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Recruitment and Treatment Practices for Help-Seeking "Prodromal" Patients

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The prodrome of psychosis has become a target for early identification and for treatments that address both symptoms and risk for future psychosis. Interest and activity in this realm is now worldwide. Clinical trials with rigorous methodology have only just begun, making treatment guidelines premature. Despite the sparse evidence base, treatments are currently applied to patients in the new prodromal clinics, usually treatments developed for established psychosis and modified for the prodromal phase. This communication will describe representative samplings of how treatment-seeking prodromal patients are currently recruited and treated in prodromal clinics worldwide. Recruitment includes how prodromal patients are sought, initially evaluated, apprised of their high-risk status, and informed of the risks and benefits of prodromal treatments and how their mental state is monitored over time. The treatment modalities offered (and described) include engagement, supportive therapy, case management, stress management, cognitive behavioral treatment, family-based treatment, antipsychotic pharmacotherapy, and non-antipsychotic pharmacotherapy. References for details are noted.

Key words: schizophrenia/at-risk/managing

The Prodrome, an Old Clinical Constellation Under a New Light

The symptomatic ultra high-risk or "prodromal" state has always been a part of schizophrenia. In the past decade, however, it has become a reliably identifiable "subsyndromal" clinical entity with clear and compelling power to predict the onset of schizophrenia within the near future, ie, within weeks, months, or one or two years. This ability has introduced the capacity to track the development of schizophrenia prospectively for the first time in history. Such a novel perspective, in turn, holds considerable promise for understanding the pathophysiology of psychosis and for developing preventive treatment strategies for this devastating and often lifelong disorder. The promise of identifying schizophrenia in its nascently active form has made the prodrome an object of increasingly intensive study for a decade, beginning in Melbourne, Australia, then moving to New Haven, Conn, North America, the United Kingdom, Scandinavia, and Europe. Currently centers studying this phase of schizophrenia exist globally.

Research in the Prodrome

Research initiatives in prodromal clinics generally follow one or more of 3 directions. First are descriptive studies. Patients meeting prodromal clinical criteria are followed longitudinally to the onset of psychosis to validate the syndrome as high risk and to refine the descriptive criteria to minimize false-positive cases. Second are neurobiological translational studies. These too track prodromal patients longitudinally but include a variety of genetic, biological, neuropsychological, and neuroimaging measures to help elucidate the organic basis of the unfolding of psychosis. Third are treatment studies which take psychological and/or biological treatments designed for schizophrenia and apply them to help-seeking prodromal patients to delay or prevent the onset of psychosis and to determine the risks and benefits of treating prodromal symptoms, distress, and disability.

Prodromal Status Packs 2 Liabilities, 1 Actual and 1 Potential

True-positive prodromal patients are a relatively unique entity to psychiatry in that they have 2 "problems."[1] The first problem consists of newly developed or worsening

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psychological symptoms, distress, and disability, for which they or their families are seeking help. The second problem they may have is one of being at risk for more psychopathology, distress, and disability to come, of which they may or may not be aware and for which they may or may not be seeking help. The "treatment" of such persons is also relatively unique to psychiatry. It involves addressing the clear and concurrent symptoms and disabilities, but it also involves addressing the high potential for a relatively imminent transition to psychosis or another mental disorder. Thus, treatment has a dual aim, treating symptoms as current disability and treating the same symptoms as risk markers for psychosis.

Controlled Prodromal Treatment Research To Date, Not Sufficient for Guidelines

Three efforts to study the impact of treatment of the prodromal patient have been completed and published. The first was a randomized nonblind trial of a combination of medication (risperidone) and psychosocial treatment (cognitive) vs supportive monitoring on 6-month rates of conversion to psychosis.[2] The second was a randomized nonblind trial of cognitive therapy vs treatment as usual (support) on 12-month rates of conversion.[3] The third was a randomized double-blind, placebo-controlled trial of medication (olanzapine) on the 12-month rate of conversion to psychosis and on the 12-month severity of prodromal symptoms.[4]

Despite the uniformity of evidence for efficacy in these studies, the total amount of data remain far too limited to justify constructing treatment guidelines, which usually requires condensing data from dozens of clinical trials. Furthermore, each of the above studies has flaws limiting its generalizability or applicability. The first[2] was not blind, and the active treatment was a combination of psychosocial and pharmacotherapeutic modalities. The second[3] was not blind and would not have been significant if 2 patients retrospectively determined to have been psychotic at intake were not dropped from the cognitive therapy group. The third[4] was blind, but the drug-placebo difference in conversion rates was only trend-level significance and the risks of medication (eg, weight gain) proved to be substantial. As a collection, these studies unquestionably support further treatment research in the prodrome, but they cannot be said to support any particular treatment strategy at the present time other than intensive follow along.[5] Any treatment that is provided for patients meeting current criteria for the prodrome must continue to be regarded as experimental.

The Queue of Potential Treatments for the Prodrome Is Long and Lively

Despite the dearth of controlled research data about the efficacy and safety of treatment interventions in the prodrome, there is no paucity of treatment experience. Currently, there are dozens of prodromal centers around the world. Many patients and their families have been seen and are being seen, and it is of interest to describe what is being done and how it is being done. Such is the aim of this communication, to describe and illustrate how help-seeking prodromal patients are recruited and treated in today's centers and especially how these centers address the dual problems presented by these persons, the prodromal symptoms as current disability and the prodromal constellation as risk for future psychosis. This report will include descriptions of the following: how patients are gathered and recruited, how they are informed of their risk status, how they are evaluated at intake, how their prodromal status is monitored over time, and how they are treated while they remain prodromal. This will include the monitoring process, active psychosocial interventions (case management, family interventions, individual supportive and cognitive therapies), and pharmacotherapeutic interventions. Our description will also include how prodromal patients are determined to have converted to schizophrenia or to some other disorders such as bipolar, depression, or schizotypal. We will not describe how such patients are treated after conversion because that is covered by current existing disorder-specific guidelines.

Once again we will be describing practices. Such practices cannot and should not be taken as guidelines without being subjected to further clinical trial research.

Recruitment and Treatment Practices

How Are Prodromal Patients Recruited?

