The “Close-in” or Ultra High-Risk Model: A Safe and Effective Strategy for Research and Clinical Intervention in Prepsychotic Mental Disorder

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Abstract

The development of a new frontier for research and early intervention in psychotic disorders is highly dependent on the construction of synergistic clinical infrastructures. This has catalyzed great progress in the recognition, enhanced treatment, and study of first episode psychosis, and the task is even more challenging when the boundaries are extended to include the earliest clinical phase of illness, the prodromal or prepsychotic phase. This article describes the conceptual and practical building blocks for the construction of service models for intervention in the postonset clinical phase prior to the attainment of current diagnostic thresholds. This is best regarded as indicated prevention, a form of very early secondary prevention, which involves a blend of immediate clinical care combined with research-oriented preventive intervention. The experience of the Personal Assessment and Crisis Evaluation (PACE) Clinic in Melbourne across several stages of growth is described and contrasted with that of several emerging centers in Europe and North America. The progress to date, the lessons learned, and the unresolved challenges and opportunities are detailed. It is concluded that service models can be developed that are acceptable and helpful to young people and their families, and that create a unique environment for the study of the transition to frank psychotic disorder. The ultimate clinical utility and general safety of this approach and the range of effective treatments remain unclear, and will be determined by more extensive research. Such research must be conducted in a logical and rigorous manner with the best designs possible, sensitive to input from consumers and caregivers and to ethical considerations.

Keywords: Psychosis, prodrome, high risk, prevention.


In recent years there has been a groundswell of clinical and research interest in early intervention in psychotic disorders (Edwards and McGorry 2002; Malla and Norman 2002). The early psychosis paradigm, which is centered on early detection and optimal treatment of first episode psychosis and the subsequent critical years, has become a sustained growth front in both the clinical and research arenas. This is due to the high stakes involved, the strong commitment to evidence-based medicine, the quality of the research endeavors, and the close integration of the research and clinical questions. Further progress is evident in this special issue of Schizophrenia Bulletin, which reflects the involvement of an increasingly broad range of researchers in the new frontier of prepsychotic or prodromal research.

The rise of the early psychosis paradigm has enabled the prepsychotic phase of schizophrenia and related psychoses to come strongly into focus for the first time. Reacting to the pessimism intrinsic to the concept of schizophrenia and also to the damage wrought by a disorder for which effective treatments were lacking, an earlier generation of psychiatrists were attracted to the notion of prepsychotic intervention (Sullivan 1927; Meares 1959). What remained a dream for decades is now starting to become a reality. This article describes principles and progress in the prospective detection and engagement of young people with incipient psychosis.

Urgent public health challenges associated with psychotic disorders (particularly schizophrenia and bipolar disorder) remain. These include the unacceptable and prolonged delay in accessing treatment even after frank psychosis, well above the diagnostic threshold, has developed (McGlashan 1999) and the all-too-often poor quality of treatment and insecure tenure within specialist mental health care. Such challenges remain, and the task is to design and implement services that are acceptable, effective, and ethically sound. This must be done in a logical and rigorous manner with the best designs possible, sensitive to input from consumers and caregivers and to ethical considerations.
health services, even when initial entry has been achieved (Lieberman and Fenton 2000; McGorry 2002; McGorry and Yung 2003). With the advent (in many countries) of widespread first episode programs aimed at addressing the two major weaknesses of current care, the prepsychotic phase offers a tantalizing additional focus for treatment. It has become possible to detect and engage a subset of young people who are subthreshold for fully fledged psychotic disorder yet who have demonstrable clinical needs and other syndromal diagnoses and who appear to be at incipient risk of frank psychosis (Yung et al. 1996). However, the extension of the early intervention paradigm from mainstream medicine to psychiatry has generated anxiety and controversy in some quarters. Concerns about the risk/benefit balance of early intervention strategies lie at the heart of this controversy and need to be addressed by an evidence-based approach.

Conceptual Issues

The prepsychotic or prodromal phase needs to be clearly distinguished from the premorbid phase on the one hand and the first episode of psychosis on the other. To understand the potential advantages of prepsychotic intervention, it is important to explicate the concept of prodrome, a concept that has only recently become widely used in schizophrenia. The period prior to clear-cut diagnosis has traditionally been referred to as the premorbid phase. However, this term has led to some confusion because it actually covers two phases, not one, and has not been useful from a preventive perspective. Studies of the childhood antecedents of schizophrenia, while demonstrating significant but minor differences between controls and those who later developed schizophrenia, paradoxically highlighted the quiescence of the illness during this phase of life (Jones et al. 1994). However, this study and the findings of Häfner et al. (1995) revealed that psychotic illnesses really begin to have clinical and social consequences after puberty, typically during adolescence and early adult life. The period of nonspecific symptoms and growing functional impairment prior to the full emergence of the more diagnostically specific positive psychotic symptoms constitutes the prodromal phase.

The fact that a very substantial amount of the disability that develops in schizophrenia accumulates prior to the appearance of the full positive psychotic syndrome (Häfner et al. 1995; Agerbo et al. 2003) and may create a ceiling for eventual recovery in young people is a key reason for attempting some form of prepsychotic intervention (table 1). Other benefits include the capacity to research the onset phase of illness and examine the psychobiology of progression from the subthreshold state to the fully fledged disorder. More proximal risk factors such as substance use, stress, and the underlying neurobiology can also be uniquely studied. The delineation of this discrete phase, the boundaries of which are often difficult to map precisely, is of great heuristic and practical value. Whether “prodrome” is the best term for it is, however, debatable (Yung and McGorry 1996a, 1996b; Yung et al. 1998; Phillips et al. 2002a). A number of obstacles to intervention during this phase should also be noted (table 2). These obstacles are largely generic to all preventive or early intervention programs.

Table 1. Potential advantages of prepsychotic intervention

- An avenue for help is provided, irrespective of whether transition ultimately occurs, to tackle the serious problem of social withdrawal, impaired functioning, and subjective distress that otherwise become entrenched and steadily worsen prior to the onset of frank psychotic symptoms.
- Engagement and trust are easier to develop, and a foundation is laid for later therapeutic interventions, especially drug therapy, if and when required. The family can be similarly engaged and provided with emotional support and information outside of a highly charged crisis situation.
- If psychosis develops, it can be detected rapidly and duration of untreated psychosis minimized, and hospitalization and other lifestyle disruption rarely occur. A crisis with behavioral disturbance or self-harm is not required to gain access to treatment.
- Comorbidity, such as depression and substance abuse, can be effectively treated and the patient therefore gets immediate benefits. If psychosis worsens to the point of transition, the patient enters the first episode in better shape with less distress and fewer additional problems.
- If treatment is influencing the underlying biological pathophysiology and/or psychosocial contributory causes, then the onset of psychosis may be either delayed or averted, with substantial health benefits.
- The prospective study of the transition process is enabled, including neurobiological, psychopathological, and environmental aspects. Patients are less impaired cognitively and emotionally and are more likely to be fully competent to give informed consent for such research endeavors.
intervention models and have been confronted in cancer and cardiovascular disease. In psychiatry they are magnified by the tenacious reality of stigma and therapeutic nihilism.

