Commentary: Progress, Issues, and Implications of Prodromal Research: An Inside View

by Thomas H. McGlashan

This issue of the Schizophrenia Bulletin focuses around research in the prodromal phase of severe mental illness, largely schizophrenia. The years since the last Bulletin issue on early detection and intervention have witnessed success at identifying the prodrome prospectively, positive initial data about treating prodromal symptoms and delaying psychosis onset, and hopeful data about elucidating the pathophysiology of psychosis through the prodrome. In this overview I will comment on some of the opportunities and challenges generated by this new line of research. Themes include the recruitment of prodromal subjects, characteristics of prodromal samples thus far collected, the process of conversion to psychosis in these samples, minimizing false positive prodromal subjects, dosing of drug treatments in prodromal clinical trials, treatment practice implications of prodromal research, defining conversion to psychosis prospectively, and screening, assessing, and naming the prodrome. It is concluded that prodromal research holds much promise but will require the formal collaboration of many investigators and the availability of resources for sustained efforts to recruit what amounts to an incidence sample.

“For thousands of years medicine has relied on what? On the fact that you have a core of people to whom you come when a disease has declared itself. Well, by that time things are really way down the path of destruction. So I believe strongly that in this century we’re going to have to understand what I call the subclinical phase of diseases, where the disease is evolving in you but you feel nothing.”

Elias Zerhouni, M.D.
Director, National Institutes of Health

This issue of the Schizophrenia Bulletin is the second on the topic of early detection and intervention. The first issue (McGlashan 1996) dealt with the early phase of schizophrenia, both pre- and post-onset, whereas this issue focuses on the pre-onset or prodromal phase exclusively. While schizophrenia remains the disorder most frequently studied, the results have relevance for the spectrum of mental illnesses we label as severe.

Since 1996 the field of prodromal research has seen considerable progress. Primary among these developments has been the crafting of assessments to identify and measure prodromal signs, symptoms, and syndromes. The paper by McGorry et al. (this issue) in this issue provides an historical overview of their pioneering contributions that identified prodromal individuals for the first time who were at substantial risk prospectively for becoming psychotic (Yung and McGorry 1996; Yung et al. 1996, this issue). Similar measures have been developed in Germany (Klosterkötter et al. 2001) and in the United States (Miller et al. 1999, 2002; McGlashan et al. 2001). The prospective conversion rate to psychosis has been substantial enough to render two clinical trials feasible, one randomized test of a treatment combining risperidone with cognitive behavioral therapy (McGorry et al. 2002) and one randomized, double-blind, placebo-controlled test of the atypical neuroleptic olanzapine (McGlashan et al. 2003a; Miller et al. 2003b; Woods et al. 2003). From these studies we have learned that a symptomatic prodrome to psychosis can be measured with predictive validity and that treatment can delay the onset of psychosis (McGorry et al. 2002) and reduce the severity of prodromal symptoms (Wood et al., this issue).

A structural MRI study by Pantelis et al. (2003) has made us more aware that the prodrome holds valuable clues to the development of psychosis by demonstrating cerebral gray matter volume attenuation that is already in process during this phase. Furthermore, this change could be used to signal the likelihood of conversion to psychosis in future patients who meet assessment criteria for the prodrome. The prodrome presents us with a laboratory in which to investigate the pathophysiology of severe mental illness. Four contributions to this special issue illustrate some of the genetic and neurobiological hypotheses that can be pursued profitably in this phase of illness (Cannon
et al., this issue; Corcoran et al., this issue; Seidman et al., this issue; Wood et al., this issue).

The studies referenced above of prodromal detection, treatment, and neuroimaging have provided the field with solid initial findings. They have also provided investigators with ideas to pursue and instruments for their pursuit. As an investigator who came to appreciate the potential of prodromal detection from Patrick McGorry and Alison Yung in 1994, and who opened a prodromal research clinic in New Haven, CT, in 1997, I wish to share some of my thoughts related to being inside the field for most of the past decade.

**Recruitment of Prodromal Patients to Research**

The identification and recruitment into studies of prodromally symptomatic individuals is the rate-limiting step to pre-onset research in psychosis. This is the central theme of Dr. Heinssen and colleagues’ contribution to this special issue (Heinssen et al., this issue). He details why gathering sufficient numbers of prodromal subjects for even modestly powered investigations is a major undertaking. The reasons include the low incidence rate of schizophrenia, subclinical symptomatic presentations that are difficult to see, and a high false positive rate in those identified as being prodromal. What he outlines is very real, as we at the PRIME Prodromal Clinic discovered when we opened our doors for studies in 1997. Initial recruitment was slow for our randomized clinical trial, so we added three sites to the project in 2000, only to find that the additional sites encountered similar recruitment difficulties. Ultimately, it took four sites and 4 years to recruit 60 patients.