Because the prodrome is basically clinical in nature, persons developing prodromal symptoms often seek a clinical caregiver they know such as a general practitioner, a school-based counselor, or a friend in a health care position. Because the prodrome is a new clinical constellation, recruiting symptomatic, help-seeking persons who are at risk for psychosis requires active outreach to potential health care–oriented referral sources. This includes efforts to educate these sources about the prodrome and training and maintaining staff to be available to triage calls and to conduct rapid, low threshold evaluations of potential referrals.

The PACE Clinic in Melbourne has accumulated the most experience with such recruitment, as detailed in 2 publications.[6,7] Yung et al, eg, outline the following strategies for community education: (1) regular professional development sessions at mental health clinics about the prodromal intake criteria and the treatment options available; (2) training sessions for non–mental health professionals (general practitioners, substance use counselors, school psychologists, clergy, etc.) about screening for the prodrome and psychosis; (3) distribution of educational brochures and posters, Web site access with

descriptions of the prodrome, clinical intake criteria, and treatment options, and 4) a regular newsletter to the above targets and to any who have referred patients to the clinic. An example of an educational brochure used in the PRIME prodromal clinic in New Haven, Conn, and sent to potential referring sources is seen in Appendix 1.

Most prodromal clinics have a triage system or team available via phone and/or in person during working hours to discuss possible referrals. Serial assessments done by the team determine whether or not a prodrome exists and what the treatment needs are, if any. If the patient is psychotic or has a definable disorder, referrals for active and specific treatments are made. Patients who are not prodromal are so informed and invited to recontact the clinic in the future if they become concerned. Those meeting prodromal criteria are invited to connect with the clinic.

How Are Prodromal Patients Informed of Their Risk Status?

Currently, most help-seeking prodromal patients eventually find their way to study centers rather than to specialized treatment clinics. As such, their understanding that their presenting symptoms are also risk markers for psychosis comes from the process of informed consent, a process which focuses initially on the informed consent document. Excerpts of such a document used in the olanzapine clinical trial at the PRIME Clinic in New Haven, Conn, are reproduced in Appendix 2, highlighting the issues of what psychosis is and the risks and benefits of participation in the research.

The risk for psychosis is real, and at the New Haven PRIME Clinic, it is conveyed as such. Psychosis is described in terms that are understandable. Its seriousness is acknowledged but counterbalanced with information about the range of potential outcomes and the availability of effective treatments and the fact that these treatments are applied as soon as possible in the event of conversion. The manner in which the Clinic deals with knowledge about risk has been discussed in an earlier *Schizophrenia Bulletin* communication[8] and is reproduced below.

> Our "prodromal" evaluations ascertain both current symptoms and risk for more severe future symptoms (psychosis). Whether the patient is a true risk or a false positive risk, the information we provide may be daunting and unwelcome. The concern is that imparting such information harbors its own risks, such as generating anxiety, depression, demoralization, panic, or self-stigmatizing behaviors such as withdrawal and isolation.
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> In actuality, experience in our prodromal clinic has been instructive. After we evaluate patients, we tell them (and their family, if appropriate) what we think the problem is, if anything. If they have a problem that does not appear to involve risk, they are so informed, and, if appropriate, a referral is made elsewhere for further evaluation or treatment. If we feel risk is present, we say so and explain why, emphasizing that by "risk" we mean probability, not inevitability. We clarify what we mean by "psychosis", adding that we will have a better picture of patients' true risk for psychosis over time, which is why we have frequent visits over time. We inform them that should they truly be at risk, they will receive treatment when they develop signs of psychosis. We add that by being in the study they would probably receive such treatment earlier than if they were being followed in the community. Should they not be at risk for psychosis and develop another disorder instead, we tell them they will receive diagnosis-appropriate referral and treatment right away. We say that if nothing more severe develops over time, the estimate of risk can be revised, bringing to us a better understanding of the source of their original "prodromal" symptoms.
>
> The reactions of patients and their families to this information have ranged from relief to concern to skepticism to denial, the modal response being mixtures of all of these. Distress may be apparent and is usually appropriate to the magnitude of the message. When distress is absent, denial is usually present (but seldom total). To date we have not observed distress that is overwhelming or that requires treatment interventions beyond further information.
>
> We feel that imparting the reality of risks is imparting information that the person may wish to know and may decide is important. When we do this, some patients (and families) also want to know what to do; in our subsequent discussions, they often secure a sense of readiness, perspective, and control over emerging changes that otherwise are ineffable, puzzling, and disorganizing. Other patients may not achieve such levels of insight and coping. Instead, they deny the reality or level of risk and refuse or withdraw informed consent, or they decide to ignore the reality of risk for the time being but play it safe and join the study. We have seen some form of coping strategy emerge in every case confronted with the news of risk.
>
> Another important concern is that labeling someone as being at risk is stigmatizing, with the label of psychosis becoming a persecutor or a self-fulfilling prophecy. This has not been our experience during our many years of working with this population. In fact, we feel that to avoid imparting the reality of risk is to court even greater stigma from the negative social consequences of active, out-of-control psychotic behavior requiring hospitalization, which is the single most stigmatizing event in the process of onset. Withholding information about risk iatrogenically sanctions denial and places the true positive prodromal patient in jeopardy of a potentially disastrous outcome. In our opinion it also violates the patient's civil liberties and right to know.
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> The anxiety generated by the news of risk can also be a benefit insofar as it heightens vigilance. One feature of this research is the close monitoring of a patient's clinical state, an activity that is maximized if everyone becomes more watchful and knows what to watch for. Greater awareness can also help to identify an emerging psychosis at the time of onset so that treatment is initiated without any delay. Psychosis often arrives like Carl Sandburg's fog; that is, silently, on little cat feet. Its progressive losses and changes are easy to ignore, to explain away, to minimize. Appropriate attention and concern for what is transpiring too often is delayed

until the situation spirals into a crisis requiring coercive intervention. First psychosis is a major life crisis; anticipatory anxiety helps to attenuate the shock surrounding onset and its potential for chaos.

What Benefits of Study Participation Are Noted for Prodromal Patients?