Focus on the Ultra High-Risk Population: The “Close-in” Strategy as a Key Methodological Advance

The model that underpins this new wave of studies is a significant departure from earlier endeavors at identifying high-risk cohorts. The new approach reflects the adage “timing is everything,” aiming to maximize the accuracy of prediction and the need for clinical care as well as preventive intervention. This means focusing on patients who have manifest symptoms and impaired functioning and demonstrate a substantially increased risk of psychosis onset.

Traditional or Genetic High-Risk Model. A range of studies recruited individuals with a family history of psychotic disorder (usually schizophrenia) during early childhood and monitored them over time—in some studies for up to 35 years (Nagler 1985; Fish et al. 1992; Cannon and Mednick 1993; Erlenmeyer-Kimling et al. 1995, 1997; Ingraham et al. 1995; Hodges et al. 1999; Johnstone et al. 2001). Selection of subjects for these studies on the basis of a crude measure of genetic risk (family history) restricts the generalizability of any findings to the early-onset condition, as in the traditional studies. Close-in followup involves shortening the period of followup necessary to observe the transition to psychosis by commencing the followup period close to the age of maximum incidence of psychotic disorders. To improve the accuracy of identifying the high-risk cohort further, Bell also recommended using signs of behavioral difficulties in adolescence as selection criteria, such as the inclusion of clinical features. This also allows the approach to become more clinical, to move away from traditional screening paradigms, and to focus on help-seeking troubled young people, who are therefore highly “incipient” and frankly symptomatic. To maximize the predictive power as well as enable the engagement of the patient to be well justified on immediate clinical grounds, the timing is critical. Patients should be as “incipient” as possible, yet this is difficult to measure and consistently sustain. Transition rates in samples may therefore vary on this basis and also because of differences in the underlying proportions of true and false positives and high rates of false positives, and they tend to become obsolete before their eventual completion date. This strategy was better suited to clarify pathophysiological candidates for schizophrenia and other psychoses and was never really a viable basis for widespread early detection.

The Ultra High-Risk or “Close-in” Strategy. The development of an alternative high-risk strategy with a higher rate of transition to psychosis, a lower false-positive rate, and a shorter followup period than in the traditional genetic studies has been central to progress in preventive interventions for psychosis. Bell (1992) proposed that “multiple-gate screening” and “close-in” followup of cohorts selected as being at risk of developing a psychosis would minimize false-positive rates. Multiple-gate screening is a form of sequential screening that involves putting in place a number of different screening measures to concentrate the level of risk in the selected sample. In other words, an individual must meet a number of conditions to be included in the high-risk sample rather than just one condition, as in the traditional studies. Close-in followup involves shortening the period of followup necessary to observe the transition to psychosis by commencing the followup period close to the age of maximum incidence of psychotic disorders. To improve the accuracy of identifying the high-risk cohort further, Bell also recommended using signs of behavioral difficulties in adolescence as selection criteria, such as the inclusion of clinical features. This also allows the approach to become more clinical, to move away from traditional screening paradigms, and to focus on help-seeking troubled young people, who are therefore highly “incipient” and frankly symptomatic. To maximize the predictive power as well as enable the engagement of the patient to be well justified on immediate clinical grounds, the timing is critical. Patients should be as “incipient” as possible, yet this is difficult to measure and consistently sustain. Transition rates in samples may therefore vary on this basis and also because of differences in the underlying proportions of true and false positives and high rates of false positives, and they tend to become obsolete before their eventual completion date. This strategy was better suited to clarify pathophysiological candidates for schizophrenia and other psychoses and was never really a viable basis for widespread early detection.
positives of those who enter the sample. It should be emphasized that young people involved in this strategy have clinical problems, and help is being sought either directly by them or on their behalf by concerned relatives.

The ideas expressed by Bell (1992) were first translated into practice in Melbourne, Australia, in 1994 at the Personal Assessment and Crisis Evaluation (PACE) Clinic (McGorry and Singh 1995; Yung et al. 1995) in parallel with the development of the Early Psychosis Prevention and Intervention Centre (EPPIC) program (McGorry 1993; Edwards et al. 1994; McGorry et al. 1996). This approach has now been adopted in a number of other clinical research programs across the world (e.g., Cornblatt 2002; Miller et al. 2002; Morrison et al. 2002). These studies have been referred to as ultra high-risk (UHR) studies to differentiate them from the traditional high-risk studies that rely on family history as the primary inclusion criteria. Intake criteria for such studies were initially developed from information gleaned from literature reviews and clinical experience with first episode psychosis patients and have been evaluated and reviewed in the PACE Clinic over the past 8 years. Although UHR studies ostensibly seek to identify individuals experiencing an initial psychotic prodrome, infallible criteria have not yet been developed toward this end. In addition, prodrome is a retrospective concept that can only be diagnosed once. Therefore, criteria used in these studies are referred to as at-risk mental state criteria (ARMS; McGorry and Singh 1995; Yung and McGorry 1997) or precursor signs and symptoms (Eaton 1995). This terminology does not imply that a full-threshold psychotic illness such as schizophrenia is inevitable but suggests that individuals are at risk of developing a psychotic disorder by virtue of their current mental state. This terminology is more conservative than prodrome. Additionally, the ARMS concept acknowledges current limitations in our knowledge and understanding of psychosis. It also has ethical advantages in underlining the reality of false-positive “cases.” It should be noted again that participants in the UHR model are seeking help on a voluntary basis; they are concerned about changes in their mental state and functioning and are requesting some assistance to address these changes. Therefore, while some turn out to be false positives for subsequent psychotic disorder, they are all “cases” in the sense of a need for care. The young people are often overtly concerned about the possibility that they may be developing a psychotic disorder.

UHR criteria currently in operation at the PACE Clinic require that the person fall into one or more of the following groups: (1) attenuated psychotic symptoms group: patients who have experienced subthreshold, attenuated positive psychotic symptoms during the past year; (2) brief, limited or intermittent psychotic symptoms group (BLIPS): patients who have experienced episodes of frank psychotic symptoms that have not lasted longer than a week and have spontaneously abated; or (3) trait and state risk factors group: patients who have a first degree relative with a psychotic disorder or who have a schizotypal personality disorder, and have experienced a significant decrease in functioning during the previous year. Operationalized criteria are shown in table 3. As well as meeting the criteria for at least one of these groups, subjects are between 14 and 30 years old, have not experienced a previous psychotic episode, and live in the Melbourne metropolitan area. Thus, the UHR criteria identify young people who are in the age range for peak incidence of onset of a psychotic disorder (late adolescence/early adulthood) who additionally describe mental state changes that are suggestive of an emerging psychotic process or who may have a strong family history of psychosis. This represents an initial effort to translate the multiple-gate screening and close-in strategies recommended by Bell (1992) into practice. Exclusion criteria are intellectual disability, lack of fluency in English, presence of a known organic brain disorder and a history of a prior psychotic episode (lasting longer than 1 week)—either treated or untreated. It is recognized that some subthreshold cases, in particular those meeting BLIPS criteria, might meet criteria for DSM-IV brief psychotic disorder.