The contribution of Kane et al. (this issue) to this issue details a variety of methodological approaches to clinical trials with prodromal patients. These include alternative randomization strategies such as “equipoise stratified randomization” and ways to reduce false positive prodromal patients in samples by selecting subjects from “enriched samples,” i.e., samples that are characterized by risk markers for psychosis such as eye tracking abnormalities and/or a history of obstetrical complications. They also describe designs comparing combined treatments and sequential treatment interventions. Such designs, while sophisticated, require sample sizes that are unrealistic given the current state of prodromal research, where experience has taught us that even simple designs are difficult to power.

Some of the forces that determine low recruitment yield are epidemiologic and inherent to the disorder’s early subtle clinical presentations. Because of this, Dr. Heinssen’s multiple site design with common protocols for pooling data is both welcome and necessary for success. The problems are formidable but not insurmountable. Prodromal patients are not rare. For example, epidemiology predicts that in the State of Connecticut alone 600 cases emerge each year. The challenge is bringing them in. The TIPS project in Scandinavia has demonstrated that intensive, educational campaigns about the early signs of severe mental illness, when applied in a sustained fashion to the general public and health care network of a large community, can bring persons who are experiencing a first psychosis into treatment significantly earlier (Johannessen et al., 2001; Larsen et al. 2001). Similar efforts and resources, if engineered to educate community practitioners about pre-onset risk status, have a very good chance of successfully priming a prodromal recruitment. The effort will be expensive but the research and public health payback is likely to make the outlay well worthwhile.

**Characteristics of Prodromal Patients Consenting to Research**

Based on the sample (n = 60) of prodromal patients recruited to our clinical trial (Miller et al. 2003b), certain characteristics stand out that are likely not to be representative of the prodrome epidemiologically or demographically. For example, assuming the prodrome precedes psychosis by 1 or 2 years, the expected median age of an epidemiological sample would be mid-20s. Such a sample would also display frequent substance use and a family history of mental illness of about 15 percent. Our patients were strikingly different in being young (median age 16 years), in coming from intact families with higher titers of mental illness, and in presenting with very little substance use or abuse.

At the present time we understand these sample characteristics to be determined in part by the nature of the emerging psychopathology, which is often subtle, subjective, and kept silent by the proband. If anything, the person experiencing new and unusual thoughts or sounds is likely to become more private, preoccupied, and less visible. The initial changes, which would usually be missed by most people, are picked up by family members who sense something has changed and become concerned, especially if they have already had experiences with mental illness in themselves or other members of the family. This is how we have reconstructed the sample we finally recruited. It is undoubtedly not representative from an epidemiological perspective, but it does provide clues as to populations that are likely to be responsive to recruitment efforts.
The Process of Conversion to Psychosis in Prodromal Samples

In the prodrome, as defined by our current research measures, conversion to psychosis is not inevitable. In fact, the rate of conversion varies from laboratory to laboratory, and from sample to sample within the same laboratory. For example, we identified and tracked two samples of prodromal patients in the PRIME Clinic beginning in 1998. The first were those who elected to take part in our clinical trial of olanzapine. The second were those who declined the clinical trial but elected to enter a naturalistic follow-along during which they could receive treatment from sources outside our clinic, but seldom did. By the 1-year point of each study the rate of conversion to psychosis was 50 percent for the follow-along sample (Miller et al. 2003a) and 25 percent for the clinical trial sample (McGlashan et al. 2003b). The difference, of course, could be that roughly half of one sample received treatment while the other received no treatment. It is also quite likely that the difference in conversion rate represents natural sample variation that should be expected because all "prodromal" samples identified with our current technologies are a mix of true and false prodromal patients. Such variation in this mix and in the rate of conversion is important to keep in mind and suggests conservatism when making power calculations for studies of this population.