Prodromal research, whether or not it includes treatment, has several benefits, both real and potential. First, monitoring and counseling occur on a regular basis, providing continuous feedback to patient and family of the proband's state of health. Troubles, if and when they occur, are apparent right away, and if psychosis supervenes, treatment begins at onset, ie, at a duration of untreated psychosis of zero. This minimizes the collateral damage and stigma too often generated by untreated irrational behaviors that alienate family, social networks, work colleagues, and sometimes the law. Among the New Haven clinical trial sample of prodromal patients who converted to schizophrenia, no patient required hospitalization, all but one continued their daily schedule at work or school, medical compliance by pill count was 93%, and relationships with family and social networks were maintained.

Research participation offers the opportunity for the patient and family to develop a therapeutic alliance and working relationship with the study clinicians. Engagement with the research and treatment system when competency and decisional capacity are rarely at issue generates trust that is not eroded early or rapidly by emerging psychosis. Another real benefit is the availability of consultation and sometimes treatment for problems comorbid with prodromal states such as depression, anxiety, or substance abuse. In addition, engagement in prodromal research allows for the possibility that preonset tracking and/or treatment will delay or prevent onset or result in a disorder that is milder and less disabling. Finally, a potential benefit important to many prodromal participants is the satisfaction that they are adding to the scientific knowledge base about schizophrenia.

Prodromal Patients in a Prodromal Clinic: Intake Evaluation

Patients entering a prodromal clinic are assumed to meet one or more of the extant prodromal syndromes. These are the attenuated positive symptom or APS syndrome and the genetic risk and deterioration or GRD syndrome. In some clinics, the brief intermittent psychosis syndrome or BIPS is regarded as prodromal, and in others, it is considered to be over the threshold into psychosis. How many syndromes are considered prodromal at each site is usually explicit.

Upon admission to clinics, all patients receive a full prodromal assessment. The prodromal criteria and assessment instruments have been developed for research but with appropriate training are easy to apply and to use clinically. The most frequently cited instruments include those developed in Australia[9,10] and America.[11–14] In Germany, an early recognition inventory has been developed[15] that assesses for 2 prodromal phases, an early initial prodromal state consisting largely of basic symptoms and a late initial prodromal state that includes the types of prodromal symptoms also assessed by the Australian and the American instruments. Please consult the above references for details.

In addition, as part of the initial assessment, most patients also receive a full diagnostic and differential diagnostic workup using a structured interview such as the SCID. Common differential diagnostic and comorbid entities are major depression with psychotic features, bipolar disorder, dysthymic disorder, substance use disorder, posttraumatic stress disorder, and schizotypal personality disorder.[16] The assessment usually includes a physical and neurological examination and standard laboratory studies.[16] Some centers, but not all, do structural magnetic resonance imaging.[6] Medical risks of note include a tendency toward weight gain, insulin resistance, and orthostatic hypotension.[6] It is important to remember that patients are symptomatic and often have a nonpsychotic diagnosis/disorder in addition to being at risk. Also, they often require attention to problems that are medical.[6]

Monitoring and Conversion

Once the patient has met screening criteria, signed informed consent, and finished the intake evaluation, treatment begins along with some form and schedule of research monitoring. The latter always includes ongoing clinical evaluation of prodromal symptoms and detailed assessment for emerging signs and symptoms of psychosis. Usually the treatment and research endeavors are conducted independently, even if done by some of the same staff from the clinic.[6]

A major research and treatment event is conversion to psychosis. The criteria for conversion are operationalized for research reliability. They vary in definition and measurement between prodromal centers. Within centers, however, the definition is usually shared and applied uniformly among clinicians. In fact, a clinician (eg, individual therapist or family therapist) may notice clinical deterioration and apprise the assessment team of the need for additional research monitoring and rating,[17] including tracking the patient by telephone if face-to-face evaluation is not possible.[18]

If conversion supervenes, the patient is no longer prodromal and starts treatment that is appropriate for their now *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*) or *International Statistical Classification of Diseases, 10th Revision*, diagnosable disorder, be it schizophrenia, bipolar disorder, or major depressive disorder. Such treatment may be provided by the research team and clinic, but more usually the patient is referred to another clinical venue and provider.[6]

Treatment Practices During the Prodrome

In the absence of conversion or remission, ie, while the patient is clinically prodromal, treatments of considerable variety are currently offered to patients and their families in prodromal clinics around the world. These include strategies of engagement; supportive psychosocial therapy; psychosocial case management; cognitive behavioral treatments; treatments of comorbid disorders, particularly substance abuse; family involvement, usually in the form of multifamily group psychoeducation; and finally pharmacotherapy with both antipsychotic and non-antipsychotic compounds.

Each treatment modality (to be described) was developed originally for dealing with established cases of schizophrenia, but our focus here will be the translation of these approaches to the prodromal patient. This literature is now quite substantial, will be quoted here frequently, and should be consulted for details. The major difference is that with the prodrome, all treatment modalities include ongoing psychoeducational discourse and active follow along. The prodrome may be the optimal period for psychoeducation because patients are worried about themselves and their cognitive resources for participating in a learning experience are not yet seriously compromised.

Engagement

Phillips and Francey[19] describe engagement as follows:

> The engagement phase is obviously crucial. It provides the opportunity for the patient to get to know the therapist (and vice versa) and allows the therapist the opportunity to set ground rules for the rest of the therapy process and to assess expectations of the client. It also enables the therapist to emphasize the collaborative nature of the therapy. It is important that the language used by the therapist, as well as the ''therapy tools'', are understood by the client and are appropriate for their developmental level. Cognitive development and other processes, which may be affected by the symptoms and experiences that contribute to the ultra high risk status of this specific client group, should also be carefully assessed. For instance, an individual who experiences brief and intermittent auditory hallucinations may have occasional concentration difficulties. Similarly, an individual who experiences persistent perplexity associated with intermittent paranoid thoughts may suffer marked social anxiety.
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> Key strategies for promoting engagement beyond basic counseling skills are:
>
> - Offering practical help
> - Working initially with the client's primary concerns and source of distress
> - Flexibility with time and location of therapy (office based, school, client's home)
> - Provision of information and education about symptoms
> - Working with family members, if appropriate, as well as the identified client
> - Collaborative goal-setting

All in all, the primary aim of engagement is to make a human connection and to help the patient find enough comfort and advantage in the relationship such that he or she continues to show up for appointments. The slide into psychosis almost by definition involves withdrawal from real others into a shadowy world of imaginary encounters with stereotypic human caricatures. Engagement counters this decathexis and sets the stage for more structured interactions.