Criteria have also been developed to define the onset of psychosis in the UHR group (table 3). These are not identical to DSM-IV criteria but are designed to define the minimal point at which neuroleptic treatment is indicated. This definition might be viewed as somewhat arbitrary but does at least have clear treatment implications and applies equally well to substance-related symptoms, symptoms that have a mood component (either depression or mania), and schizophrenia spectrum disorders. The predictive target is first episode psychosis that is judged to require antipsychotic medication, arbitrarily defined as the persistence of frank psychotic symptoms for over 1 week. Schizophrenia is a subset or subsidiary target, because although the majority of progressions from the ARMS fall within the schizophrenia spectrum (schizoaffective disorder or schizophrenia), a significant minority do not. In fact, the broader first episode psychosis target is a more proximal and therapeutically salient one than schizophrenia, which can be considered a subtype to which additional patients can graduate distal to the first episode psychosis (as well as being one of the proximal categories). This logic applies to the early intervention field generally, where first episode psychosis is a more practical and safer concept than first episode schizophrenia (again best considered as a subtype) (McGorry 1995).

This strategy derived subsequent support from a landmark publication addressing contemporary conceptualiza-
Table 3. PACE Clinic Inclusion criteria according to CAARMS* scores

Group 1: Attenuated Psychosis Group This criterion identifies young people at risk of psychosis due to a subthreshold psychotic syndrome. That is, they have symptoms which do not reach threshold levels for psychosis due to subthreshold intensity (the symptoms are not severe enough) or they have psychotic symptoms but at a subthreshold frequency (the symptoms do not occur often enough)

2a) Subthreshold Intensity:
- Severity Scale Score of 3-5 on Disorders of Thought Content subscale, 3-4 on Perceptual Abnormalities subscale and/or 4-5 on Disorganized Speech subscales of the CAARMS; plus
- Frequency Scale Score of 3-6 on Disorders of Thought Content, Perceptual Abnormalities and/or Disorganized Speech subscales of the CAARMS* for at least a week, or
- Frequency Scale Score of 2 on Disorders of Thought Content, Perceptual Abnormalities and Disorganized Speech subscales of the CAARMS on more than two occasions

2b) Subthreshold frequency:
- Severity Scale Score of 6 on Disorders of Thought Content subscale, 5 or 6 on Perceptual Abnormalities subscale and/or 6 on Disorganized Speech subscales of the CAARMS*; plus
- Frequency Scale Score of 4-6 on Disorders of Thought Content, Perceptual Abnormalities and/or Disorganized Speech subscales; plus
- Each episode of symptoms is present for less than one week and symptoms spontaneously remit on every occasion; plus
- Symptoms occurred during last year and for not longer than five years

Group 2: Brief Limited Intermittent Psychotic Symptoms (BLIPS) Group This criterion identifies young people at risk of psychosis due to a recent history of frank psychotic symptoms which resolved spontaneously (without antipsychotic medication) within one week
- Severity Scale Score of 6 on Disorders of Thought Content subscale, 5 or 6 on Perceptual Abnormalities subscale and/or 6 on Disorganized Speech subscales of the CAARMS; plus
- Frequency Scale Score of 4-6 on Disorders of Thought Content, Perceptual Abnormalities and/or Disorganized Speech subscales; plus
- Each episode of symptoms is present for less than one week and symptoms spontaneously remit on every occasion; plus
- Symptoms occurred during last year and for not longer than five years

Group 3: Vulnerability Group This criterion identifies young people at risk of psychosis due to the combination of a trail risk factor and a significant deterioration in mental state and/or functioning
- First degree relative with a psychotic disorder or schizotypal personality disorder in the identified patient (as defined by DSM-IV); plus
- Significant decrease in mental state or functioning maintained for at least a month and not longer than 5 years (reduction in GAF Scale of 30 percent from pre-morbid level); plus
- The decrease in functioning occurred within the past year and has been maintained for at least a month.

Full threshold psychosis criteria
- Severity Scale Score of 6 on Disorders of Thought Content subscale, 5 or 6 on Perceptual Abnormalities subscale, and/or 6 on Disorganized Speech subscales of the CAARMS; plus
- Frequency Scale Score of greater than or equal to 4 on Disorders of Thought Content, Perceptual Abnormalities, and/or Disorganized Speech subscales; plus
- Symptoms present for longer than one week.

Note.—CAARMS = Comprehensive Assessment of At-Risk Mental States; GAF = Global Assessment of Functioning.

“Close-in” or Ultra High-Risk Model

Mrazek and Haggerty (1994) wrote that the current lack of definitive knowledge about the etiology and risk factors for psychotic disorders, particularly schizophrenia, meant that developing universal (targeting the entire population) and selective (targeting groups whose risk of developing psychosis is significantly higher than average) preventive interventions is not currently possible. Rather, they suggested that indicated prevention—targeting individuals who exhibit subthreshold signs and symptoms of psy-
chosis—was the most appropriate approach. They further suggested that combining known risk factors provides the best chance for identifying high-risk individuals—that is, the multiple-gate screening approach. The theoretical basis for this drew on the work of Eaton (1995), who was looking at subthreshold clinical features as a form of proximal risk factor for full clinical disorder, in this case depression, and opened up the whole notion of how disorders actually “onset” and what constitutes an initial “case.” Acquisition, intensification, and coherence of symptoms and syndromes are necessary but perhaps insufficient dimensions for “caseness” (Eaton 1995). Other variables such as distress, additional comorbidity (van Os et al. 1994), functional impairment, and perceived and objective “need for care” also need to be considered as necessary features or alternatively as “risk factors for caseness.” Clearly, greater precision is necessary for defining the onset of mental disorders generally, not only schizophrenia and psychotic illnesses.

The criteria described above were evaluated in a series of studies at the PACE Clinic between 1994 and 1996. Young people meeting the ARMS criteria were recruited and their mental state was monitored over a 12-month period. Forty-one percent of the cohort had developed an acute psychosis and had been started on appropriate neuroleptic treatment at the end of the followup (Yung et al. 1998, 2003). This occurred despite the provision of minimal supportive counseling, case management, and selective serotonin reuptake inhibitor medication if required. The primary diagnostic outcome of the group who developed an acute psychosis was schizophrenia (65%) (Yung et al. 2003).

The high transition rate to psychosis indicates that the PACE criteria accurately identify young people with an extremely high risk of developing a psychotic disorder within a short followup period. These results cannot be easily generalized to the wider population or even to individuals who have a family history of psychosis but are asymptomatic. Participants recruited to research at the PACE Clinic are a selected sample, characterized perhaps by high help-seeking characteristics or other nonspecific factors. It undoubtedly includes only a minority of those who proceed to a first episode of psychosis, and a possibly unstable proportion of false positives, depending on sampling and detection factors, which in turn are difficult to define and measure but can affect the base rate of true positives in the sample. Hence, the transition rate may vary and needs to be validated and monitored because the UHR criteria are not the only variable involved. However, these criteria are now being utilized in a number of other settings around the world, with preliminary results indicating that they predict as well in the United States, the United Kingdom, and Norway as they do in Melbourne, Australia (Larsen 2002; Miller et al. 2002; Morrison et al. 2002). Undoubtedly, there are other clinical features and nonclinical variables that need to be identified and incorporated into future definitions of the UHR state. In our view, the UHR concept better lends itself to this task than does the concept of prodrome.

Establishing a Prepsychotic Clinical Research Environment

Aims and Principles. There are several key, interdependent aims of such clinical research programs:

1. To improve the understanding of the neurobiological and psychosocial processes that occur during the prepsychotic phase and contribute to the onset of acute and persistent psychosis. Conversely, processes that protect against progression and promote recovery and resolution of symptoms and impairment may be clarified.

