# EARLY DETECTION AND INTERVENTION FOR PSYCHOSIS: PERSPECTIVES FROM NORTH AMERICA

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## Abstract

Clinicians and researchers in Canada and the United States have established a number of early intervention programs and research sites on the early course of psychosis and the prodromal period that commonly precedes psychotic disorders. In Canada, early detection and treatment programs for psychosis have been established in many areas of the country, and typically serve specific catchment areas. Canadian research on early psychosis is often built on to these clinical sites, and covers a broad array of topics including interventions during the prodromal stage of the illness, treatment-seeking behaviors, and development of optimal pharmacological and psychosocial treatment approaches for early psychosis. In the United States, clinical programs for early intervention in psychosis are often located at academic programs with ongoing research on the early course of psychotic disorders. Researchers from sites across the United States offer a plethora of information, including neuroimaging studies, research on treatment response, and the development of standardized rating scales and research instruments. Researchers from sites in both countries have formed a consortium to launch the North American Prodrome Longitudinal Study, a multi-site collaboration to gain a better understanding of the prodromal period of the illness and prediction of conversion from the prodrome to psychosis.

**Key Words**: Early detection – Early intervention programs – Prodrome – Psychosis – Schizophrenia

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> "… *Few things have captured the attention of the field of psychiatric research and mental health care more than the prospect of early detection of schizophrenia and intervention during its premorbid or prodromal stages to prevent its onset. Adding to the enthusiasm is the fact that this goal seems achievable and could potentially dramatically limit the consequences of the illness if not reduce the incidence of psychotic disorders. However, while the future prospect for early intervention in schizophrenia is excellent, the present is a challenge, and we have our work cut out for us*…"
>
> Jeffrey Lieberman and Cheryl Corcoran 2007

## Introduction

Early detection and intervention for psychosis truly is an exciting prospect for psychiatric research and mental health care. Many opportunities are apparent and will arise as the field embraces a prevention perspective for schizophrenia and related psychotic disorders (Compton 2004, Compton et al. 2007b). By facilitating rapid entry into psychiatric care, early detection and intervention seeks to reduce treatment delays and the detrimental duration of untreated psychosis. Further, intervention during the prodromal phase of the illness to prevent or delay the onset of psychosis is also a critical and emerging aspect of the early intervention paradigm. Programs and research pertaining to both of these aspects of early intervention

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—efforts to enhance rapid treatment in response to the first episode of psychosis and efforts aimed at preventing the first episode among individuals with prodromal symptoms—are discussed in this overview. Aside from the obvious clinical distinction between these two types of patients (a prodromal level of symptomatology as opposed to the presence of frank psychosis), another clinical difference between prodromal and first-episode patients is that the former retain a level of insight that may allow them to more readily engage in early treatment.

The excitement and burgeoning interest in the area of early detection and intervention for psychosis is partly related to the fact that early psychosis research is an international effort. This overview provides a brief synopsis of some of the early intervention clinical and research efforts in North America, including both Canada and the United States. Additionally, a research consortium involving sites in both Canada and the United States—the North American Prodrome Longitudinal Study—is briefly described. Though the present overview generally summarizes some of the developments in early detection and intervention in a number of North American sites, readers are referred to websites and publications of particular programs for more in-depth information on the various approaches that are being taken.

## Developments in Canada

### *Early Detection and Intervention Clinical Programs in Canada*

At least 19 programs specializing in early psychosis have been established in Canada, making it one of the leading countries globally in terms of adopting and disseminating the early detection and intervention paradigm. Although eligibility criteria vary, most of these early psychosis programs serve a specific catchment area-based population and admit patients from 12–18 years through 30–65 years of age who are experiencing a first episode of nonaffective psychosis with previous treatment limited to antipsychotic medications for less than three months. Canada's early detection and intervention programs are generally structured as primarily outpatient treatment services, offering a combination of optimal pharmacological and psychosocial therapies that address a wide range of concerns in both group and individual settings. They typically offer 2–4 years of follow-up, often with intensive case management. Community outreach to schools and/or medical providers in their locale is common, and family work in individual and group formats is an important component of the majority of programs. In addition to outpatient and inpatient programs specializing in early psychosis, often offering specialized inpatient services, numerous urban areas have mobile teams that respond to mental health crises not limited to psychosis. A few programs are highlighted below to show the breadth of early psychosis services offered throughout the country.