Supportive Therapy

Yung et al[6] describe supportive therapy as follows:

> Although it does not specifically target psychotic symptoms, supportive therapy endeavors to provide the patient with emotional and social support and incorporates many of the constituents of Rogerian Person Centered Therapy including empathy, unconditional positive regard and patient-initiated process. The therapist aims to facilitate an environment where the young person is accepted and cared for and they can discuss concerns and problems as well as share experiences and feelings with the therapist.
>
> In addition to promoting change through non-directive strategies, basic problem-solving approaches are also offered. This may include assisting the patient to develop skills, such as brainstorming responses to situations, role-playing possible solutions, goal setting, time management and so forth. The patient is encouraged to be pro-active and to monitor his or her own progress. Some degree of role-playing may occur within sessions as a springboard to changes in behavior outside the sessions.

Other elements of this ''holding environment'' include availability for crisis intervention and after-hours contact.[6,20] Many prodromal clinics rotate beeper coverage for nights, weekends, and holidays, a concrete sign that the patient's risk for psychosis is taken seriously.

Supportive therapy often targets the social and instrumental domains of the patient's daily life rather than symptoms and psychopathology, the aim being to keep the patient ''in the world'' and to prevent attenuation of social ties secondary to intensified symptom formation. The therapies are usually highly structured, prescriptive, and time limited so as not to be perceived by the patient as too demanding or overwhelming.

Supportive Interpersonal Therapy, or SIT, is an example of such a therapy. It was developed for the prodromal clinics collaborating in the National Institute of Mental Health–sponsored PREDICT consortium that recruits and follows prodromal patients.[21] The aim of SIT is to improve the ongoing functioning and social integration of persons in the study. It is divided into 5 phases over 23 weeks. Phase 1 (3 sessions) establishes a therapeutic alliance using supportive interactive techniques similar to those outlined by Yung et al[6] above. Phase 2 (2 sessions) determines and articulates what social and functional areas in the patient's daily life are the most problematic. A list of potential goals is given to patients who have

difficulty formulating specific targets (see Appendix 3). Phase 3 (2 sessions) prioritizes the social and functional problems and develops a mutually agreed-upon treatment plan. Phase 4 (13 sessions) mobilizes the treatment plan with the goal being better integration of the patient into his or her social world. This includes modeling appropriate social skills, role-playing problematic social situations, identifying and monitoring the patient's positive attributes over the course of each week, reality testing experiences of stigmatization, and assigning tasks that will bring patients in contact with other people. Phase 5 (3 sessions) reviews the goals attained and the skills learned, develops a post-SIT treatment plan, and elicits feelings and issues regarding termination.

Case Management and Stress Management

Case management is a form of supportive therapy that deals with more immediate stressors and concrete administrative issues. As noted by Yung et al[6] and by Phillips and Francey,[19] with case management the therapist assists the patient with more practical issues (finding housing, handling money, applying for work or school, etc.). They feel such management must be provided in addition to other therapeutic efforts because neglect of basic daily living needs can generate stress and undermine the effect of even the best of therapies.

Stress management emerges from the stress-vulnerability model of schizophrenia and aims to reduce both the occurrence of stress in the patient's life as well as the patient's dysfunctional responses to stress. Phillips and Francey[19] wrote about it as follows:

> The components of this module are drawn from traditional stress-management approaches including relaxation training, education about stress and coping, and more specific cognitive strategies. As well as being primarily cognitive-behavioural in orientation, these strategies educate the clients to recognize and monitor their own stress levels, to develop an understanding of precipitants to distress, to recognize associated physiological and behavioural correlates of stress, and to develop appropriate strategies for coping with stressful events.
>
> Strategies include:
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> • Psychoeducation about the nature of stress and anxiety. This entails a detailed discussion of the physical, behavioural and cognitive signs of stress. The physiological reactions concomitant with "flight and fight" responses are described to help in the process of distinguishing adaptive stress from unhealthy levels of stress. Personal signals of maladaptive levels of stress may also be identified.
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> • Stress monitoring: Diary use is encouraged to record varying stress levels over specific time periods and to identify precipitating events or situations, and consequences of anxiety or stress.
>
> • Stress management techniques, such as relaxation, meditation, exercise, distraction are introduced.
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> • Maladaptive coping techniques are identified—for example, excessive substance use and/or excessive social withdrawal. The psychoeducation provided is aimed at reducing health damaging behaviours and promoting more adaptive responses to stress.
>
> • Cognitions associated with subjective feelings of stress or heightened anxiety are identified through monitoring (which may include completion of an inventory of dysfunctional thoughts/irrational beliefs to identify maladaptive cognitions).
>
> • Cognitive restructuring is introduced, which counters dysfunctional thoughts (e.g., negative self-talk, irrational ideas), with more positive coping statements, positive reframing, and challenging.
>
> • Goal-setting and time management is introduced.
>
> • Assertiveness training is provided.
>
> • Problem-solving strategies are discussed.

Case management may target the patient's environment as well. Certainly this includes the family and is detailed below. For the youthful prodromal patient, this may also include the school. Counselors at the PRIME Clinic in New Haven, eg, reach out to educate school personnel about prodromal symptoms present in general and/or in a particular patient/student. In the latter instance, eg, it might be explained that a student is very sensitive to noise and may need assistance during the changing of classes or during lunch period in the noisy cafeteria. Or a patient experiencing disorganizing communication may need single-step directions. Schools have proven to be appreciative of such suggestions and their implementation has often diminished the patient's level of stress.

Prodromal symptom monitoring on a regular (eg, weekly) basis in clinics with a research agenda can prove to be a form of stress management. During weekly reviews of their prodromal symptoms, patients become educated about their "psychopathology" and how it is context dependent and often fluctuates with daily stress. Patients become reliable observers of their symptoms, often quantifying their variable severity based on the research rating scale ("I would score my idea that my friends are talking about me a 4 this week … I think it happened more because I didn't sleep too well over the weekend"). Objectifying and quantifying psychopathology with such monitoring can make it seem less foreign, mysterious, and overwhelming.