2. To improve the predictive power for identification of individuals at risk for psychosis (or schizophrenia vs. affective psychosis) to better target treatment interventions.

3. To develop and evaluate a range of psychosocial and biological interventions to treat current syndromes and prevent future disorders from fully expressing themselves. Effectiveness and safety issues, including stigma, need to be evaluated hand in hand.

4. To establish a clinical service that is not only highly accessible but also acceptable to young people at ultra high risk of developing psychosis.

5. To educate the community about early signs of mental illness in general and psychosis in particular.

The PACE Clinic: An Example of an Integrated UHR Clinical/Research Program. The PACE Clinic was established in Melbourne, Australia, in 1994 (Yung et al. 1995). It is one arm of a comprehensive early psychosis research program affiliated with EPPIC (McGorry 1993; McGorry et al. 1996). Although the clinic initially operated on a limited basis with a part-time consultant psychiatrist and one research psychologist, its team now comprises 12 clinical/research staff. The modest beginnings with a necessarily limited research agenda of mapping the onset of psychosis and establishing valid criteria for identifying the UHR cohort have blossomed into a more sophisticated clinical research structure. This growth has also mirrored an increased focus on youth mental health in Melbourne over the past few years and the establishment of a youth mental health service (ORYGEN Youth
The PACE Clinic, EPPIC, and ORYGEN Youth Health have always sought to distinguish themselves from mainstream mental health services, which are typically viewed in an extremely negative light, particularly by young people. PACE’s name is deliberately generic in order to avoid stigma and labeling. This reduces disincentives to help-seeking and engagement. Furthermore, PACE has always been located within nontraditional mental health settings such as generic youth health or community health settings or, more recently, within a large metropolitan shopping center. Where possible, clinicians and researchers do not limit themselves to working within the office but initially aim to engage with young people in their own environment (e.g., at home, at school, or in primary care settings). These methods seem to largely overcome the effects of stigma, with 72 percent of all accepted referrals coming for three or more visits and 55 percent agreeing to involvement in research.

A much more flexible approach is required when working with young people, who typically are naïve users of mental health services. An initial willingness to go to them—to meet them “on their own turf”—helps minimize initial nonattendance. This flexibility is now expected within the service system, and clinicians tend to self-select to embrace this model of care. Similarly, the multidisciplinary PACE team, reflecting changes within the local mental health scene, undertake a broad range of case management and therapy tasks. Clinical case management in Australia is handled by professionals in a range of disciplines, including psychologists. Cognitive therapy tends to remain the province of psychologists and, within PACE, psychologists provide both types of intervention. PACE services are free and offered as part of the public mental health system, even though the bulk of the funding derives from research grants.

Although PACE seeks to distinguish itself from traditional mental health services, which tend to focus on those who already have diagnosable levels of disorder, it also benefits from close relationships with such services, especially EPPIC. Many referrals to PACE come from other mental health services. Such patients experience less stigma through diversion from traditional psychiatric settings into the low-stigma PACE environment. Additionally, if members of the UHR cohort do develop acute psychosis, then referral to another service (preferably an early psychosis-specific service) for treatment is necessary.

Other referrals to the PACE Clinic come from the educational sector, primary health services, drug and alcohol services, and other youth-oriented services (Phillips et al. 1999, 2002a). A key challenge facing the clinic, therefore, has been to educate potential referrers about psychotic disorders and the signs of an emerging psychotic disorder, and also about the PACE Clinic itself. Given the specificity of the intake criteria, a widespread saturation campaign about these issues is normally considered too expensive and time-consuming (although such a comparison is now underway in our region, with the broader objective of early intervention in youth mental health). A more strategic approach is usually necessary.

Incidence rates of first episode psychosis indicate that within the Northwestern Melbourne region there are potentially 500 UHR cases per year (Krstev et al., submitted). Referrals to PACE in previous years clearly indicate that many of these young people seek some assistance or explanation for the mental state changes they are experiencing. Most commonly, they go first to someone already known to them (e.g., a general practitioner or school-based counselor, rather than a mental health service). Therefore, community education at PACE has targeted these potential referrers: general practitioners, psychiatric services, school and university counseling services, and other support agencies working with young people, such as drug and alcohol services (Phillips et al. 1999). Support groups for siblings and children of individuals with psychotic disorders are also provided with information about PACE as an available clinical service. The clinic works closely with other mental health services, as previous experience shows that these services tend to refer most accurately to PACE. Formal professional development and training forums as well as informal case discussions and secondary consultation are used to inform potential referrers about the clinic. Close working relationships are established with the most relevant services in an attempt to address some of the usual barriers to referral. These activities are described in detail elsewhere (Phillips et al. 1999, 2002a).

Additionally, brochures, newsletters, a promotional video, and various other materials about the research and clinical program at PACE and the profile of young people attending the service are regularly produced and distributed. Staff members with a clinical background carry out these tasks as well as provide secondary consultation. The same clinicians provide the triage component for the clinic as a whole. This allows for continuity between the professional development/training activities and the referral triaging process—making referrals smoother. Community education strategies have ensured that PACE is recognized as a potential referral point for professionals who may have concerns about a young person they are working with. The capacity to offer a clinical service to patients from their early teens to their late twenties has been a critical factor.
behind the growth of PACE, EPPIC, and the ORYGEN Youth Health concept. The creation of a third tier, one positioned between child psychiatry and adult psychiatry, is a challenging long-term objective that has attracted strong support from many clinicians, consumers, and families but considerable resistance from health bureaucrats and professional groups within psychiatry. The partial breaking of the mould achieved by the PACE/EPPIC models has been based upon local opportunities, a strong theoretically and clinically oriented model, and the capacity to attract substantial research funding to underpin the clinical reform agenda. From the PACE standpoint, the link with a very substantial first episode psychosis program has been critical. In Australia, the creation of this third tier is inhibited by the global undersourcing of mental health services, although the new approach may not be intrinsically more expensive (McGorry and Yung 2003). The public mental health service system is not fundamentally insurance-based but derived from historical reallocations of the resources of the former asylum model. With funding growth, a wider adoption, as in the United Kingdom, of early intervention models will be quite feasible.

**Measurement.** Early in the establishment of the PACE Clinic and the associated research program, it became obvious that existing psychopathology measures were inadequate for assessing prepsychotic symptomatology. Although scales such as the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham 1962; McGorry et al. 1988), the Scale for the Assessment of Negative Symptoms (Andreasen 1982), and the Positive and Negative Syndrome Scale (Kay et al. 1987) are commonly used in research with psychotic patients—including those with first episode psychosis—it was felt that they did not allow for a sufficiently fine-grained assessment of the subthreshold positive symptoms or the full range of precursor symptoms required at this earlier phase (Yung and McGorry 1996b). For this reason, in 1994, a semistructured interview aimed at assessing prepsychotic (prodromal) symptomatology began to be developed in serial fashion: the Comprehensive Assessment of At-Risk Mental States (CAARMS). Unlike other symptom assessment tools, which collapse the intensity, frequency, and duration of symptoms into one score, the CAARMS tease out each of these individual aspects. Therefore, it can track small changes in the symptoms and individual experiences, such as an increase in the frequency of hearing voices from weekly to daily with no change in the intensity of the experiences. A cruder instrument such as the BPRS may not pick up such subtle changes. Drawing on the work of the Bonn-Cologne group of Huber and Klosterkötter (Klosterkötter et al. 1997), the CAARMS also enables assessment of subjectively experienced changes such as the subjective sense of cognitive impairment, which can be rated on the Conceptual Disorganization scale on a continuum with other objectively observed formal thought disorder, as well as subjective emotional changes. The CAARMS has been found to have good to excellent interrater reliability and predictive validity (Yung et al., submitted). More recently, the UHR criteria have been operationalized using CAARMS rather than BPRS scores (table 3). A copy of the CAARMS is available from Dr. Yung on request.