The Prevention and Early Intervention Program for Psychoses (PEPP; www.pepp.ca) was designed for patients with first-episode psychosis in London, Ontario (PEPP-London) and Montreal, Quebec (PEPP-Montreal). This two-year integrated program includes pharmacological and psychosocial interventions overseen by a nurse case manager and other clinicians. Low-dose second-generation antipsychotic agents serve as the first-line antipsychotic regimen. Patients meet with their case managers weekly and a psychiatrist biweekly until clinical stability is achieved (PEPP 2009a). Patients requiring hospitalization are admitted to a first-episode psychosis unit (PEPP 2009b). A battery of cognitive and other tests are administered at regular intervals for continuous assessment of patients' functioning (PEPP 2009b).

Full participation in PEPP is available to people who are experiencing first-episode psychosis; however, the program provides screening and referral services to others. For those who are considered at risk for developing psychosis, follow-up with a psychiatrist and assessments are completed monthly for three months, then every three months for the following year (PEPP 2009b). PEPP relies on referrals to reach new clients in the clinic setting, but will also meet with prospective clients in a location of their choice. In addition to offering specialized first-episode psychosis treatment, the program also has a community outreach campaign. Outreach efforts include placing print media such as posters in public locations, running radio commercials, establishing communication with health care providers and educational institutions that may come into contact with at-risk youth, and working with consumers and their families to raise awareness in the community at large (PEPP 2009b). Like many other early intervention services in Canada, a user-friendly website assists potential patients and families who may self-refer (www.pepp.ca).

In Calgary, Alberta, the Early Psychosis Treatment Service (EPTS; www.calgaryhealthregion.ca/mh/sites/EPTP/epp) was established in 1996 to meet the needs of young people experiencing a first episode of psychosis (Addington and Addington 2001a, Calgary Health Region 2009a). This program is part of the broader Calgary Health Region Mental Health and Addictions Services, which provide community-based, inpatient, and outpatient services along a continuum of care for the Alberta catchment area. EPTS is a three-year outpatient program that offers optimal pharmacotherapy and a range of psychosocial interventions. These include cognitive-behavioral therapy with a focus on the reduction of depression and anxiety related to the disorder and a range of group programs to facilitate psychoeducation, support, and coping skills. The program also offers a comprehensive family program (Addington et al. 2005a, Calgary Health Region 2009b). The EPTS group program consists of a psychosis education group, a 12-session group focusing on early recovery, and a 12-session evening group (Addington and Addington 2005b). Each patient has a case manager who assists in developing an individualized treatment plan. Patients are eligible for EPTS services if they are 16–54 years of age, are experiencing a first episode of nonaffective psychosis, and have taken antipsychotic medications for less than three months. Approximately one-third of EPTS patients are referred from inpatient units. Other referral sources include family physicians, community

and outpatient mental health services, emergency rooms, families, and schools (Addington and Addington 2005a).

The Center for Addiction and Mental Health (CAMH; www.camh.net) is affiliated with the University of Toronto and has 32 community locations, in addition to its central facilities in Toronto, Ontario. CAMH established a first-episode psychosis program in 1994. With 50 clinicians from a variety of disciplines, this program offers a wide range of services for individuals experiencing a first episode of psychosis, including inpatient care, outpatient case management, mobile team assessments, psychosocial recovery programs, and family interventions for patients ages 16–45 years (CAMH 2009). In 2001, CAMH established a First Assessment Clinic Team consisting of eight multidisciplinary clinics in the region of Peel (Ontario Working Group on Early Intervention in Psychosis 2009). These community-based clinics provide assessment, treatment, and case management services for up to three years.