Not only can the rate of conversion to psychosis vary from sample to sample, but also the timing. The two existing clinical trials both reveal that conversion can happen quite rapidly, i.e., within the first 6 months of the trial (McGorry et al. 2002; McGlashan et al. 2003b). This suggests that our current assessment instruments often identify persons who are frequently in the late stages of the prodrome, which makes clinical sense insofar as our diagnostic procedures rely largely on manifest clinical and functional signs and symptoms, especially positive symptoms. Future research may identify nonclinical risk markers for the prodrome and for conversion and allow us to capture people in earlier stages of the prodrome, but for now we must recognize that many of our prodromal recruits to research will be on the cusp of psychosis onset.

Cornblatt et al. in this issue assert that the positive symptom focus has resulted in an "overly narrow" definition of the prodrome. They are correct, but it is with positive symptoms that we must begin. Affective dysphorias, negative symptoms, and social deficits may characterize earlier phases of the prodrome, but they are harder to identify with specificity using clinical phenomenology. For example, it is possible that the group of adolescents from the Hillside Hospital RAP Clinic who were categorized as Clinical High Risk Negative (CHR−, n = 14, see figure 6) are primarily false positive prodromal patients, not an earlier clinical form of true positive prodromals. This hypothesis is supported by the fact that none of this group converted to psychosis over an average of 1 year (minimum of 6 months), and only 1 of 14 became CHR+ moderate. Applying the term "phases" to the samples in figure 6 suggests they differ in time, but in fact they are contemporaneous groups cross-sectionally sampled and defined by differences in severity (mostly of positive symptoms), not by differences in time or age.

We do not know, in fact, what the entire prodrome looks like phasically from prospective observations because we cannot yet identify early phase true positives well enough phenomenologically. We have an idea of what to look for from retrospective studies (Hafner et al. 1999), but we do not yet have prospectively collected and validated phenomenological data.

Minimizing False Positive Prodromal Subjects

Our current prodromal assessment instruments, as noted above, use clinical signs and symptoms to identify prodromal high-risk subjects. Their ability to capture substantial numbers of true positive prodromals has been pivotal and made our past 7 years of prodromal research possible. However, the instruments also capture substantial numbers of false positive prodromals. Furthermore, it is likely that the ratio of false positive to true positive cases fluctuates depending on the presence clinically of reliably identifiable positive symptoms. As per the preceding discussion, the specificity of our instruments will be higher in the later stages of the prodrome and lower in the earlier stages. If we wish to minimize the ratio of false to true positive, and to sample accurately for true positives in the early and mid phases of the prodrome, we will need to go beyond phenomenology to the laboratory for identifying markers. The signals separating schizophrenia from normals and from other disorders that have emerged from venues such as neuropsychology, neurophysiology, psychophysiology, and neuroimaging need to be added to our prodromal assessment batteries and tested for their ability to predict conversion. In this way we can improve on our clinical markers and identify true positive prodromals, both earlier and with greater precision.

Differing Prodromal Assessment Instruments

As detailed in the articles by McGorry et al. (this issue) and Miller et al. (2003a), the field of prodromal research has developed more than one set of assessment instruments. The measures being used that have generated pub-
lished data include the Basic Symptoms of Klosterkötter et al. (2001), the Comprehensive Assessment of At Risk Mental States, or CAARMS (McGorry et al., this issue), and the Structured Interview for Prodromal Syndromes, or SIPS (Miller et al. 2003a). The latter two were designed to identify syndromes common to the symptomatic prodromal phase. The way in which the instruments differ is detailed by Miller et al. (issue a) in this issue. Variation also arises when investigators use the same instrument in different ways. Lencz et al. (this issue), for example, use the SIPS but do not require recent onset of attenuated positive symptoms (within the past year) to include a person in the prodromal category.

Some regard this instrument diversity with concern, but multiple assessment instruments are the rule, not the exception, in clinical research. Furthermore, we do not yet have data on which to base decisions concerning priority or consolidation because few if any studies have used more than one instrument on the same population. Integration may ultimately be optimal, but not until sufficient comparative psychometric data have been collected to inform the decisions to be made. One advantage of multiple site (consortium) research is that it provides an opportunity for such data to be gathered.

Prodromal Screening Instruments

Screening whole populations for prodromal signs and symptoms has been regarded as one way of addressing the problem of recruitment. Ross et al. (this issue) in this issue discusses creating school-age versions of semi-structural interviews for the prodrome to schizophrenia. The paper offers useful suggestions about how to probe for psychosis in children. Given the problems with prodromal recruitment and the heightened risk for psychosis expected in populations of adolescents and young adults, screening is an attractive direction to pursue. The effort needs to include careful thought about how such an instrument would actually be used, however, and what would be done when (not if) someone screens positive for being at risk. Issues of informed consent and voluntary participation are paramount here, and will probably require more time and attention than the actual administration of the screen.