A similar instrument, now well validated, has also been developed by the PRIME group (the Structured Interview for Prodromal Symptoms [Miller et al. 1999, 2002]). While there was initial close correspondence between the two assessment procedures because of their common ancestor, the ARMS criteria, the process of separate local evolution may have introduced some variation. The further development of reliable and valid methods for assessing prepsychotic symptomatology across multiple centers is a crucial step for research progress in this area.

In addition to establishing the validity of the intake criteria for the clinic, early work at PACE increased familiarity with the profile of clients meeting ARMS or UHR criteria and their clinical needs. Young people attending the clinic were offered clinical care and treatment, as it was felt that offering monitoring alone was unethical in view of the patients' clinical status and help-seeking nature. Treatment with neuroleptics at this early stage was clearly premature, as the high-risk nature of the client group had not yet been established, and the risk/benefit balance of such treatment had not been researched. Thus, clients attending PACE at this stage received supportive counseling and more specific psychotherapeutic strategies (particularly cognitive-behavioral) where appropriate. Antidepressant and anxiolytic medication was also provided if deemed necessary. Treatment was therefore focused on the presenting clinical problems and was offered for a period of 1 year, after which time clients were referred elsewhere if appropriate. Those who developed acute psychosis were commenced promptly on low-dose atypical neuroleptic medication and transferred to a more appropriate service for continuing care—in most cases the EPPIC program. This careful and relatively standardized approach minimized confounding factors that might have masked the transition to psychosis. In our view, naturalistic studies that permit treatment that is not standardized by protocol and carefully monitored, particularly if the use of "doctor's choice" neuroleptic medication is allowed, will not provide useful information in terms of prediction or treatment efficacy. Open trials of particular types of medication or psychotherapy may still have a place, but unregulated, non-protocol-driven intervention is unlikely to add clarity. This will probably
become an area of controversy as data from a range of centers accumulate.

Studies of Prediction and Neurobiology of Transition. The development and validation of criteria that identify young people at very high risk of developing a psychotic disorder within a short follow-up period have created a novel channel for further research evaluating putative risk factors for psychosis onset. These include mental state changes such as presence of mood and anxiety features, Huber’s basic symptoms (Koehler and Sauer 1984; Gross 1989; Klosterkötter et al. 2001), drug and alcohol usage, neurocognitive impairment, obstetric complications, delayed childhood milestone achievement, and possible trait markers, including neurological abnormalities and poor premorbid adjustment (Olin and Mednick 1996; Buckley 1998; Ismail et al. 1998). The investigation of the presence of viral antibodies (Torrey 1988; O’Reilly 1994; Yolken et al. 2000) as a risk factor for future psychosis has also recently commenced within the clinic.

Some factors have been found to be associated with increased risk of transition to psychosis within the UHR group. Clinical variables include long duration of nonspecific symptoms, poor psychosocial functioning, comorbid depression, and disorganization (Yung et al. 2003). Preliminary results examining central nervous system structure indicate that within the UHR group those who subsequently developed psychosis had reduced grey matter in right medial and lateral temporal areas, in the right inferior frontal cortex, and in the cingulate gyrus at baseline compared with those who did not develop psychosis (Pantelis et al. 2003). Thus far, no clear neuropsychological or developmental risk factors have emerged.

Many studies have suggested that the hippocampal volumes of individuals with established schizophrenia or first episode psychosis are smaller than those of controls (reviewed by Velakoulis et al. 2000). Magnetic resonance imaging (MRI) scans of the brains of UHR patients are obtained to determine whether volume changes in this region precede the development of acute psychosis or emerge as mental state deteriorates. Consistent with the neurodevelopmental hypothesis, hippocampal volumes of PACE UHR patients at intake lie midway between those of normal controls and patients with chronic schizophrenia or first episode psychosis (Phillips et al. 2002b). More puzzling and challenging to the original neurodevelopmental model are the results of survival analysis, which revealed that UHR patients with larger (although in the normal range) left hippocampal volumes at intake were more likely to develop a psychotic episode in the subsequent 12-month period (Phillips et al. 2002b). Consistent with this finding, a comparison of PACE UHR patients’ MRI scans taken prior to the onset of psychosis and again after an acute disorder developed has revealed reduction of gray matter volumes in the left insular cortex and the left posterior medial temporal structures, including the hippocampus and posterior hippocampal gyrus, during the transition to psychosis (Pantelis et al. 2003). This finding suggests that brain changes occur during the process of transition to psychosis and opens up the possibility that with sufficiently early treatment such changes could be minimized or aborted, although the basis of this latter possibility remains uncertain. These MRI and more recent magnetic resonance spectroscopy (MRS) studies are ongoing, and other brain regions are also being investigated.

The possible role of stress and the hypothalamic-pituitary-adrenal axis (HPA axis) in the development of psychosis is also being studied (Corcoran et al. 2001, this issue). Cortisol levels and other indexes of HPA function are being monitored in UHR patients to assess whether there is a relationship between stressful life events, coping strategies, HPA axis functional change, neurocognitive variables, hippocampal volume change, and development of acute psychosis. These studies are examining the validity of the time-honored stress-vulnerability model of psychosis.

Intervention Studies. The aim of treatment provided at PACE is to reduce a young person’s symptoms and, if possible, to prevent these symptoms from worsening and developing into acute psychosis. Hence, there are two clinical foci, one immediate and linked to presenting syndromes and problems, and the second preventive and aimed at reducing the risk of a future syndrome developing. The more proximal syndrome or target to be prevented is acute psychosis (more than 1 week of sustained and severe psychosis), with a subsidiary and often more distal target of schizophrenia itself also in the clinician’s sights. A stress-vulnerability model of the development of psychosis underpins the treatment approach, incorporating medical and psychological strategies. Treatment options are discussed with patients and their families and are reviewed regularly as mental state changes unfold over the course of treatment. Young people attending the clinic are allocated to a treatment team consisting of a psychiatrist and a psychologist/case manager.

The medical staff at PACE undertake a range of assessments, including blood tests and neurological and physical examinations. The medical staff are also responsible for managing and monitoring medication that may be prescribed. Furthermore, general physical conditions are taken into consideration and treated accordingly, with considerable attention being paid to the way general health status (e.g., sleep, diet, substance use) may be affecting mental health.