Cognitive Behavioral Therapy

Unlike supportive therapy and stress management, which generally targets functioning and anxiety but avoids psychopathology, the primary focus of cognitive behavioral treatment is on the patient's anomalous positive symptomatic experiences (aberrant auditory or visual percepts, suspiciousness about strangers, etc.) and his or her culturally unacceptable attempts to explain these experiences (eg, transmitter in my ear or being followed by the FBI). These explanations, in turn, usually arise in the context of relative isolation and are usually kept secret, at least at first. The patient does not try to "make sense" out of

these experiences with another person or persons, thereby "normalizing" the experience.[22]

Cognitive behavioral therapy (CBT) attempts to provide the missing or avoided "normalization" with a variety of strategies.[19,22] These include the following:

1. Developing a relationship with the patient.
2. Education about symptoms, their biopsychosocial germination, their frequency in the population, and their manageability.
3. Avoiding the term schizophrenia and psychosis.
4. Verbally challenging and reality testing delusional thoughts and hallucinations while generating and testing alternate explanations.
5. Teaching coping strategies such as stress management, distracting attention, and strategic withdrawal.
6. Normalizing psychotic-like experiences by suggesting that symptoms experienced are relatively common and manageable.
7. Reality testing perceptual aberrations and suspiciousness by devising experiments to test the beliefs held by the patient.
8. Self-monitoring of symptoms to enhance the connection between external events and emotional states.
9. Modeling insight, judgment, and metacognitive functions for the patient.
10. Reducing the distress and fear of catastrophe attending psychotic-like experiences.

Active efforts at engaging patients and normalizing their experiences may be especially effective in the prodromal clinical state given that substantial elements of insight are still present. Psychosis flourishes in isolation, but CBT can keep the patient connected with others by avoiding cognitive and interpersonal closure in the form of delusional certainty.

Combined Psychosocial Treatments

Most prodromal centers around the world currently offer psychosocial treatment packages that are mixtures or hybrids of engagement, supportive therapy, case management, stress management, and cognitive behavioral approaches.[23,24] The German Research Network on Schizophrenia divides the prodrome into early and late phases, the early phase characterized primarily by basic symptoms and the late phase by prodromal symptoms and disability. This group recommends CBT for the earlier phase and pharmacotherapy for the later phase.[25,26]

Family-Based Treatment

Family-based treatment of prodromal patients has been modeled upon multifamily group psychoeducation approaches with first-episode schizophrenic patients.[27] This approach is also formulated around the stress-vulnerability model of psychosis and the assumption that this model applies to cases that are prodromal as well as to cases that are already psychotic.

The treatment addresses several domains of risk factors. These were originally identified as mediators of relapse in established schizophrenia, but they may also be mediators of onset in prodromal patients, especially if onset is viewed as the "original" relapse. Among the risk factors identified and targeted by family treatment are high levels of expressed emotion (criticism, overinvolvement) in families toward patients, high levels of stigma aimed at patients and families resulting in unhealthy social isolation, and high levels of communication deviance resulting in poor family focus and uncoordinated familial collaboration.

Family intervention usually is initiated when the patient is admitted to the study. It tries to involve family and patient together and consists of 4 treatment stages: (1) engagement, (2) education, (3) re-entry, and (4) social/vocational rehabilitation.

The engagement phase aims to establish rapport and gains consent of the family and patient to enter ongoing treatment. The education phase is conducted via workshop sessions that provide classroom-like information about the biological, psychological, and social nature of psychotic disorders and their management. Following the workshop, meetings begin twice monthly with the family and the patient in the multigroup format. Content of sessions includes treatment compliance, stress reduction, modifying and mollifying life events, avoiding drugs and alcohol, and modifying expectations while patient and family are dealing with symptoms and their functional consequences. With time and better symptom control, the themes change to encompassing social and vocational rehabilitation. As noted by McFarlane,[27] much of the effectiveness of this treatment results from increasing the size of the patient's and family's social networks by reducing the experience of being stigmatized and by providing a forum for sharing similar problems and finding collaborative solutions.

McFarlane's Psychoeducational Multi-Family Group (PMFG) approach has been adapted by O'Brien and Cannon at University of California Los Angeles, with slight modification, for adolescents in the prodrome. M. O'Brien and T. Cannon (Personal Communication, 2006) report as follows:

> … we have implemented PMFG procedures patterned after those described by McFarlane (2002) and modified so as to be appropriate for a prodromal population (O'Brien et al., in preparation), along with a parallel set of procedures for group therapy with individual patients who do not have a family member available to participate. Each PMFG consists of approximately 7 families and is co-led by two specially trained therapists. There are separate groups for young adolescents (ages 12-14-middle school age), and older adolescents (ages 15-17 or 18). Before each group begins, a series of "joining sessions" allow the therapists to address individual family concerns and to forge a working alliance

with each family. All participants are invited to a half-day long psycho-educational workshop, led by the co-therapists and other relevant project staff, during which they are presented with information about the prodromal state, reasons for early intervention, biological basis for mental disorders, stress-vulnerability theories, psychopharmacological treatment, psychological treatment, school interventions, and recommendations for creating a protective environment. Following the workshop, groups begin meeting bi-weekly for 90-minute sessions over nine months (i.e., a total of 18 sessions). Meetings are structured to allow for the development of social, communication, and problem-solving skills and to support families' efforts to manage symptoms.

The first two group meetings focus on building comfort and a sense of a common mission among group members. In the first session, participants are asked to talk about themselves outside of the context of mental illness. The focus in on getting to know each member as a person and to understand each person's interests and strengths. The goal is to build some common ground among members, and to encourage them to maintain their involvement in these important pursuits. During the second session, each member is asked to discuss some of the symptoms that brought him or her to the treatment group. Typically, during this meeting, people report feeling relief as they hear they are not alone in their struggles with symptoms and they report feeling some hope that together with the other group members they will be able to solve some of the problems they are currently confronting. All remaining sessions are structured similarly. The first 15 minutes are spent socializing so that symptomatic young people and isolated families have the opportunity to practice talking about everyday matters with others. These skills are essential to building relationships in the community. Next, there is a "go-around" where each group member talks about what is going well that week, and what could be going better. After hearing about current challenges the group members are experiencing, the co-leaders identify a problem for the group to focus on during the remaining time. The problem is clarified and some contextual information is provided by the group member who is the focus of the problem solving. Then the group brainstorms possible solutions to the problem. Once a range of solutions has been listed, the group evaluates the pros and cons of each suggestion. Then, the individual member who has reported the problem is asked to select some solutions that he/she is willing to try. A detailed action plan is developed and a description of the problem solving session is later e-mailed to all group members for their reference. Each group meeting concludes with some socializing. This group format is supplemented by individual and/or individual family sessions as needed (i.e., to handle crises, etc.)