The South Fraser Health Area of British Columbia developed a community-based early detection and intervention service (www.psychosissucks.ca) that has close affiliation with hospital services for when they are necessary (rather than being hospital-based) (Tee et al. 2003). Like some other Canadian early intervention services, the South Fraser program includes training in early detection of psychosis and case identification, as well as a full range of clinical services for individuals aged 13–30 years experiencing first-episode psychosis. Standardization of intake forms, clinical rating scales, and ongoing evaluation instruments facilitates research (Tee et al. 2003) on such topics as brain imaging, genetics, cognition, educational histories, group interventions, treatment adherence, and pathways to care.

St. Joseph's Hospital in Hamilton, Ontario, partnering with McMaster University, created the Cleghorn Program (www.stjoes.ca/default.asp?action=article&ID=365) to focus on early intervention for psychosis by providing rapid assessments, low-dose antipsychotic medications, psychoeducation, family education, and support based on a recovery model (Archie et al. 2005). This program primarily serves first-episode patients ages 14–40 years from the city of Hamilton (Ontario Working Group on Early Intervention in Psychosis 2009). St. Joseph's Hospital also partners with the Hamilton Police Force to provide a mobile intervention team—the Crisis Outreach and Support Team (COAST; www.coasthamilton.ca) (Inform Hamilton 2009). This team is not limited to cases of suspected psychosis, but may respond to such cases in the community. As a multi-disciplinary team of social workers, nurses, and occupational therapists, COAST services are available through a toll-free hotline. When responding to crises in the community, a mental health worker and a non-uniformed police officer travel in an unmarked police car to assess the situation and, when necessary, provide referrals to various services. COAST also has a mobile team specifically for responding to youth, through schools and other referral sources.

## *First-Episode and Early-Course Research in Canada*

Many of the early psychosis programs across Canada conduct research that is closely linked to the treatment services they offer. Research on early psychosis covers a broad array of topics, including studies on interventions in the prodromal stage of illness; treatment-seeking behaviors, including predictors of the duration of untreated psychosis and the efficacy of community outreach programs to reduce this period; and development and evaluation of pharmacological, as well as cognitive-behavioral and other psychosocial, treatment approaches for early psychosis.

Researchers in Toronto and Calgary have joined a consortium of clinics in the United States in treating putatively prodromal patients. Collaboration with Yale University's Prevention through Risk Identification, Management and Education (PRIME) program (www.camh.net/Care_Treatment/Program_Descriptions/Mental_Health_Programs/PRIME_Clinic) included a double-blind trial comparing presumably prodromal patients randomized to receive olanzapine versus placebo for one year. Nearly significant findings suggested that it may be possible to reduce the proportion of prodromal patients transitioning to psychosis using pharmacological interventions (McGlashan et al. 2006). However, there was a very high dropout rate, and the active agent (olanzapine) was associated with dramatic weight gain, which was problematic not only from a health perspective but also because it may have compromised the blind. This study complements several others conducted in other sites around the world that explore a range of pharmacological and psychological interventions aiming to delay or avert psychosis in high-risk, presumably prodromal individuals (McGorry et al. 2002, Morrison et al. 2004). The study by McGorry and colleagues in Australia was successful, though it remains unclear whether the low-dose antipsychotic (in this case, risperidone) or the psychosocial treatment (cognitive-behavioral therapy) provided the preventive effect. The study by Morrison and coworkers in the United Kingdom is noteworthy because a purely psychological treatment with few side effects was tested, cognitive-behavioral therapy.