The psychological treatment provided at the clinic is primarily based on cognitive-behavioral therapy principles and draws not only on mainstream cognitive-behav-
ioral therapy techniques but also on the treatment approaches that have been developed and evaluated for use in established psychotic disorders. The therapist and client work together to develop a personal formulation or model for understanding the symptoms the young person is experiencing and strategies for coping with and reducing these symptoms. The clinical psychologist working with the young person also functions as a case manager and helps connect the young person with housing, education, employment, or other services, as difficulties in these areas may contribute to the increased risk status through increasing stress levels. In the Australian setting, such a blend of case management and psychological intervention is now commonplace. In addition to providing treatment for the young person, family members are actively invited to be involved in both individual sessions and family education sessions. The principle of family involvement is as central as it is in established schizophrenia, but the focus and content are obviously different.

The first randomized controlled trial specifically developed around the needs of the UHR population with the aim of preventing or delaying the onset of psychosis, or at least ameliorating presenting symptoms, was conducted at PACE between 1996 and 1999. This was felt to be required because of the high transition rate in the earlier study, which occurred despite comprehensive psychosocial intervention and active treatment of presenting syndromes (e.g., depression) and problems. In the randomized controlled trial, the impact of a combined intensive and specific psychological (cognitive) treatment plus very low dose atypical antipsychotic (risperidone) medication (specific preventive intervention [SPI]; \( n = 31 \)) was compared with the effect of supportive therapy (needs-based intervention [NBI]; \( n = 28 \)) on the development of acute illness in the high-risk group. At the end of the 6-month treatment phase, significantly more subjects in the NBI group had developed an acute psychosis than had subjects in the SPI group (\( p = 0.026 \)). This difference was no longer significant at the end of a posttreatment 6-month follow-up period (\( p = 0.16 \)), although it did remain significant for the risperidone-adherent subgroup of cases. This result suggests that it is possible to delay the onset of acute psychosis in the SPI group compared with the NBI group. Both groups experienced a reduction in global psychopathology and improved functioning over the treatment and follow-up phases compared with entry levels (McGorry et al. 2002). Longer term follow-up of the participants in this study is now taking place. A second randomized trial commenced in 2000. This is a more sophisticated study with three treatment groups and blind randomization to these groups. The three groups are (1) risperidone (antipsychotic medication—up to 2 mg) and cognitive-behavioral therapy, (2) placebo and cognitive-behavioral therapy, and (3) placebo and befriending. All treatments are offered for 12 months. Participants are interviewed monthly to assess side effects and the impact of the treatments and are then interviewed for a further 12 months to determine the long-term impact of the treatment.

Young people who attend PACE but who do not wish to be involved in a clinical trial are still provided with comprehensive treatment (but not antipsychotic medication) for their presenting clinical problems, as it is felt (as noted above) that it is unethical to withhold treatment for current problems—particularly from those who are seeking it. This treatment is governed by a specified clinical pathway (figure 1). All clients are assigned a case manager who provides practical assistance, supportive counseling, and more specific interventions (e.g., antidepressants and cognitive-behavioral therapy if necessary).

Ethics. Obviously, there are many ethical questions surrounding this clinical research endeavor. They have been at the forefront of the planning and development of PACE (Yung and McGorry 1997). We have consulted extensively with our local institutional review board (IRB) and family and consumer organizations at each stage of the evolution of our clinical research strategy. This has enabled us to be sensitive to and address the risks of stigma and labeling and has increased our confidence that we are appropriately responding to a significant clinical need. The IRB members (some of whom are caregivers for people with serious mental illness) appreciated the efforts to provide low-stigma access to young people and to examine the risks as well as the benefits of intervention but clearly saw these as second order issues; the primary goal remained providing much more timely access to help. Their confidence in our strategy was enhanced by their firsthand knowledge of our local commitment and track record in providing and improving mental health services for young people over more than a decade—efforts independent of our research agenda. This has led to a high degree of trust and mutual understanding between the IRB, consumer organizations, and our clinical research endeavor, but the IRB's independence of view has never been compromised. Ethical considerations have been addressed at a number of forums and in recent journal articles (DeGrazia 2001; Heinssen et al. 2001; McGlashan 2001; McGorry et al. 2001; Schaffner and McGorry 2001; Wyatt and Henter 2001; Bentall and Morrison 2002). These questions include the following:

1. Should antipsychotic medication be used in such a heterogeneous group of individuals who do not fulfill diagnostic criteria for psychosis at the time of treatment?
Figure 1. Clinical pathway for ultra high-risk or subthreshold patients in PACE clinic

Referral Sources

Failed to attend/engage

Triage & Assessment

Meets UHR criteria?

No

Referral to other clinical service

Offer rejected

referred back to referral agent or elsewhere

Yes

Offered clinical care

Offer accepted

Clinical trial participation offered

Rejected

Accepted

Enter RCT

Needs Based Intervention (NBI) & regular monitoring for at least 12 months.
- 2-4 weekly visits with psychiatrist & case manager
- supportive psychotherapy & problem solving
- family psychoeducation & support
- specific treatment of clinical syndromes esp. anxiety, depression & substance abuse
- careful monitoring of level of positive psychotic mood symptoms, risk of self harm & functional status
- if meets criteria for acute psychosis – antipsychotic medications offered/commenced with referral to EPPIC or other specialist mental health agency
2. Should treatment studies with this cohort be naturalistic, blinded, or randomized?
3. Should minors (the definition varies across cultures) be included in this research?
4. Will individuals who meet UHR criteria but turn out to have been incorrectly labeled—at least in the short term—(false positives) be harmed by the treatment approaches offered?
5. Should the level of risk a patient has for the development of psychosis be made explicit to that patient, and how should this be done?
6. Do the potential benefits of proposed preventive interventions outweigh the potential side effects?
7. Does this form of early intervention stigmatize and unnecessarily label the young person?
8. Can the patient give "informed consent" to a prophylactic treatment given the unknown degree of risk being faced?

Obviously, these are all legitimate areas of concern. We are currently in a state of "equipoise" in relation to the issue of medication, particularly neuroleptics, in the UHR group (McGlashan 2001). That is, it is not clear whether such treatment will be of benefit, but there is sufficient evidence to suggest that further clinical trials are warranted. Hence, those affiliated with the PACE Clinic believe that psychopharmacological treatment of young people identified as being at high risk of developing a psychotic disorder—particularly the use of neuroleptics—should be provided only in the context of a research trial (where standards of informed consent are highest) at present. However, the widespread use of antipsychotic medication outside the protection and close monitoring afforded by a clinical trial, such as in naturalistic studies where clinician's choice prevails, is not recommended.

Our experience in the PACE Clinic is that sometimes young people are prescribed antipsychotic medication by psychiatrists and even general practitioners in the absence of a clear-cut psychotic disorder when the prescribing physician suspects that a psychotic disorder is emerging. We believe that such treatment is not currently sufficiently evidence-based and should be rigorously evaluated. The effects of stigma also need to be investigated. In some settings, if there is an inappropriately pessimistic mindset linked to the diagnosis of schizophrenia or psychotic disorder (a widespread phenomenon still) and the treatment is provided in a traditional mental health service, there may indeed be iatrogenic effects of this type in the newly identified UHR patient. We have not seen such impact in the PACE Clinic, where an optimistic attitude is consistently projected about prospects for patients with psychotic illnesses, including schizophrenia, but this reassuring experience cannot necessarily be generalized and needs to be demonstrated empirically.

