the process (a list of workshop participants appears in the appendix). The intention of this first workshop was to begin brainstorming about five areas of current concern: (1) vulnerability and risk factors, (2) developmental issues, (3) neuroimaging and cognition, (4) alternative prevention strategies, and (5) clinical trials. For each area, a half-day discussion was held; the major points of these are summarized below. The new data, concepts, and theoretical models presented during these sessions launched a number of cross-site collaborations and the collaborative articles that follow in this special issue. The enthusiasm generated by the first meeting led to the planning of similar future workshops and to the organization of the International Prodromal Research Network (IPRN, co-directed by Barbara Cornblatt and Tyrone Cannon). The second workshop was recently held in Santa Monica, CA, and hosted by Tyrone Cannon, and a
Vulnerability and Risk Factors

Moderator: Barbara Cornblatt
Presenters: Kathleen Merikangas, Kristen Cadenhead, Cheryl Corcoran, Dolores Malaspina, and Larry Siever
Discussant: Philip Harvey

The initial discussion of vulnerability to schizophrenia and how to identify and define risk factors set the stage for the remainder of the meeting. Workshop discussions continued to return to the concepts and controversies that arose during this session.

A major focus of discussion was the distinction between vulnerability markers and causal risk factors. Vulnerability markers are epiphenomena that do not necessarily affect the causal chain of events leading to illness. If valid, these markers will identify individuals who are at risk for later psychosis, but modifying them is not likely to affect the course of illness. As a result, they may not be appropriate targets for intervention. On the other hand, risk factors, if causal and mutable, are ideal candidates for intervention. Identifying causal risk factors (e.g., brain abnormalities, cognitive deficits, early negative and positive symptoms) is a major goal of prevention research. Additional research concerns include identifying protective factors, determining whether a particular intervention will be designed to reduce risk factors or enhance protective factors, and attempting to improve predictive ability by using composite profiles instead of individual factors.

A related issue that was raised in this session involves differentiating early symptoms from risk factors. If it is assumed that attenuated positive symptoms precede frank psychosis, are such symptoms reflective of the underlying vulnerability, or are they the earliest symptoms of the illness? If the latter, are we actually preventing psychosis with early treatment? Or are we attempting to reduce disease prevalence by providing treatment shortly after onset, as in first episode research? Such a distinction has implications not only for our pathophysiological understanding of the development of the disorder but also for treatment and service delivery models.

Similar issues were raised concerning the status of nonspecific symptoms related to the prodromal period, such as depression, anxiety, and social difficulties. Many participants agreed that patients considered to be prodromal for schizophrenia display high rates of comorbid disorders. However, a question to be resolved in future research is the extent to which these symptoms represent (1) core features of the prodrome; (2) separable, comorbid disorders; or (3) the presence of false-positive cases (e.g., depressed individuals who developed affective syndromes and who were never truly at risk for psychotic disorders).

Although a number of potential risk factors and vulnerability markers have been identified, none, either alone or in combination, have been established as reliable or valid predictors of schizophrenia or psychosis. A number of issues contribute to the difficulty of establishing clear predictors, including heterogeneity of samples, nonstandard assessments, and lack of specificity of risk factors. These factors also make replication across sites unlikely. Some of these problems can be offset with the creation of large samples and standardized procedures, which is possible only with collaborative multisite research programs. The need for such collaborations has led to the formation of the IPRN, one of the major outcomes of this workshop, and is being increasingly recognized as a future research priority (Heinssen et al., this issue).

Alternative ways of conceptualizing “vulnerability” emerged as another major research issue. There was general acceptance of the traditional neurodevelopmental model of a biological vulnerability predisposing to illness. However, several specific questions were raised about details of the model. For example, a major question is vulnerability to what: mental illness, psychosis, or schizophrenia? One view was that the “vulnerability” is an underlying, nonspecific brain dysfunction that, depending on other biological factors and specific triggers, can lead to a diversity of psychiatric symptoms. The risk, then, is to psychiatric illness in general. Moreover, it can be asked whether the nonspecificity of this vulnerability is a major reason that specific predictors of schizophrenia cannot be identified. Finally, the issue was raised as to what we should be trying to predict: underlying vulnerability, specific illness, or nonspecific disability. Implicit in these discussions was a tension between broad and narrow definitions of the prodrome. The narrow definition is based primarily on the presence of attenuated positive symptoms; the broad approach also includes nonspecific symptoms and has a more developmental perspective. Each of these strategies has advantages and disadvantages, with the comparison between them an ongoing theme throughout the workshop.

