Preventive Strategies for Severe Mental Disorders

Abstract
Since the 1990s, there has been a tremendous upsurge in research on early intervention in psychotic disorders. The neurodevelopmental hypothesis enabled the development of clinical staging models of schizophrenia, which in turn demonstrated that early intervention is possible before the onset of psychosis. Such intervention relied on early detection using prodromal vulnerability indicators and on targeted and stage-specific treatments. Initial efforts were focused on reducing the duration of untreated psychosis to improve outcome. As these efforts were not always successful, research moved on to the examination of prodromes and high-risk states. The “at-risk mental state” strategy based on principles of indicated prevention consisted of the “ultra-high risk” and the “basic symptoms” approaches. A large body of evidence indicated that about 30% of the patients who met criteria for either approach went on to develop full-blown psychosis in the next 2–3 years. Several early psychosis detection programs have been set up worldwide, and controlled trials have shown efficacy of early intervention in first-episode psychosis as well as prodromal or at-risk states. However, several issues regarding identifying and managing such patients still need to be sorted out before prevention of severe mental disorders becomes a reality.

Keywords: Early intervention, preventive strategies, several mental disorders

Introduction
Although the efficacy of psychiatric treatments is comparable to those of physical disorders, reductions in morbidity and mortality achieved by preventive efforts in physical disorders have not been matched by psychiatry.[1-3] However, since the 1990s, there has been a tremendous upsurge in research on early intervention in psychotic disorders focusing on the prodromal periods before the onset of psychosis and on the early phases of established psychosis. It has been shown that timely recognition and phase-specific treatment during these periods has the potential to prevent distress and disability associated with psychotic disorders. Although this research offers hope of reducing the currently prevalent, substantial burden of psychotic disorders, it is still a work in progress.

The neurodevelopmental hypothesis of schizophrenia
The impetus for early intervention in psychotic disorders was provided by two separate strands of research. The first of these was the evidence establishing that early intervention is feasible and beneficial. In a seminal paper in 1991, Richard Wyatt reviewed the results of 22 studies, 19 of which were of patients with first-episode schizophrenia and concluded that early intervention improved long-term outcome.[4] Subsequent research on first-episode psychosis led to the development of early intervention services and further examination of stages of early psychosis.[2,4] Research on first-episode psychosis revealed a pattern of remission followed by relapses.[9,10]

The neurodevelopmental hypothesis enabled the development of clinical staging models of schizophrenia, whereas the other was the empirical data indicating the efficacy of early intervention.[4] The key components of the neurodevelopmental model are depicted in Box 1.[1,4,4]

First-episode psychosis and duration of untreated psychosis
Research on early intervention actually began with the study of first-episode psychosis in the late 1980s as a research-driven attempt to study the illness relatively free of confounders.[1,7] However, the clinical imperative soon supervened when this research suggested that early intervention was both feasible and beneficial. In a seminal paper in 1991, Richard Wyatt reviewed the results of 22 studies, 19 of which were of patients with first-episode schizophrenia and concluded that early intervention improved long-term outcome.[9] Subsequent research on first-episode psychosis led to the development of early intervention services and further examination of stages of early psychosis.[2,4]

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The neurodevelopmental hypothesis enabled the development of clinical staging models of schizophrenia,
which in turn demonstrated that early intervention is possible before the onset of psychosis, with such intervention relying on early detection using prodromal vulnerability indicators and on targeted and stage-specific treatments. An example of such staging models is depicted in Table 1.

One of the principal predictors of poor outcome in this population turned out to be the duration of untreated psychosis (DUP). Despite initial scepticism, DUP proved to be a predictor of outcome in schizophrenia. Moreover, early detection through public health measures appeared to reduce DUP and improve outcome but not consistently enough. Finally, several other conceptual and methodological problems created uncertainty about the impact of DUP; consequently, research moved on to the examination of prodromes and high-risk states [9-27].