Canadian researchers have contributed to the understanding of the duration of untreated psychosis, including its impact on treatment outcomes (Addington et al. 2004) and potential confounders that merit future research (Norman and Malla 2001, Schmitz et al. 2007), including premorbid adjustment (elaborated by Verdoux et al. 2001 in France). Other recent Canadian research on the duration of untreated psychosis includes studies on help-seeking behaviors during early psychosis (Addington et al. 2002) and the impact of an intervention for early identification on the duration of untreated psychosis (Malla et al. 2005b). Particularly informative in this area is the Treatment and Intervention in Psychosis (TIPS) project in Scandinavia (www.tips-info.com), which consists of both educational campaigns aimed at the general population through local media and targeted information for general practitioners, social workers, and high-school

health professionals. That program, which combines these informational campaigns with early detection services, has demonstrated a reduction in median DUP (Melle et al. 2004). Canadian researchers also have produced crucial research data on substance abuse in the first episode of psychosis (Addington and Addington 1998, Addington and Addington 2001b, Pencer and Addington 2003, Van Mastrigt et al. 2004, Archie et al. 2007), as well as on premorbid and social functioning (Addington et al. 2003b, Addington and Addington 2005a) and cognition (Malla et al. 2002, Addington et al. 2003a, Addington et al. 2005b).

Determining an optimal treatment combination for first-episode psychosis is among the main goals of CAMH's program. That research team is evaluating the effectiveness of Cognitive Behavioral Therapy and antipsychotic medications, as well as innovative approaches such as home interventions and mobile teams. In a double-blind trial in patients with first-episode psychosis, this group found that olanzapine has a slightly more beneficial effect on neurocognition than low doses of haloperidol (Keefe et al. 2004). Other recent publications from CAMH researchers include findings that the early use of clozapine can reduce psychotic symptoms for patients with first-episode psychosis who respond poorly to first- and second-line treatment options (Agid et al. 2007), and an evaluation of the one-year outcomes of first-episode psychosis programs at three sites (Malla et al. 2007). In the latter study, a significant effect of time and the time by center interaction on positive, negative, and general symptoms was observed after controlling for ethnicity, education, and diagnosis; sex had a significant effect on negative and general symptoms, while DUP had no effect on any outcome measure.

The foregoing review highlights just a few of the many innovations in both clinical programming and research from multiple sites in Canada (Addington 2007). The structure of the national health services in Canada is likely conducive to the implementation of early detection and intervention clinical programs, as is probably true of other countries with national health services (e.g., Australia and the United Kingdom). The Canadian experience is informative for other countries working toward developing early intervention efforts based on catchment areas serving large populations.

## Developments in the United States

### *Early Detection and Intervention Clinical Programs in the United States*

A number of early detection and intervention programs have been developed in the United States, though perhaps less systematically than in Canada. While early detection and intervention efforts in Canada appear to have begun primarily with provincial clinical programming that then incorporated intensive research efforts, in the United States, early psychosis research has a rich history based primarily in academia. Thus, in the United States, research efforts have oftentimes led to clinical programming, rather than vice versa. Whereas early detection and intervention efforts in Canada are largely catchment area-based and driven by services, such efforts in the United States are more often supported by university-based recruitment for research studies which may include intervention research that fosters the establishment of clinical programs. Some examples of well known programs in the United States, especially those studying the prodrome, include, but are not limited to: Cannon and colleagues' Center for the Assessment and Prevention of Prodromal States (CAPPS; www.npistat.org/CappsWeb) clinic at the University of California, Los Angeles; Cadenhead and colleagues' Cognitive Assessment and Risk Evaluation (CARE; http://psychiatry.ucsd.edu/CAREProgram. html) program at the University of California, San Diego; McGlashan and colleagues' PRIME program (http://info.med.yale.edu/psych/clinics/prime/pintro.html); McFarlane and colleagues' Portland Identification and Early Referral program (PIER; www.preventmentalillness.org/pier_home.html) of the Main Medical Center; Carter and colleagues' Early Diagnosis and Preventive Treatment clinic (EDAPT; http://earlypsychosis.ucdavis.edu/home/index.php) of the University of California, Davis; the Early Assessment and Support Team (EAST; www.eastcommunity.org) of the Mid-Valley Behavioral Care Network; Cornblatt and colleagues' Recognition and Prevention Program (RAP 2009) at Zucker Hillside Hospital; and Corcoran's Center of Prevention and Evaluation (COPE; www.cumc.columbia.edu/dept/pi/research/clinics/pc.html) at the New York State Psychiatric Institute/Columbia University. These are discussed briefly below to illustrate early detection and intervention efforts, both in the prodromal phase and in early psychosis, within the United States.