The Prodrome and Other Names That Nobody Likes

The question frequently arises in discussions about what ultra high-risk (UHR) or prodromal patients should be called. McGorry et al. (this issue) argue in this issue that At Risk Mental State (ARMS) and Ultra High-Risk (UHR) are superior. It is true that the term prodrome suggests a clinical syndrome that will evolve into a psychosis when in fact much of the time it will not. On the other hand, terms such as ARMS or CHR+ mod from the RAP Clinic (Comblatt et al., this issue), while they incorporate the concepts of risk and clinical state, tend to be awkward in common parlance. No proposal yet appears to condense these concepts into a term that rolls easily off the tongue as both noun and adjective. Most of the time when we are among colleagues, the term prodrome is understood. When used among the uninitiated it requires definition, but so too does every other candidate term. I vote for the prodrome by default and for pragmatics.

Dosing of Drug Treatments in Prodromal Clinical Trials

The McGorry et al. (this issue) contribution usefully reviews the work of prodromal centers around the world, and lists elements the centers have in common. They note that “where atypical agents are offered, low doses of atypical agents is the norm.” In the PRIME Clinic treatment trial this was not the norm. In fact, we used therapeutic doses of olanzapine; the mean maximum dose over the first 8 weeks was 10.2 mg/day (Woods et al. 2003). We consider it important for research purposes to use standard dosing of medication; i.e., doses that have been proven to be effective for active cases of schizophrenia. Otherwise, the clinical trial is at risk of being underpowered from a treatment-delivery standpoint.

Because symptoms in the prodrome are “attenuated” or less severe does not automatically translate into the idea that the effective drug dose should be less than standard. Keshavan et al.’s contribution to this issue is relevant here. The study defines the duration of untreated illness (DUI) as the prodrome plus the duration of untreated psychosis (DUP), and finds that DUP relates similarly to outcome as DUP. This implies that the pathologic process active in the prodrome (and producing attenuated symptoms) is similar to the pathologic process post-onset that produces florid symptoms. If the pre- and post-onset pathologic processes are similar (and continuous), then the treatment(s) for either process may need to be similar, including dose.

Current Treatment Implications of Prodromal Research

Enthusiasm for treatment research into the prodrome is healthy and should be fostered. Enthusiasm for introducing standard treatments for psychosis into this population, however, should be tempered. This applies especially to treatments that have a high rate of negative side effects such as pharmaceuticals. Thus far only one clinical trial
has been completed testing combined antipsychotic medication and cognitive-behavioral therapy, and while initial results are promising, they constitute but a fraction of the data necessary to delineate treatment guidelines.

On the other hand, all that is mutative need not be chemical. Much can be done for persons and their families who arrive at prodromal clinics. Among the services that can and should be supplied is a thorough medical and psychiatric evaluation that includes assessment of prodromal risk status. If the person proves not to be prodromal, he or she should be evaluated for other problems and referred to appropriate alternative services, if indicated. If the person meets criteria for the prodrome, a careful assessment of the differential diagnostic possibilities should ensue because the prodromal picture can result from other disorders such as depression, anxiety, drug intoxication, etc. Treatable disorders that emerge from such an evaluation should receive diagnosis-specific intervention, either in the clinic or by appropriate referral elsewhere.

If and when differential diagnostic possibilities have been ruled out, patients who are prodromal should be given information about their risk status and offered regular and frequent clinical monitoring; i.e., visits on a weekly basis at first. The visits can be modulated down to less than weekly if prodromal symptoms do not progress, or up to twice or thrice weekly if they do. Psychosocial intervention can be varied and includes support, befriending, stress management, problem solving, psychoeducation, family support, and so on, the aim being to reduce stress in the person’s life. Comorbid difficulties such as substance abuse should be targeted with disorder-specific treatments (e.g., substance dependence groups).

The status of prodromal symptoms should be checked regularly, and if the patient converts to psychosis, psychosis-specific active treatment is instituted immediately. If the patient does not develop psychosis but develops another treatable disorder, he or she is referred for appropriate treatment accordingly. If the patient’s prodromal symptoms remit, then regular monitoring can be terminated, although the patient should be given an open invitation to revisit the clinic should symptoms return.