**Prodromes of psychosis**

The prodromal period refers to the period of time from the first change in a person in terms of symptoms, altered behavior, or altered functioning until the development of the first frank psychotic symptoms. The concept of prodromes of psychosis was developed by Gerd Huber from the 1960s to 1980s; though the path-breaking study of prodromes was the Age-Beginning-Course (ABC) schizophrenia study by Heinz Hafner et al. The ABC study demonstrated for the first time that the majority of patients with schizophrenia (70%-90%) had prodromal symptoms lasting as long as 5-6.5 years. The earliest symptoms were

### Box 1: Neurodevelopmental model of schizophrenia

Although the brain continues to develop throughout life by means of plasticity, neurodevelopmental processes are at their most active from birth to early adolescence or early adulthood. Normal brain development involves proliferation, migration, arborization (synapse formation), and myelination of neurons. This is a delicate process of sequential and timely changes extending from the prenatal to the first two decades of life. Changes chiefly include progressive replacement of gray matter by white matter, pruning of excitatory synapses, and proliferation of inhibitory synapses leading to an overall predominance of inhibitory activity and dopaminergic innervation of the prefrontal cortex. The neurodevelopmental hypothesis proposes that because of genetic and in utero environmental factors people with schizophrenia are born with a defect in the normal maturational processes of the brain; this defect confers a heightened vulnerability to the development of schizophrenia. However, the defect lies latent with only subtle indicators of its presence till the emergence of psychosis during adolescence. During adolescence, the defect interferes with the normal maturational processes leading to defective myelination, excessive loss of gray matter, and an abnormal excitatory imbalance; this contributes to the “disconnectivity” characteristic of schizophrenia and eventually results in onset of the disorder.

### Table 1: Staging models of schizophrenia

| Stage                        | Features                                           | Manifestations                                      | Interventions                                      |
|------------------------------|----------------------------------------------------|-----------------------------------------------------|---------------------------------------------------|
| Presymptomatic               | <12-13 years; people with genetic or environmental risk, for example, first-degree relatives of probands | Subtle but definite evidence of progressive cognitive, emotional, and neurobiological deficits | Unknown, possibly improved mental health awareness, social skills training of adolescents |
| Early prodrome               | 13-17 years; at risk because of both trait or state factors | Nonspecific symptoms, for example, depression, anxiety, irritability, sleep disturbances; negative symptoms; mild social and functional decline (appearance of basic symptoms) | Detection through public health measures, applying early initial prodromal criteria derived from basic symptoms approach; CBT and psychoeducation |
| Late prodrome                | 17-18 years; ARMS/UHR | APS, BLIPS, GRD; late initial prodromal criteria (basic symptoms); marked social and functional decline | Early detection through application of UHR and basic symptoms criteria; early intervention through phase-specific pharmacological and psychosocial treatments |
| First-episode psychosis      | 18-24 years | Frank psychotic symptoms; continuing functional decline | Care by a specialist early intervention service with phase-specific pharmacological and psychosocial treatments |
| Critical period              | Up to 3-5 years after the first-episode of psychosis | Usually remission followed by relapse | Care by a specialist early intervention service with phase-specific pharmacological and psychosocial treatments |
| Chronic illness              | From 3 to 5 years after the first-episode of psychosis extending throughout life | Remissions, relapses, stable deficit, or further decline | Usual care by a specialist or nonspecialist team with added emphasis on long-term stabilization, recovery, and rehabilitation |

Assumes onset of psychosis at 18 years of age, prodrome of 5 years, late prodrome of 1 year and critical period of 3-5 years. APS: Attenuated psychotic symptoms, ARMS: At-risk mental state, BLIPS: Brief limited intermittent psychotic symptoms, CBT: Cognitive behavioral treatment, GRD: Genetic risk and deterioration criteria, UHR: Ultra-high risk
Although people at high risk for schizophrenia demonstrate a number of neurobiological, cognitive, behavioral, and functional abnormalities from a very early age, the high-risk approach (selective prevention) has poor predictive power and utility in detecting individuals who eventually develop psychosis.\textsuperscript{[1,3,6,12,28,38,39]} Instead, indicated prevention, in which subthreshold syndromes are regarded as risk factors for the full threshold syndromes of psychosis, was the approach more likely to be successful and formed the basis of the ARMS concept.\textsuperscript{[3,33,36]} Two main methods have been used in the ARMS approach for early detection including the ultra-high risk approach (UHR) sometimes called the clinical high-risk approach and the BSs approach.\textsuperscript{[29,30]}