The CAPPS clinic aims to establish a knowledge base for predicting the development of psychotic disorders and to study changes in brain function over time in individuals deemed at risk for developing psychotic disorders (CAPPS 2009). Services include diagnostic evaluation, psychiatric and neuropsychological assessment, magnetic resonance imaging, genetic studies, psychoeducation (as well as skills groups, multifamily groups, and group therapy), treatment planning and case management, and psychiatric treatment. The CARE program is also interested in the identification of risk factors for the later development of serious psychiatric disorders (CARE 2009).

The PRIME clinic, mentioned above, attempts to identify and monitor signs of risk for psychotic illnesses, reduce symptoms, and better understand the development of psychotic disorders (PRIME 2009a, PRIME 2009b). PRIME utilizes detailed clinical assessments for diagnostic clarification, neurological evaluations and neuropsychological testing, longitudinal monitoring of symptomatology, and participation in clinical trials or studies involving brain imaging and functioning. Community education fosters collaborations with school systems and community providers by developing a better awareness of prodromal symptoms and more effective ways to cope with them, further cultivating the popular awareness of early detection and intervention if symptoms should progress into a more serious condition (e.g., psychotic illness).

PIER is comprised of three main components: education for professionals and the community, clinical services (extensive assessment and psychosocial and pharmacologic treatment), and research (PIER 2009). The community education aspect of PIER focuses on: reducing stigma; providing information about modern concepts of psychotic disorders; increasing understanding of the early stages of mental illnesses and prodromal symptoms; conveying how to quickly obtain consultation, specialized assessments, and treatment; and encouraging ongoing inter-professional collaborations. This program reaches out to family practitioners, college health services, mental health clinicians, military bases and recruiters, clergy, emergency and crisis services, the general public, employers, school teachers, guidance counselors, school nurses, and pediatricians. The treatment component is described as "Family-aided Assertive Community Treatment (FACT)", involving a number of key components: rapid, crisis-oriented initiation of treatment; psychoeducational multifamily groups; case management using key Assertive Community Treatment (ACT) methods (e.g., integrated treatment, a multidisciplinary team, outreach as needed, rapid response, continuous case review); supported employment and education (involving collaboration with schools, colleges, and employers); cognitive assessments; low-dose atypical antipsychotic medication; and mood stabilizers or antidepressants as indicated by symptomatology. An integral component of the PIER program is family intervention, particularly to strengthen relationships and create an optimal, protective home environment.

In the EDAPT clinic, services include medication management, psychosocial interventions (such as individual or group therapy and multifamily support groups), case management, and advocacy (involving, for example, schools, employers, providers, and insurance companies) (EDAPT 2009a, EDAPT 2009b). EAST focuses on reduction of long-term disability by fostering collaboration between a clinical team and an extensive community network (EAST 2009a, EAST 2009b). Such collaboration aims to identify individuals experiencing psychosis early, provide comprehensive assessments for diagnostic and treatment planning purposes, stabilize symptomatology and living/family situation, develop support for and management of symptoms within the community, and create more appropriate treatment programs.

The RAP program is dedicated to the prevention of serious psychological disturbances through early treatment based on the recognition of early warning signs for a developing psychotic disorder (RAP 2009). Services include clinical assessment for diagnostic clarification and treatment planning; neurocognitive assessment; brain imaging studies; medication management; and individual, family, or group therapies involving cognitive-behavioral therapy, interpersonal therapy, and social skills training. The administration of extensive baseline assessments, provision of a standardized treatment protocol for antipsychotic medications, and assessment of treatment response has provided a wealth of longitudinal data on the prodrome.