International Experience With the UHR Paradigm

Since the late 1990s, several other international centers have established clinical research programs focusing on the prepsychotic or prodromal phase of illness. While many of them have been influenced by the PACE model, others (e.g., the FETZ centre in Cologne) derive from a different tradition and have developed different criteria. Centers or clinics have been established in the United States (6), Canada (2), Germany (1), the United Kingdom (2), Australia (2), and Norway (1) (Cornblatt et al. 1998, 2002; Carr et al. 2000; Bechdolf et al. 2002; Cadenhead 2002; Cannon, personal communication, 2002; Johns et al. 2002; Larsen 2002; McFarlane et al. 2002; Miller et al. 2002; Morrison et al. 2002; McGlashan et al. 2003). Some of these have been described in this issue of the journal; a more detailed description of each initiative is beyond the scope of this article. There has been good communication and cooperation between all of these centers through a network structure during recent years, and consequently the research approach has remained relatively homogeneous across centers during this period. The main lessons learned are summarized in table 4. Nevertheless, important local variables and valid differences of opinion have created variation in the clinical criteria, research strategy, and treatment approach in different settings. These commonalities and differences are summarized below.

Commonalities Among Centers
1. All centers attempt to identify young people in their teens and twenties suspected to be at high risk of psychosis in the near future; that is, they are trying to pick up those in the prodromal phase of illness. This involves community-based educational and recruitment strategies.
2. All services utilize criteria that involve mental state changes, and in most, family history and functional decline also contribute to the entry criteria.
3. Help-seeking by the young people in their own right or on their behalf by relatives or friends is a requirement for entry. Those who do not wish to receive assistance cannot be compelled to attend. Screening for asymptomatic, non-help-seeking, nondistressed young people does not occur.
Table 4. The prepsychotic phase: The lessons so far

- It is possible to provide access for and engage in clinical care a subset of young people at substantially increased risk for first episode psychosis.
- The provision of a quality clinical service to both participants and nonparticipants in research studies is essential. Capacity and expertise in treating nonpsychotic disorders in young people must be available.
- Reliable and valid operational criteria for ultra high risk of early transition to psychosis can be developed. Clinical research interview schedules to rate these features can be developed and utilized in treatment settings.
- Clinical criteria seem to be the best immediate predictors of transition so far.
- Stigma and sequelae of labeling can be minimized by creating a youth-friendly environment combined with a realistically optimistic attitude to the treatment of psychotic disorders.
- It is possible to openly discuss current problems and the risk of future disorders, namely psychosis and schizophrenia, with patients and families, provided the clinician does not have a pessimistic or therapeutically nihilistic attitude regarding these disorders.
- This clinical phase is dynamic, and progression to psychosis seems not to be predetermined. It also seems possible to at least delay progression to psychosis in a proportion of cases.
- The terms ultra high risk or at-risk mental states better reflect the clinical focus of this work than the term prodrome, which runs the risk of becoming reified as a quasi-disorder in itself. The term chosen needs to make clear that we are dealing with a clinical state that indicates risk.
- A broad range of biological and psychosocial interventions are likely to be effective.
- Good communication with all stakeholders, especially patients, families, funding agencies, other clinicians, and institutional review boards, is essential. Judicious and cautious use of the media can also be helpful.
- Providing access to a proportion of patients in this incipient or subthreshold phase enables unique studies of the onset process from clinical, biological, and epidemiological perspectives to be conducted. These studies, including imaging, are acceptable to many patients, and valid informed consent to participation in research is more readily obtained than in established psychotic disorder.
- The base rate for transition has been relatively reproducible across the various centers, but despite the criteria for ultra high risk and for transition being carefully operationalized, base rates may still fluctuate. This is probably because of differing base rates according to referral source (variable "enrichment" of sample) and differing thresholds and interpretations for the criteria themselves between individual raters and across centers.
- The lessons from screening and early detection strategies for subclinical disorder in general medicine have been poorly understood and applied in psychiatry. Examples include screening for cancer, especially breast and cervical cancer, and the detection and treatment of transient ischemic attacks to prevent stroke.
- The concept of staging could be better developed in psychiatry.

4. Funding is usually provided through research grants, and the center is therefore rarely a stable element of the local service system.
5. All centers provide a clinical service as well as conducting research and evaluation of interventions. It appears that no programs offer clinical services without research occurring.
6. There are two discrete but overlapping clinical foci: management of current difficulties, and monitoring and possible prevention or attenuation of emerging psychosis.
7. Where antipsychotic medications are offered, low doses of atypical agents are the norm.
8. Transition rates are comparable across centers, ranging from 22 percent to 54 percent within 12 months.

Differences Between Centers
1. Criteria for entry and transition to psychosis are similar but not identical across centers. The greatest difference lies between the Cologne model and the others, but there are increasing differences between the transition criteria for the PRIME group (McGlashan et al. 2003), the recognition and prevention (RAP) group (Cornblatt et al. 2002), and the PACE group.
2. Some centers have pursued an approach based on the need for randomized controlled trial data to evaluate the differential efficacy of alternative treatments. Others have preferred to conduct naturalistic follow-along studies in which treatment has been deregulated. This has been largely driven by local research funding policies. In practice, the latter approach has had the effect of allowing liberal use of antipsychotic medications to occur in this population.

3. Some centers have close relationships with first episode psychosis programs, while others are stand-alone “prodromal” clinics.

4. Neurobiological research is central to several research programs but has not been part of the focus of others.

**Unsolved Problems**

Despite a number of publications and a prominent presence at recent psychiatry conferences, especially schizophrenia conferences, the aims of this field of clinically oriented research remain unclear to many. Similar issues have also been faced in early intervention in serious medical disorders, and experience there could be usefully applied in psychiatry. This lack of understanding has resulted in potentially inappropriate impediments being placed in the way of further progress in this field. There is also concern that this approach to identifying individuals and providing treatment prior to the onset of acute phases of disorder is an attempt to medicalize distress in adolescence rather than an effort to identify the early stages of serious mental illness in the context of a broad, flexible approach to youth mental health issues. These misunderstandings appear to have had a greater impact in some countries than they have in others and have influenced research funding policies. In Australia, such concerns have so far been assuaged through close dialogue and consultation with, and subsequent support of, consumer and caregiver groups; an open relationship with ethics committees that oversee psychiatric research; and cautious use of the media to inform the community about progress. A positive reputation and demonstrated commitment to comprehensive services for young people in general have also helped this endeavor to move forward in a broader context than the treatment of schizophrenia per se.

Nevertheless, for progress to occur, a genuine effort to address obvious and legitimate concerns is not only appropriate but necessary. The most pressing of these concerns relates to fears concerning possible harm to the false-positive group, which represents one-half to two-thirds of the UHR population currently identified. Harm could flow from the effects of stigma and labeling or from the side effects of treatment. So far, there is some evidence from trials of mild/moderate side effects where atypical antipsychotic agents have been used. Mild sedation and modest weight gain have been reported. However, patients have been free to withdraw from the research and cease medication if these effects concern them, and indeed the withdrawal rate in these studies has been appreciable, although for a variety of reasons, not merely adverse events. No ill-effect of psychosocial intervention has so far been recorded. Indeed, when 6- and 12-month ratings of psychopathology and functioning are contrasted with baseline scores, all patients entering the PACE Clinic improve substantially—including those who progressed to first episode psychosis and were promptly treated (McGorry et al. 2002). Engagement and retention rates in the clinic are high (over 70%), and the acceptability of the model as a whole to young people, their families, and local IRBs has been very high as well. These features need to be more systematically measured to reassure those who are concerned about these issues.