### The ultra-high risk approach

The UHR approach was first developed by Yung and Nelson in the early 1990s at the personal assessment and crisis evaluation clinic at Melbourne. The term “ultra” was used to distinguish the criteria from the genetic high-risk approaches.\textsuperscript{[40]} The UHR criteria relied on prospective identification of prodromes and the implementation of an indicated prevention approach.\textsuperscript{[36]} The techniques of “multiple-gate screening” involving the use of more than one criterion to define the risk state and “close-in follow up” consisting of shortening the follow-up period by commencing follow-up closer to the age of maximum incidence of psychosis were used for risk enrichment or identifying a population with a significantly high risk of developing psychosis.\textsuperscript{[29,39]} The exclusive focus on help-seeking populations was used both as a filter for reducing the rate of false-positive transitions and addressing ethical concerns of treating normal, asymptomatic participants.\textsuperscript{[29]} Accordingly, to meet the UHR criteria, the person had to be a help-seeking individual aged between 14 and 30 years who fulfilled any of the three state or trait risk factors in the year before assessment. These included APS consisting of psychotic disturbances of form and content of thought or of perceptions, which were subthreshold in intensity or frequency; brief limited intermittent psychotic symptoms (BLIPS) consisting of a recent history of frank psychotic symptoms, which resolved spontaneously within 1 week; and the trait and state risk or genetic risk and deterioration criteria (GRD) consisting of having a first-degree relative with a

### At-risk mental state and indicated prevention

To overcome the problems posed by research on prodromal symptoms, the concept of an at-risk mental state (ARMS) was devised in the 1990s.\textsuperscript{[34]} This term was reserved for those with clinical features suggesting an impending psychosis but without the certainty of onset.\textsuperscript{[5]} The ARMS concept represented a departure from the conventional wisdom that prevention of psychotic disorders would only be possible when effective treatments based on target mechanisms became available.\textsuperscript{[2]} Instead, effective prevention was possible by prospectively identifying and using specialized interventions during the prodromal period to positively influence the outcome of the disorder. The ARMS approach was in line with the neurodevelopmental and clinical staging models of schizophrenia, as well as the new framework of prevention strategies [Box 3].\textsuperscript{[35-37]}

### Box 2: Duration of untreated psychosis and outcome of psychosis

- DUP refers to the interval between onset of psychotic symptoms and institution of treatment
- DUP is usually between 1 and 2 years with a median of about 26 weeks
- A DUP ranging from 6 to about 18 months appears to have a significant adverse effect on outcome
- The adverse impact of a prolonged DUP is found on several outcome parameters including treatment responsiveness, negative symptoms, psychopathology, functioning, and quality of life, both in the short- and in the long-term course
- Early detection through public health measures appeared to reduce DUP and improve outcome, but results are not consistent
- Problems with research on DUP include the lack of causal associations with outcome; a modest effect on outcome (13% variance); negative studies with no associations with outcome; differing methodology; possibility of spurious associations with outcome; effect of confounds such as premorbid status; uncertainty about underlying mechanisms linking DUP with poor outcome
- DUP: Duration of untreated psychosis
psychotic disorder or schizotypal disorder and a significant decrease in mental state or functioning maintained for at least a month. These criteria were operationalized, and assessment instruments developed by the authors and others. Initial results from early intervention centers in several countries and indicated that about 40% of those who met UHR criteria went on to develop psychosis within a year.

Clinical and functional characteristics of the UHR group indicated that they were distressed individuals who retained insight into their symptoms (unlike those with frank psychosis). They were more concerned about their presenting problems than about their risk of developing a psychotic disorder. The vast majority had APS, whereas those meeting GRD or BLIPS criteria were rare. A remarkable aspect of their presentation was the high rates of comorbidity, with one meta-analysis of 1683 participants revealing high prevalence of comorbid depression, anxiety, and substance use disorders. Such comorbidity was often associated with self-harming, suicidal, and other inappropriate behaviors. Higher levels of negative symptoms, significant impairments in socio-occupational functioning, and compromised quality of life were often observed. Marked impairment in psychosocial functioning appeared to be a core feature of the UHR state and strongly correlated with outcome.

However, most of the data regarding the UHR group have been derived from studies of help-seeking population. The few general population studies that are available have yielded rates between 0% to 10% among adolescents and young adults depending on the criteria used.