Center of Prevention and Evaluation (COPE, http://www.cumc.columbia.edu/dept/pi/research/clinics/pc.html), in New York, emphasizes the identification of putative imaging biomarkers of schizophrenia risk and their interaction with proximal risk factors such as cannabis use and stressors in the evolution of symptoms. This may potentially inform the pathophysiology of schizophrenia within a developmental context, such that predictive value is increased and stage-specific interventions can be developed (Lieberman and Corcoran 2007). Services are informed by those provided to first-episode patients in aforementioned studies, including cognitive-behavioral therapy and group therapy to address social dysfunction and substance abuse; family support; and psychoeducation. COPE uses a conservative psychopharmacological approach that targets prevalent anxiety and dysphoria, while minimizing the use of antipsychotics and exposure to their serious side effects unless patients have clear psychotic symptoms. COPE works closely with schools and universities, referring clinicians, family organizations, and state mental health services.

## *First-Episode and Early-Course Research in the United States*

A number of very productive first-episode research sites and studies have yielded a plethora of information on the early course of schizophrenia. A sampling of these includes neuroimaging studies from the University of Iowa and the University of Pittsburgh, research on treatment response from Hillside Hospital in New York, and the multi-site Comparison of Atypicals in First Episode Psychosis (CAFÉ) study. Early psychosis researchers in the United States also have focused attention on the development of rating scales and research instruments, in addition to the duration of untreated psychosis and other research domains.

A number of neuroimaging studies involving first-episode and early-course patients conducted within the United States have produced results that inform the field's understanding of the neurobiology of early psychosis. For example, findings from Andreasen, Flaum, Ho, and colleagues at the University of Iowa Mental Health Clinical Research Center include: (1) progressive decrements in frontal lobe white matter volume and enlargements in frontal lobe cerebrospinal fluid volume are associated with greater negative symptom severity in the early course of schizophrenia (Ho et al. 2003); (2) smaller temporal lobe gray matter volume (both left and right) is associated with persistence of hallucinations during follow-up (Milev et al. 2003); (3) the presence of cerebellar signs in neuroleptic-naïve patients with schizophrenia is associated with poorer premorbid adjustment, more severe negative symptoms, poorer cognitive performance, and smaller cerebellar tissue volumes (Ho et al. 2004); (4) conventional neuroleptic exposure over time is correlated with increased anterior cingulate volume over time, but increased exposure to atypical agents is correlated with decreased anterior cingulate volume (McCormick et al. 2005); (5) psychotic symptoms are inversely correlated with insula volume, and increasing drug exposure (measured in dose-years) is correlated

with larger insula volume (Pressler et al. 2005); and (6) Met allele carriers of the brain-derived neurotrophic factor (BDNF) val66met variant have significantly greater reductions in frontal gray matter volume, with reciprocal volume increases in the lateral ventricles and sulcal (especially frontal and temporal) cerebrospinal fluid compared to BDNF val66met Val homozygous patients (Ho et al. 2007).

Keshavan and colleagues at the Western Psychiatric Institute and Clinic and the University of Pittsburgh Medical Center also have conducted extensive neuroimaging research involving first-episode patients. Such research has sought to better understand pathophysiology during the critical periods of the prodrome, transition to psychosis, and the early course of schizophrenia. For example, support for a neurodevelopmental pathogenesis has been provided through investigations revealing abnormalities of the caudate nucleus (Keshavan et al. 1998, Jayakumar et al. 2006), basal ganglia (Gangadhar et al. 2006), entorhinal cortex (Prasad et al. 2004a), frontal and temporal lobes (Keshavan et al. 2005) and parahippocampal gyrus (Prasad et al. 2004b).