Developmental Issues

Moderator: Sanjiv Kumra
Presenters: Todd Lencz and Larry Seidman
Discussant: Randy Ross

Several developmental issues are of concern to prodromal researchers. First, from the perspective of child psychiatrists and developmental psychopathologists, normal adolescent development must be distinguished from abnormal
with risk versus presence of psychosis. Notions of brain plasticity have been changing recently as imaging results emerge, and it is now clear that the cortex undergoes prolonged changes up to age 30 and beyond. As a result, long-term studies of brain development will provide information as to whether changes are static versus dynamic, at what developmental period brain changes occur, and which changes are necessary for illness.

**Neuroimaging and Cognition**

_Moderator:_ Tonmoy Sharma  
_Presenters:_ Larry Siever, Todd Lencz, and Peter Falkai  
_Discussant:_ Matcheri Keshavan

Neurocognitive problems have been associated with various psychiatric disorders for decades, especially those in the schizophrenia spectrum. With the advancement of cutting-edge technology, neuroimaging has become a primary method of investigating the underpinnings of mental disorders. There are several distinct issues, both longitudinal and cross-sectional, that imaging procedures can address: (1) prediction of outcome based on the presence of brain abnormalities; (2) identification of causal neurocognitive risk factors amenable to intervention during adolescence; (3) identification of regions/functions related to specific subtypes of illness (e.g., positive vs. negative schizotypy); and (4) identification of protective factors and interventions that may enhance them.

One key methodological issue raised was the extent to which the focus should be directed at heritable markers that are found in asymptomatic relatives of patients. For example, the Gyrification Index, a magnetic resonance imaging measure comparing the inner and outer circumference of cortex, was discussed by Peter Falkai. This index, reflecting complexity of cortical development, was suggested as a suitable marker, in that it is linked to cognitive function, has high heritability, and is unaffected by degenerative changes. As such, it may provide a window onto the neurodevelopmental etiology of psychosis.

A contrasting approach proposed by other session members was to concentrate on markers sensitive to environmental or state change that are found in only clinically affected individuals. One example that bridges both approaches and that has attracted considerable attention is limbic pathology, particularly hippocampal volume deficits. Such abnormalities may reflect both heritable vulnerability factors, and illness-related degenerative processes. It was brought out that the possibility of degeneration occurring with the onset of psychosis is supported by the only longitudinal data currently available in the prodromal literature (i.e., data reported by Christos Pantelis, in collaboration with Patrick McGorry).
Alternative Prevention Strategies

*Moderator:* Robert Heinnisen  
*Presenters:* Richard Warner, Ming Tsuang, Tyrone Cannon, C. Hendricks Brown, Wolfgang Maier, and Ezra Susser  
*Discussant:* Patrick McGorry

Prevention strategies are a complex and controversial topic in the prodromal field. There has been much debate over which prevention approach (universal, selective, or indicated) is most appropriate. Universal prevention is targeted to the general population and not to individuals identified on the basis of individual risk factors. An example of a universal intervention is adding chlorine to the water supply. This strategy is best when the cost is low, the intervention effective, and the risk to individuals low. Selective preventive intervention targets a high-risk subgroup of the population (e.g., “truth” campaigns to reduce smoking in teenagers). The cost in this case may be moderately high, but the risk to individuals is low. Indicated prevention, on the other hand, targets particular high-risk individuals with subtle but detectable symptoms indicating a vulnerability to disorder. These individuals do not meet criteria for the full illness. This type of intervention is considered acceptable even if the costs are high and some degree of risk is involved.