Antipsychotic Pharmacology

The greatest diversity of treatment practices in the prodrome exists around the use of antipsychotic medication. One double-blind clinical trial of medication vs placebo has been conducted to date,[4] hardly a sufficient database to be informative or directive. Nevertheless, antipsychotic medication treatment recommendations still exist because these medications are powerful and because they constitute the mainstay of therapy for established psychosis. Without data, however, the recommendations are heavy on opinion and light on informed direction.

Indeed, no common direction emerges from the practices that exist and have been outlined. Some prodromal centers recommend against long-term antipsychotics unless and until an established *DSM-IV* diagnosis of psychosis can be made[20] or until frank positive symptoms have emerged for at least 1 week.[17] Another center endorses psychosocial interventions and symptom-focused drug treatment for depression or anxiety in the early prodromal phase and additional antipsychotics in the late prodromal phase for psychotic symptoms and provides detailed recommendations concerning drugs and doses, eg, perphenazine 4–6 (12) mg, risperidone 0.5–1 (2) mg, olanzapine 2.5–5 (10) mg, or quetiapine 25–200 mg (R. Salokangas and M. Heinimaa, Personal Communication, 2006). Still others recommend against antipsychotics in principle but not in situations where there is risk of self-harm or aggression.[17] Finally, the German Research Network on schizophrenia recommends against drug treatment of the early prodromal (basic symptoms) but is conducting a clinical trial of amisulpride for the late prodrome,[15,26] the criteria for which are similar to the attenuated symptom groups of other centers.

The only clear conclusion that can be drawn from the existing practices is that much more clinical trial research needs to be done. Open-label trials of aripiprazole[28] and of non-antipsychotic compounds such as glycine[29] and omega-3 fatty acids[30] are being conducted, and such efforts should be welcome. Ultimately, however, the risk-benefit ratio of antipsychotic medication treatment for this new clinical entity will not become clear until multiple clinical trials utilizing Cochrane-strict methodology are conducted.

Non-Antipsychotic Pharmacotherapy

In addition to meeting criteria for a prodromal syndrome, many patients struggle with additional problems and symptoms suggesting the presence of one or more concomitant symptom constellations and/or disorders. Common "adjunctive" psychopathologies include bipolar disorder, major depressive and/or dysthymic disorder, anxiety disorders (especially social phobia), personality disorders (especially avoidant), and substance use disorders (especially marijuana). Many patients come to the prodromal clinic already being treated for one or more of these, eg, antidepressants for low mood, mood stabilizers for cycling mood or irritability, benzodiazepines for anxiety, and 12-step dual diagnosis programs for substance abuse and dependence.[20]

Such adjunctive problems are treated rather uniformly across prodromal centers. If the patient is already being treated with medication for mood, anxiety, or substance use at intake, it is usually continued. Should such problems emerge while the patient is being followed in the

center, non-antipsychotic pharmacotherapy is often begun, eg, mood stabilizers for bipolar mood swings, anti-depressants for depressed mood, and benzodiazepines for anxiety (for limited periods of times).[20] Such an approach is often labeled "symptomatic treatment," a term which suggests that the prescribed drug is specific to the symptom and does not affect the trajectory of the prodrome. This assumption that adjunctive medicine is orthogonal to the prodrome may be in error. Certainly no studies have been conducted to date demonstrating that symptomatic treatment is limited to the symptom and fails to impact the prodromal syndrome. Indeed, anti-depressants and mood stabilizers such as lithium are felt by some[31] to reduce the probability of conversion to psychosis. Such studies are clearly needed given the popularity of off-label symptom-focused prescriptions.

Important Issues for the Future

Many issues not addressed here are important foci for future studies of prodromal recruitment and treatment. One is the distinction between being at risk and being disordered, ie, what is meant by "conversion" or "onset" and how this point can be tested for validity. Another is how recruitment can maximize the ratio of true- to false-positive prodromal cases. The recruitment practices described in this article target "help-seeking" prodromal patients and, as noted by Van Os and Delespaul[32], the high ratio of true- to false-positive cases ascertained in the study centers described here means that current recruitment has been successful in drawing, encountering, or finding highly selected samples that are "enriched" with risk. How and why these recruitment strategies accomplish this enrichment is an important clinical epidemiologic question. While this communication samples descriptively the nature of existing recruitment practices among nascent prodromal clinics in research samples, careful comparative epidemiological studies of recruitment practices and resulting samples are needed to answer the question as to how enrichment happens and how it might be engineered.

Summary: Toward Treatment Guidelines

As noted above, the symptomatic prodromal state is a new clinical entity. As such, all treatments of this entity are experimental or "off-label." Furthermore, much more research will be required before clear treatment guidelines can be articulated that maximize benefit and minimize risk. Nevertheless, certain clinical strategies appear close to achieving guideline status because they are common to most if not all prodromal centers worldwide. Those have been highlighted in this communication, and they are summarized by Yung et al[6] in their book on prodromal treatment. Their core elements of the current treatment of the prodromal patient are reproduced below.

- Young people who are distressed by signs and symptoms of an at risk mental state (ARMS) and are seeking treatment should be:
  - —engaged and assessed by a mental health service that is aware of the unique needs of this clinical group;
  - —offered regular monitoring of state;
  - —offered specific treatment for syndromes, such as depression, anxiety or substance misuse, and assistance with other problem areas as necessary (such as interpersonal, vocational and family-related);
  - —provided with psychoeducation and support to better understand the symptoms they have experienced;
  - —offered treatment to assist in developing skills to cope with subthreshold psychotic symptoms that might be experienced;
  - —offered family education and support;
  - —provided with information in a flexible, clear and careful way about risks for mental disorders, as well as existing syndromes
  - —provided with appropriate treatment with minimal delay if symptoms worsen and an acute psychotic episode develops.