In addition to neuroimaging studies and other research that could illuminate the early detection and intervention paradigm, a number of early-course intervention studies have been conducted in the United States. For example, the first-episode psychosis studies conducted at Hillside Hospital in Glen Oaks, New York have examined treatment response in the early course of the illness (Lieberman et al. 1992). In one study from Hillside, the duration of untreated psychosis was found to be significantly correlated with time to response for delusions but not for hallucinations (Gundez-Bruce et al. 2005). Despite high response rates to antipsychotic treatment in the first episode, research at Hillside has revealed specific clinical and biological predictors that impact responsiveness (Robinson et al.1999a). Specifically, a lesser likelihood of responsiveness was associated with male sex, a history of obstetric complications at the time of the patient's birth, more severe hallucinations and delusions, poorer attention at baseline, and the development of parkinsonism secondary to antipsychotic treatment. Furthermore, the risk of relapse within five years of recovery from a first episode was shown to diminish with maintenance antipsychotic medication treatment (Robinson et al. 1999b). In addition, randomized comparisons of antipsychotic agents have been conducted at Hillside (Robinson et al. 2006).

The CAFÉ study, a 52-week, randomized, double-blind, flexible-dose, multi-center investigation involving 400 first-episode patients, provided important findings regarding the use of olanzapine, quetiapine, and risperidone in the early course of schizophrenia and related disorders (Keefe et al. 2007, McEvoy et al. 2007, Perkins et al. 2008). Analyses revealed comparable effectiveness in early-psychosis patients, as indicated by similar all-cause treatment discontinuation rates across the three agents (McEvoy et al. 2007). Highlighting the importance of interventions to improve adherence, further analyses demonstrated that poor treatment response and low medication adherence were independent predictors of discontinuation of medication (Perkins et al. 2008). Furthermore, research has shown significant relationships between neurocognition and functional outcomes and that all three medications used in the CAFÉ study were associated with significant, though modest, improvement in neurocognition (Keefe et al. 2007).

Researchers in the United States also have sought to advance the early detection and intervention paradigm through the development of assessment tools. For example, the Structured Interview for Prodromal Symptoms (SIPS) and the Scale of Prodromal Symptoms (SOPS) operationally define prodromal syndromes while providing a quantitative rating of symptom severity (Miller et al. 1999, Miller et al. 2003); the Symptom Onset in Schizophrenia (SOS) inventory operationalizes and dates the onset of prodromal and psychotic symptoms retrospectively (Perkins et al. 2000); and two global measures of social and role functioning have been developed for use with potentially prodromal research participants (Cornblatt et al. 2007). As in Canada, research in the United States also has focused on the measurement (Compton et al. 2007a) and predictors of the duration of untreated psychosis (Compton et al. 2008), as well as pathways to care in first-episode psychosis (Compton et al. 2006, Corcoran et al. 2007, Chien and Compton 2008).

## The North American Prodrome Longitudinal Study

In 1999, the National Institute of Mental Health (NIMH) in the United States issued a program announcement entitled, "Prevention and Early Intervention in Psychotic Disorders". This program served as a major impetus for applications dealing with research on the prodrome of psychosis, and seven projects were subsequently funded by NIMH. These studies were concerned with refining diagnostic criteria for the prodrome, characterizing its developmental course, and identifying predictors of conversion to psychosis. The projects yielded some important findings, but at the same time brought into clearer focus some of the challenges confronting this line of investigation. Chief among these obstacles is the problem with predictive power that ensues when sample sizes are small and the annual incidence of new cases of psychosis is relatively low (i.e., about one case per 10,000 persons per year in the general population). As a result, progress is limited when relying on single-site studies.

In response to this limitation, the principal investigators from eight research sites—seven in the United States and one in Canada—joined forces to form a consortium (Addington et al. 2007). The various cohorts differ somewhat in terms of recruitment strategies and inclusion criteria; for example, the Harvard University site focuses primarily on genetic high-risk subjects; the Emory University site recruits adolescents with schizotypal personality disorder, which overlaps with but is not isomorphic to the psychosis prodrome; and the Zucker Hillside site includes some "clinical high risk–negative" subjects, who have attenuated negative/disorganized symptoms, but not attenuated positive symptoms. The consortium established by this group of research centers is now

known as the North American Prodrome Longitudinal Study (NAPLS), and its formation is described in detail in a prior report (Addington et al. 2007).