There was some advocacy for the use of primary prevention, particularly in the area of universally improved prenatal care to reduce obstetric complications. The advantages of this approach are the reduction of risk for many disorders, not just schizophrenia, and no risk to individuals. As a result, this type of universal preventive strategy would be highly cost-effective. Nevertheless, while population prevention strategies such as improved prenatal care may benefit the community, they offer few advantages for a high-risk individual in need of immediate intervention. In addition, some participants stressed that it was premature for universal preventive strategies to target perinatal care.

By contrast, indicated interventions that target treatment-seeking populations potentially benefit those individuals at greatest risk for imminent illness. However, while of considerable help to the at-risk individual, this approach does little to affect the general population and therefore to reduce incidence of the given disorder. It was noted that there will inevitably be many false negatives involved in indicated prevention, that is, patients who develop schizophrenia who never present themselves to prodromal clinics before full illness onset. There are also high false-positive rates, resulting in unnecessary treatment. This is particularly undesirable when treatment results in stigma or has a detrimental effect on development. The most optimistic lesson from epidemiological research, however, is that prevention strategies are not mutually exclusive and, in fact, can work together synergistically. For example, as has been illustrated by the HIV/AIDS experience, individual prevention can encourage advocacy, which, in turn, generates population prevention that drives incidence rates down. Similarly, aggressive mental health education and community outreach can help reduce the rates of false negatives by increasing the number of at-risk individuals seeking evaluation in clinics.

Considerable discussion focused on the question of how to measure conversion—a major problem across prodromal studies. It is difficult to measure the success of a given preventive intervention if outcome (i.e., rate of conversions to schizophrenia) is not measured the same way across different research groups. Differences in the operational definitions of “conversion” are partly due to methodological issues such as inclusion/exclusion criteria and choice of measurement instruments. It is becoming increasingly apparent that more research is needed to explore the impact of the varying prodromal symptoms and stages of illness on conversion rates. For example, rates will be higher in samples requiring high degrees of attenuated positive symptoms versus high levels of impairment in global functioning. Thus, systematic recruitment across studies is essential to compare relative rates of outcome.

As discussed at several points throughout the workshop, there was no true consensus among research groups as to what the specific targets of prevention should be. All groups are attempting to prevent the functional decline and lifelong disability related to chronic mental illness. To some, prevention of psychosis is the main goal; to others, the goal is prevention of schizophrenia in patients who have already developed a psychotic level of symptomatology. There was widespread recognition that improved cognitive functioning should be a treatment target, because this is expected to affect functional outcome. However, it was also conceded that the relationship between improved cognition in the laboratory and functioning in the real world has not yet been solidly demonstrated.

Clinical Trials

*Moderator:* John Krystal  
*Presenters:* Patrick McGorry, Barbara Cornblatt, Christoph Correll, and Nina Schooler  
*Discussant:* John Kane

One area of consensus among participants was that the dissemination of prevention data to the general prescribing community is premature at this point and that much more
clinical research is needed. Clinical trials, especially placebo-controlled trials, are considered to be the most scientifically rigorous way of evaluating the effectiveness of interventions. However, only a few clinical trials have been conducted within the prodromal field to date. The scarcity of placebo-controlled clinical trials in this area is partially a function of its particular challenges: difficulties with feasibility, methodology, and ethics. Prospective naturalistic treatment studies offer an alternative that overcomes many of the clinical trial problems but generate data that are difficult to interpret. A major challenge to the field at this time is to develop strategies to promote the effectiveness of both approaches.

One topic of general interest was the need to evaluate nonpharmacological treatments, including psychosocial interventions (e.g., cognitive-behavioral therapy, skills training, stress reduction). It was also pointed out that staging should be applied to prodromal treatment. That is, treatment may be more benign and more effective when initiated during earlier rather than later stages, comparable to treatment for breast cancer, which is more effective when begun at Stage I than at Stage IV. Moreover, a suggestion for future directions involved an effort to teach mental health literacy more systematically than has thus far been the case, with the goal of teaching the public to recognize early signs of mental illness, similar to the Early Treatment and Intervention in Psychosis project in Norway that has been recently conducted by McGlashan and colleagues.

There are several important steps in designing clinical trials: (1) recruiting as large a sample as possible, because lack of power is a major difficulty across these trials; (2) identifying whether the objective of the trial will be treatment or prevention, which will have implications for whether outcome is based on symptom reduction or reduced incidence, respectively; and (3) selecting the comparator (e.g., placebo vs. other medications).