Appendix 1. Educational Brochure About the Prodrome

PRIME (Prevention through Risk Identification, Management & Education) Research Clinic. Mental and emotional problems are similar to other medical illnesses. If left untreated, they are likely to get worse over time. The PRIME Research Clinic is dedicated to the early identification and treatment of serious mental and emotional problems. Is someone you know at risk?

Risk Factors

- Trouble at school or work
- Difficulty concentrating or thinking clearly
- Suspiciousness or mistrust of others
- Changes in the way things look or sound
- Odd thinking or behavior
- Withdrawal from friends and family
- Poor personal hygiene

Through integrated and comprehensive services, PRIME aims to:

- Identify and monitor signs of risk for psychotic illness
- Reduce symptoms of mental and emotional difficulties
- Better understand the development of pre-psychotic illness

PRIME Research Clinic Overview

The PRIME Research Clinic is specifically designed for persons, ages 13 to 45, who are experiencing worrisome

changes in their thoughts, experiences, and/or feelings. The PRIME Research Clinic offers:

- Clinical evaluations
- Diagnostic clarification
- Clinical consultation
- Follow-along monitoring
- Clinical trials
- Neuropsychological testing
- Neurological evaluations
- Community education

The PRIME clinical team works collaboratively with school systems and community providers. All study-related services are free of charge.

How the PRIME Research Clinic Can Help

As with physical illnesses, the early identification and treatment of mental and emotional problems may lead to a better prognosis. The longer an illness is left untreated, the greater is the disruption to the person's ability to study, work, meet new friends, and socialize comfortably.

Individuals at risk for serious mental illness often are concerned with changes in their thoughts, feelings, or experiences. These changes, however, are often difficult to describe. Although something may not feel right, an individual has a hard time pinpointing what has changed or understanding what the changes mean.

The PRIME Research Clinic aims to reduce early symptoms of serious mental illness. At PRIME, people have the opportunity to discuss their concerns and participate in research studies focusing on identifying, monitoring and managing troubling symptoms and at-risk signs of serious mental illness.

Appendix 2

Consent for Participation in a Research Project

(Parent/Guardian of Minor)

Yale University School of Medicine

Invitation to Participate and Description of Project.

Title of Study: Delaying or Preventing Psychosis: A Clinical Trial of Olanzapine in Persons Prodromal to Psychosis

You (your child) are invited to participate in this research study designed to determine if certain kinds of early treatment reduce the risk for serious mental illness. Psychosis is a type of serious mental illness in which people can hear or see things that others cannot hear or see, hold strong beliefs about things that are not really true, take poor care of themselves, and/or have trouble making sense. People may experience milder forms of these symptoms such as having unusual perceptions, feeling suspicious of others sometimes without true cause, having trouble organizing their speech such that others have trouble following what they are saying, or feeling flat, unreal, unmotivated, and unrelated like they have lost their emotions. Sometimes these milder experiences don't go away or get worse and lead to psychosis, which is serious. Other times these milder symptoms go away with time or treatment. At the present time, we do not know what makes the difference between these symptoms going away, staying, or getting worse. Understanding these outcomes better is one of the purposes of this study.

Psychotic experiences can be treated effectively with counseling and what are called antipsychotic medications. Preliminary studies suggest that these types of medications can also be used to treat milder forms of psychotic experiences as well. Therefore, in this study we plan to test whether an antipsychotic medication called olanzapine is better than placebo (sugar pill) in reducing symptoms and possibly preventing the symptoms from coming back, getting worse, or leading to psychosis.

You have been invited to participate because you have been struggling with symptoms and problems that may be milder forms of psychotic experiences. Please note that we do not know this for sure. What you are going through may be temporary and/or unrelated to psychosis. We want to find out by inviting you to participate in this study where we can follow you with clinical tests over time.

While the goal of this study is to help you feel better and more in-control of your life, it is possible that you will feel worse, especially if you are receiving placebo. This is a risk of your being in the study. You may also feel worse due to the side effects of olanzapine. If you are in the study and your condition gets worse it will be noticed rapidly because you will be making regular visits to the doctor. If this happens, you will get more treatment; for example more study drug and/or counseling.

There may be risks from your participation in this study. Olanzapine has to date been taken by about 6,900 (study) patients and has been used in the treatment of over three and one half million people.

(Next is detailed all common and uncommon side effects of the drug.)

Your participation in this study may involve receiving treatment that is not necessary or specific to your problem. Furthermore, participation in this study may lead you to worry unnecessarily about having or developing a more serious problem when in fact that might not happen. We hope that by paying careful attention to you and your clinical symptoms over time, the study doctors will help you to manage such anxieties by giving you the benefit of reassurance if things are well and help if things are not.

This study may provide some benefit to you. You will receive family and/or individual counseling on a regular

basis and for any crisis. You may receive information about your health from any physical examinations and laboratory tests that are done in this study. Furthermore, the availability of careful and responsive ongoing clinical testing is one of the benefits of this study. The study offers a system of careful monitoring that could spot troubles rapidly and start appropriate treatments early. If you develop problems they may be identified and evaluated much faster since you will be making regular visits to the doctor.