In January 2004, NAPLS principal investigators began work on the design of their multi-site collaboration, with active participation from NIMH program staff. The main objective was to form a collaboration that would make it possible to aggregate data from the eight sites in order to maximize sample size and thereby enhance statistical power for detecting predictors of conversion to psychosis. The NAPLS consortium used a recent Institute of Medicine report on large-scale approaches to biomedical research as a guideline for structuring the collaboration. By July of 2006, the NAPLS consortium had succeeded in: (1) obtaining Institutional Review Board (IRB) approval for the consortium, (2) determining cross-site consistency in diagnosis, (3) establishing the core set of variables, and (4) designing a common platform for electronic data and procedures for data management. The integrated NAPLS database contains demographic and clinical information for 888 at-risk and comparison subjects who were enrolled in one of the research projects between 1998 and 2005. The largest subgroup in the database ($n$=370) is comprised of subjects who met criteria for the prodrome based on SIPS/SOPS interviews. Another 149 met other risk criteria, 174 were help-seeking controls, and 195 were normal control subjects. The NAPLS dataset thus constitutes the largest currently available longitudinal dataset of potentially prodromal individuals and is currently being utilized to address a series of scientific questions about the nature of the prodromal syndrome.

In one study based on the NAPLS dataset, researchers determined the risk of conversion to psychosis and evaluated a set of prediction algorithms aimed at maximizing power for predicting psychosis onset (Cannon et al. 2008). They examined longitudinal data spanning a 2½-year follow-up on 291 subjects meeting SIPS/SOPS prodromal criteria at baseline. The outcome variable was time to conversion to a diagnosed psychotic disorder. Risk of conversion to psychosis was 35%, with a decelerating rate of transition during the 2½-year follow-up. The variables assessed at baseline that contributed uniquely to prediction of psychosis were a genetic risk for schizophrenia with recent deterioration in functioning, higher levels of unusual thought content, higher levels of suspicion/paranoia, greater social impairment, and a history of substance abuse. Prediction algorithms combining two or three of these variables resulted in significant increases in positive predictive power (68–80%) compared with the clinical prodromal criteria alone. The results of this study led the authors to conclude that prospective identification of individuals at risk for psychosis is feasible, and that it can be done at "a level of predictive accuracy comparable to that in other areas of preventive medicine".

It is anticipated that the NAPLS consortium will be issuing more reports from the retrospective combined dataset, and that these studies will further illuminate the predictors of psychosis conversion in prodromal subjects. The next generation of prospective studies of the prodrome will be informed by these findings, in addition to research on the identification of biomarkers (e.g., Brewer et al. 2005, Lencz et al. 2006, Whyte et al. 2006).

## Conclusions

More than a decade ago, McGlashan pointed out the need to focus greater research attention on defining and describing the early course of psychotic disorders, detecting cases early at onset or even during the prodrome, testing whether or not early detection and intervention enhances treatment response and prognosis, and predicting at-risk cases early in the prodromal phase (McGlashan 1996). A number of other psychiatric researchers from North America similarly noted the promises and challenges associated with early intervention (Lieberman and Fenton 2000, Wyatt and Henter 2001, Norman et al. 2004, Malla et al. 2005a). Some of the challenges include the aforementioned problem with predictive power, in addition to the poor specificity of many prodromal symptoms, the potential harms of interventions in the pre-psychotic phase, conflicting evidence from some studies, and the inherent difficulty in conducting longitudinal studies, to name a few. Nonetheless, early psychosis researchers in Canada and the United States offer a wealth of accumulating knowledge that supports and informs the early detection and intervention paradigm for psychotic disorders. Clinical programs in both countries are providing services, developed based on information from international early psychosis research, to ameliorate prodromal and early psychotic symptoms in a timely fashion while aiming to reduce chronicity and morbidity. Research, ranging from modern neuroimaging to cutting-edge prodromal intervention research, will undoubtedly continue to inform clinical programming and the larger preventive paradigm. Both Canada and the United States have established a very rich recent history in both clinical and research programs that will advance the early detection and intervention paradigm.

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