Another obvious limitation is related to the population-attributable risk of the UHR criteria and hence the generalizability and clinical utility of this early intervention approach. Although transition rates are high within this group, most cases of first episode psychosis are not currently identified as UHR prior to detection of the full-blown syndrome (although the Portland Identification and Early Referral [PIER] program suggests this may be possible) (McFarlane et al. 2002). This low yield is a structural consequence of any screening process, even though here the “screening” is relatively reactive, nonsystematic, and clinically based. Although the risk is substantially higher in the UHR group and the false-positive problem can be greatly minimized, most cases of first episode psychosis still come from the low-risk and undetected groups. This places a ceiling on the utility of the strategy, as pointed out by Warner (2001), and is a fact of life for any form of screening, even a clinically grounded variant like this. However, we contend that the strategy still has substantial value and that the ceiling may be able to be raised using broader enrichment strategies via a youth mental health model (see below).

It could be argued that one possible contributing factor is that health and educational professionals do not yet apply the UHR criteria widely enough and that if they were publicized more broadly, perhaps more UHR young people could be encouraged to seek help. This belief has led some to suggest that large-scale active screening may be justified (e.g., in schools) to identify students with high levels of attenuated psychotic symptoms and promote them into a clinical service. However,
recent community surveys (Eaton 1995; van Os et al. 2000, 2001) have suggested that attenuated and even frank psychotic symptoms are not uncommon in the general population, with lifetime prevalence estimates of 12 percent (Tien et al. 1992) to 17.5 percent (van Os et al. 2000) for some positive “psychotic-like” symptoms. Many people experiencing these phenomena were not distressed by them and did not seek help, in contrast to those who request treatment from high-risk services such as PACE. It is not fully clear what degree risk of psychosis is associated with these nondistressing attenuated symptoms, although it could be greater than estimated by van Os et al. (2001) because a lack of awareness of impairment is commonly associated with psychotic experience. It is readily conceded, however, that it may be unwise to embark on such a screening strategy now, unless its focus includes a broad range of mental disorders, because the accuracy of prediction of true clinical disorder will probably be low and there may be significant risks associated. More research is needed into community samples to investigate stability and outcome of attenuated and frank psychotic symptoms that do not come to the attention of clinical services.

**Intervention Research: What Methodologies Are Relevant?**

The growth of the UHR or prodromal field was catalyzed by naturalistic follow-along studies that demonstrated that relatively simple clinical criteria were capable of predicting rapid transition to first episode psychosis under certain conditions, despite the availability of need-based clinical care (Yung et al. 1998, 2003). The replication of this finding in several centers demonstrated that a highly incipient group of cases could be reliably recognized and safely engaged in clinical care. What methodologies are available to further clarify the appropriate range of interventions in such cases?

First, further naturalistic follow-along studies could be considered. The advantages of these are that further data can be collected with the same or different criteria sets to enlarge and refine the evidence base for prediction of outcome. This approach will have maximum value if the treatment options are restricted to interventions that target major presenting problems (e.g., depression, interpersonal problems) rather than those that may more powerfully influence the process of transition to first episode psychosis (e.g., antipsychotic medications, potential neuroprotective agents such as lithium and eicosapentaenoic acid). A minimalistic or safety net approach to intervention is probably ideal. Supporters of this methodology have been critical of the use of antipsychotic medications in randomized controlled trials with prepsychotic patients. However, unless naturalistic studies are tightly protocol limited, the use of antipsychotics, driven by clinician’s choice or consumer pressure, is likely to be very widespread. While it will be possible to measure adverse effects of such use, any benefits will be difficult to determine.

Second, open trials of specific agents or of specific psychosocial interventions have a place because they would involve adherence to a specific protocol with measurement of benefits and harm.

Third, both open and double-blind placebo-controlled randomized trials are clearly justified in a field where the value of all interventions remains in equipoise. Such trials are more demanding to perform and generally require a multicenter approach, yet they yield higher quality data and evidence and involve better measurement of adverse events and a higher standard of informed consent for consumers and families.

**Future Progress**

**The Youth Model.** Because of the low annual incidence rates, trying to detect young people at risk of psychosis has been likened to searching for a needle in a haystack (Jones 2000). However, one approach to making this task feasible could be the development of a comprehensive youth mental health service with the capacity to manage young people with established and emerging nonpsychotic as well as psychotic disorders. This service would therefore aim to find not just needles but all sharp metallic objects, which could be attracted via a “magnetic” clinical strategy (an attractive youth-friendly environment) and sorted out later. Enriched samples of this type would give predictive measures a much better chance of accuracy. Community links and secondary consultation with primary care, education, and other youth services would increase the ability of the program to provide assistance to young people with a range of problems and turn the ubiquitous comorbidity seen in young people from a diagnostic problem into an opportunity. Many young people may move in and out of ARMS, and the ability to monitor them and provide timely intervention as appropriate may aid our understanding of the process of onset not only for psychosis but for other syndromes, and also our ability to provide preventive treatment. Perhaps this is one type of “naturalistic” approach that should be supported.

**Neuroprotection.** It is becoming more likely that the onset phase of illness during which clinical features and functional impairment emerge for the first time is associ-
ated with active yet subtle neurobiological changes in the patient (Pantelis et al. 2003a). In contrast to the original neurodevelopmental model of schizophrenia (Weinberger 1995), which proposed a dormant lesion that becomes activated around the time of adolescence, it seems that complex neuronal dysfunction may develop as a new process around the time of psychosis onset (Pantelis et al. 2003b). Thus early treatment, before full-blown psychotic disorder occurs, may prevent some brain changes and thus alter the neurobiological pattern of illness (Wolkin and Rusinek 2002). Earlier crude models of neurotransmitter imbalance, derived in reverse from the mechanism of action of psychotropic medications, may ultimately give way to models based on intracellular disturbances and influences via gene expression upon neuronal integrity and connectivity (Berger et al. 2003). The therapeutic paradigm linked to such models is neuroprotection. If neuroprotective agents, such as lithium (Manji et al. 1999) and eicosapentaenoic acid (Berger et al. 2002, 2003), which have been shown in laboratory models to have specific neuroprotective effects, could be shown to reduce the risk of progression from early to more severe forms of disorder, then early intervention would receive even stronger support as a strategy.

Conclusion

This article has explored the development and expansion of services specifically designed for the detection, monitoring, and treatment of the prepsychotic or UHR phase of illness and the study of the psychobiological processes contributing to onset. The conceptual underpinnings, practical issues, and ethical issues related to UHR research and clinical intervention have been described. This is truly a growth area with the potential to benefit such symptomatic UHR young people and their families. Our ability to identify those at particularly high risk is being refined and the biological basis for psychosis onset investigated. Caution must be exercised, however, and each step evaluated in an evidence-based manner. Continued modification of UHR criteria and a better understanding of the process of screening and sample enrichment may be needed. Randomized clinical trials of medication and other interventions must be ongoing and rigorously evaluated. Large-scale screening of population samples in order to expand the scope of "prepsychotic" treatment is probably not justified merely for this purpose at this stage of knowledge. As an alternative, either enriching strategies could be developed to enable interventions to be evaluated, or a broader screening strategy for the full range of emergent mental disorders in young people could be explored.

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