Close monitoring and timely treatment of disorders that emerge is not only active treatment but it also constitutes tertiary and possibly secondary prevention as defined by Mojobai et al. in this issue. Treating severe psychiatric disorders at onset reduces considerably the collateral damage that accompanies active and irrationally symptomatic behaviors (tertiary prevention). Whether it also reduces the morbidity potential inherent in the disorder’s pathophysiology is unknown, and one of the reasons we currently study early intervention.

Defining Conversion to Psychosis for Prodromal Studies

Tracking the prodromal patient forward challenges the clinical researcher with a critical question: How do you define the point of conversion, or when does psychosis begin? DSM–IV is essentially a retrospectively applied metric, and provides no definition of the onset of schizophrenic psychosis. As such, prodromal researchers have found it necessary to define that transition de novo. For example, in our PRIME Clinic prodromal studies, we define psychosis as being present if any SOPS positive symptom item rates at the psychotic level of intensity for a specified duration (at least 4 days per week for 1 month). No time duration is required, however, if the symptom is seriously disorganizing or dangerous (e.g., a suspicion that has become paranoia leading to throwing a hammer at a family member).

The definition of onset varies among study centers, e.g., see table 2 of Miller et al. (this issue a) for a comparison of the SIPS versus the CAARMS definitions. Because the process of conversion to psychosis is usually dimensional, even when rapid, the “point” of transition from sanity to psychosis is as impossible to determine as the “point” of transition from night to day. Ultimately, the “actual” point is arbitrary, but it should be defined with sufficient clarity that it can be rated reliably among raters, rating instruments, and study centers.

Like DSM–IV, our PRIME Clinic definition requires positive symptoms of delusions, hallucinations, and/or disorganized speech. Unlike DSM–IV, we have a dual duration criterion. If positive symptoms are at psychotic intensity but not disruptive, a duration of approximately 2 weeks applies. If the symptoms are associated with significant functional disorganization or dangerousness, conversion to psychosis is declared immediately and no duration applies. Dangerousness, of course, includes homicidal and suicidal thoughts and grave disability, but it also includes highly visible new, bizarre, uncharacteristic behaviors that could be labeled as “crazy,” i.e., behaviors that could end up stigmatizing the patient in his/her social milieu. We are as concerned about the safety of the patient’s reputation as we are about the safety of his/her person.

In our double blind clinical trial we followed 11 prodromally symptomatic patients to the point of conversion to psychosis. When this happened the patients stopped taking double blind study pills and began taking open label olanzapine. In this context, we had the opportunity of “capturing” first episode schizophrenia at the point of onset and initiating nonblind antipsychotic treatment at a duration of untreated psychosis of zero. Our anecdotal experience has been instructive. All of the patients made the transition to active treatment without any disruption in
their lives, school, work, or social networks (Rosen et al. 2002). None required hospitalization and all continued with their usual lives and activities. Although the sample is small, preliminary experience indicates that the transition to psychosis need not be disorganizing or traumatic. It may also indicate that early detection and diagnosis is a new standard that should be incorporated in our clinical nosology.

Discussion

Dr. Maier et al. (this issue) reviews the current state of prodromal research for this issue and concludes “an increase in research efforts in this field is highly needed.” I could not agree more. The intervening years since 1996 have seen much attention and activity gathering to and focusing on prodromal detection and intervention in psychosis. The reasons behind this enthusiasm, schizophrenia’s chronicity and limited treatability, have unfortunately not changed. In fact the recalcitrance of schizophrenia to active treatment has been one element behind the paradigm shift articulated by the current Director of NIH toward pre-onset detection and intervention strategies.

This perspective provides hope, which is a welcome change to the grinding despair that has surrounded schizophrenia for a century. Hope, however, becomes a liability if it rises too far above the gravity of schizophrenia's data base as it has countless times over the century since the disorder’s birth at Kraepelin’s hand. As in supply side economics, we need enough hope to fuel new efforts and directions, but not too much hope that it becomes inflationary. Solid empirical research links hope to a productive tether.

We have much research to do before we are going to see clear pathophysiological avenues to solid secondary prevention in schizophrenia. Research has already oriented us toward the pre-onset phase of the disorder, and the prodrome is a new and potentially major focus for investigations. This issue of the Bulletin has elucidated much of what we know about the prodrome but more about what we don't know and need to study. I hope the issue also makes it clear that much of the research we need to do in this arena will only be possible through collaborative efforts. I look forward to another special issue about early detection and intervention several years from now, hopefully still as an insider, and hopefully as a member of an investigative consortium.

Reference


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