Appendix 3. SIT Manual

Potential Functional Goal Targets

Please circle the areas that are problems for you or those that you'd like to work on in therapy

- I don't have enough friends
- I don't know what to do with my free time
- I don't have enough hobbies
- I don't have a good job
- I don't socialize enough
- I stay home too much
- I am bored a lot
- I don't like where I live or my living situation
- I have trouble interviewing for jobs
- I have trouble starting and keeping up conversations
- I don't have a boyfriend/girlfriend
- I would like to go back to school but don't know how to get started on it
- I am nervous around other people
- I am not very independent
- I don't do any of my own food or clothes shopping
- I don't like coming to the clinic
- I don't take good care of myself
- I am worried about my health
- I have bad habits that I would like to change (eg, smoking)
- I don't spend enough time with my family

References

1. Woods SW, Miller TJ, McGlashan TH. The prodromal patient, both symptomatic and at risk. *CNS Spectrums*. 2001;6: 223–232.
2. 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.
3. Morrison AP, French P, Walford L, et al. Cognitive therapy for the prevention of psychosis in people at ultra-high risk: randomised controlled trial [see comment]. *Br J Psychiatry*. 2004;185:291–297.
4. McGlashan TH. Randomized, double-blind trial of olanzapine versus placebo in patients prodromally symptomatic for psychosis. *Am J Psychiatry*. 2006;163:790–799.
5. Proctor Guideline for the Treatment of Patients with Schizophrenia. Second Edition: Vol 161(2):1–56, 2004.
6. Yung A, Phillips L, McGorry PD. Treating Schizophrenia in the Prodromal Phase. London, England: Taylor & Francis; 2004.
7. McGorry PD, Yung AR, Phillips LJ. The "close-in" or ultra high-risk model: a safe and effective strategy for research and clinical intervention in prepsychotic mental disorder [see comment]. *Schizophr Bull*. 2003;29:771–790.
8. McGlashan TH, Miller TJ, Woods SW. Pre-onset detection and intervention research in schizophrenia psychoses: current estimates of benefit and risk. *Schizophr Bull*. 2001;27: 563–570.
9. Yung AR, McGorry PD. The initial prodrome in psychosis: descriptive and qualitative aspects. *Aust N Z J Psychiatry*. 1996;30:587–599.
10. Yung AR, McGorry PD, McFarlane CA, Jackson HJ, Patton GC, Rakkar A. Monitoring and care of young people at incipient risk of psychosis. *Schizophr Bull*. 1996; 22:283–303.
11. McGlashan TH, Miller TJ, Woods SW, Hoffman R, Davidson L. A scale for the assessment of prodromal symptoms and states. In: Miller TJ, Mednick SA, McGlashan TH, Libiger J, Johannessen JO, eds. *Early Intervention in Psychotic Disorders.* Dordrecht, Netherlands: Kluwer Academic, 2001, pp. 135–150.
12. Miller TJ, McGlashan TH, Woods SW, et al. Symptom assessment in schizophrenic prodromal states. *Psychiatric Q*. 1999; 70:273–287.
13. Miller TJ, McGlashan TH, Rosen JL, et al. Prospective diagnosis of the initial prodrome for schizophrenia based on the Structured Interview for Prodromal Syndromes: preliminary evidence of interrater reliability and predictive validity. *Am J Psychiatry*. 2002;59:863–865.
14. Miller TJ, McGlashan TH, Rosen JL. Prodromal assessment with the structured interview for prodromal syndromes and the scale of prodromal symptoms: predictive validity, interrater reliability, and training to reliability. *Schizophr Bull*. 2003; 29:703–715, [2004; correction, following 217].
15. Hafner H, Maurer K, Ruhrmann SW, et al. Early detection and secondary prevention of psychosis: facts and visions. *Eur Arch Psychiatry Clin Neurosci*. 2004;54:117–128.
16. White T, Anjum A, Schulz SC. The schizophrenia prodrome. *Am J Psychiatry*. 2006;163:376–380.
17. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the treatment of schizophrenia and related disorders. *Aust N Z J Psychiatry*. 2005;9:1–30.
18. Rosen JL, Woods SW, Miller TJ, McGlashan TH. Prospective observations of emerging psychosis. *J Nerv Ment Dis*. 2002; 90:133–141.
19. Phillips LJ, Francey SM. Changing PACE: psychological interventions in the prepsychotic phase. In: Gleeson JFM, McGorry PD, eds. *Psychological Interventions in Early Psychosis.* West Sussex, England: John Wiley & Sons; 2004.
20. Haroun N, Dunn L, Haroun A, Cadenhead KS. Risk and protection in prodromal schizophrenia: ethical implications for clinical practice and future research. *Schizophr Bull*. 2006; 32:166–178.
21. Addington J, Penn D, Perkins DO, Woods SW. Supportive therapy in studies for ultra high risk individuals. *Schizophr Res*. 2004;70:52–53.

22. French P, Morrison AP. Early Detection and Cognitive Therapy for People at High Risk of Developing Psychosis. Chichester, England: John Wiley & Sons; 2004.
23. Larsen TK, Bechdolf A, Birchwood M. The concept of schizophrenia and phase-specific treatment: cognitive-behavioral treatment in pre-psychosis and in nonresponders. *J Am Acad Psychoanal Dyn Psychiatry*. 2003;31:209–228.
24. Bechdolf A, Phillips LJ, Francey SM. Recent approaches to psychological interventions for people at risk of psychosis. *Eur Arch Psychiatry Clin Neurosci*. 2006;256:159–173.
25. Ruhrmann S, Schultze-Lutter F, Klosterkotter J. Early detection and intervention in the initial prodromal phase of schizophrenia. *Pharmacopsychiatry*. 2003;36:S162–S167.
26. Bechdolf A, Ruhrmann S, Wagner M. Interventions in the initial prodromal states of psychosis in Germany: concept and recruitment. *Br J Psychiatry Suppl*. 2005;5–8.
27. McFarlane WR. Family-based treatment in prodromal and first-episode psychosis. In: Miller T, Mednick SA, McGloshan TH, Libiger J, Johannessen JO, eds. *Early Intervention in Psychotic Disorders.* Netherlands: Kluwer Academic Publishers; 2001.
28. Walsh BC, Tully E, McGlashan TH, et al. Aripiprazole treatment of the psychosis prodrome. *Schizophr Res*. 2006;86:s7.
29. Woods SW, Walsh B, Pearlson GD, et al. Glycine treatment of prodromal symptoms. *Schizophr Res*. 2006;86:s7.
30. Amminger GP, Schafer MR. Indicated prevention with omega-3 fatty acids in adolescents at ultra high risk for psychosis-rationale, methods, and 3-months outcome. *Schizophr Res*. 2006;86:s97.
31. Cornblatt BA, Lencz T, Smith CW, Correll CU, Auther AM, Nakayama E. The schizophrenia prodrome revisited: a neurodevelopmental perspective. *Schizophr Bull*. 2003;29:633–651.
32. Van Os JV, Delespaul P. Toward a world consensus on prevention of schizophrenia. *Dialogues Clin Neurosci*. 2006; 53067.