Also discussed was the issue of sample selection and the pros and cons of recruiting homogeneous samples versus samples that are heterogeneous in terms of prodromal inclusion criteria and the presence of comorbid disorders. Both approaches have important implications for generalizability of findings. Researchers must also determine the balance between the ethical benefits of a naturalistic design that excludes placebo conditions and the scientific benefits of a placebo-controlled trial. Related issues included the method of subject assignment and the problem of high dropout rates. Although random assignment is ideal for reducing potential study confounds, patient preferences and retention of subjects are also priorities. The issue of high rates of false positives and the number needed to treat are also primary considerations for researchers conducting clinical trials. Researchers must consider the costs and benefits of treating many subjects in order to prevent the development of a disorder in a few subjects.

**General Topic Discussed Throughout Workshop: A Prodrome by Any Other Name . . .**

Throughout the workshop, a recurring theme was what to call the syndrome now known as the "prodrome." The general feeling was that the "prodromal" label has many disadvantages but that there appears to be no acceptable substitute. The negative connotations of the term revolve around the implication that illness is inevitable rather than probable. It was agreed that the possible outcomes in prodromal studies include the development of schizophrenia, other psychotic disorders, or other nonpsychotic disorders, or the absence of any disorder. Thus, the term prodromal, as typically used in other areas of medicine, is clearly not accurate in its implication of an inevitable predetermined outcome.

It was therefore argued that the term prodromal was obsolete, having originated in the retrospective studies that preceded the current prospective research. In recognition of this labeling problem, many of the research groups represented at the workshop have developed alternate terms to describe the prodrome. These range from the label "schizotaxia," a modified revival of a previously used term, to new terms such as "clinical high risk," "ultra high risk," and "at-risk mental states." A variety of novel suggestions were also made throughout the workshop sessions, including neurosocial dysfunction (NSD) and sub-threshold negative and positive symptoms (SNAPS), although none of the suggestions caught on.

An alternative notion was that the prodromal label is not satisfactory because the concept it refers to is too simplistic. It was suggested that a taxonomy of vulnerability states needs to be developed as a more adequate way of communicating this concept. As suggested by a few of the participants, the term prodromal appears to be the most effective communicator and, as such, it remains firmly entrenched in the literature.

**Future Directions**

The discussions throughout this first workshop have emphasized that many of the methodological problems of clinical trials can be resolved only by establishing large-scale, multisite collaborations. The need for this new research orientation is now being increasingly recognized, as emphasized by Heinssen and Cuthbert in this issue. In response to this emerging research direction, the IPRN was formed to foster international collaborations. How-
ever, it was recognized that a first critical step toward forming multisite studies was to develop a common clinical assessment that could be used across sites. At present, a number of different rating systems are popular and limit cross-study generalizations. It was therefore decided that developing a common rating system would be the focus of the Second Prodromal Workshop, held in Santa Monica, CA, in May, 2003. Considerable progress was made at that meeting, and a third session is planned for 2004 to generate the actual instrument. It is expected that this will represent a major methodological advance, making it possible to pool data that are difficult to obtain and interpret in individual, small sample studies (e.g., neuroimaging data). It is hoped that this strategy will lead to major research breakthroughs that will be reported in the next special issue dedicated to prevention.

Appendix: Overview of the First Annual Workshop on the Schizophrenia Prodrome

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Co-organizer: Todd Lencz, Ph.D.

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Acknowledgments

We would like to thank Janssen Pharmaceutica Products, L.P., for providing the support that made this workshop possible and, in particular, Gahan Pandina, Ph.D., Janssen's Associate Director, CNS Medical Affairs, Clinical Development, who had the vision to recognize the potential of this meeting; as well as Jacquelyn McLemore, M.D., Janssen's Medical Science Liaison Manager, CNS Medical Affairs, who supported us in so many ways from the very beginning. We would also like to thank John Kane, M.D., and the Department of Psychiatry Research of the Zucker Hillside Hospital for cosponsoring the workshop.

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