### The basic symptoms approach

BSs were first conceptualized by Gerd Huber et al. in the 1960s. Unlike the UHR criteria, BSs were formulated as subtle, subjectively experienced subclinical disturbances in drive, affect, thinking, speech, (body) perception, motor action, central vegetative functions, and stress tolerance. The subjective nature of these symptoms and the presence of insight differentiated them from the more objective positive and negative symptoms of psychosis. They were thought to be the early experiential expression of the neurobiological substrate of schizophrenia and occurred not only in prodromal but also in psychotic and residual phases of schizophrenia.

In the Bonn long-term study, BSs were observed in 37% of patients before onset of psychosis. BSs were subsequently operationalized and examined for their usefulness in predicting psychosis. In the Cologne Early Recognition study, the presence of at least one BS from a set of 66 symptoms predicted conversion to psychosis in 78% of the 160 patients followed up to 9.6 years. The mean transition time to psychosis was 5.6 years indicating that BSs were better than UHR criteria for detection of early prodromes. Further analyses showed that two groups of ten symptoms, the cognitive-perceptive group (COPER) and the cognitive disturbances group (COGDIS) were more useful in predicting psychosis. Roughly calculated, the conversion rate for patients with COPER and COGDIS varied from 20% to 38% in the first 12 months. Subsequent studies by the German Research Network on Schizophrenia found that the COGDIS appeared to be more specific but less sensitive than the COPER in predicting transitions. These studies were also able to delineate an early initial prodromal state characterized by the presence of at least one of the ten predictive BS several times per week for 3 months along with positive family history and social decline, whereas the late initial prodromal state was defined by the UHR criteria. Finally, the European Prediction of Psychosis Study suggested that combining UHR and COGDIS criteria best-predicted transitions to psychosis.

### Transition to Psychosis: Rates, Outcomes, Prediction, and other Developments

A host of studies both small scale and large scale have examined the rates of conversion to psychosis among patients who satisfy UHR or BSs criteria. Not surprisingly, a wide variation in rates from 6% to 76% has been found depending on the criteria used, the follow-up period, and the design of the study.
A definitive meta-analysis of transition rates included 27 studies with 2502 patients at risk. Transition rates were relatively consistent across studies and independent of the assessment methods used. Transition rates were 18% at 6 months, 22% at 1 year, 29% at 2 years, and 36% at 3 years. The average rate was 29% in the 31 months following the first clinical presentation. Moderators of the heterogeneity across studies included the age of participants, publication year, treatments received, and diagnostic criteria used. Risks estimated using BSs were higher but based on fewer studies. Contrary to expectations, combined BSs and UHR criteria yielded lower risks (23%) than either criterion set. This rate was confirmed by another meta-analysis of 23 studies consisting of 2182 patients at risk, 26% of whom developed psychosis over 2.35 years. This conversion rate represented 400 times higher risk than general population studies (risk of 0.02%-0.03%) and a 3-4 fold higher risk than people with family history of psychosis. In addition, the ARMS criteria were more sensitive to an imminent risk of psychosis onset as most of the conversions occurred during the first 1-2 years.

Another meta-analysis on transition outcomes including 23 studies with 2182 patients at risk found that among those who developed psychosis 73% were diagnosed with schizophrenia spectrum disorders, 16% with other psychoses, and only 11% with mood disorders. The authors concluded that the current ARMS criteria relied heavily on positive than negative symptoms and were strongly biased toward the occurrence of schizophrenia.

However, a 26%-30% rate of conversion to psychosis over 2.5 years means that the majority of patients who meet ARMS criteria do not go on to develop psychosis. The largest examination of nonconverters was a part of the North American Prodrome Longitudinal Study (NAPLS), which found that 71% of the participants had not made the transition to psychosis by 2.5 years. Although there were significant improvements in symptom ratings, 41%-43% of nonconverters had least one attenuated positive symptom over 1-2 years. More pertinently, nonconverters had poorer social and role functioning than nonpsychotic participants. A systematic review of 31 UHR studies also found that 76% of the UHR groups (range 46%-92.6%) did not develop psychosis during follow-up of 6-40 months, whereas 15%-54% of those with UHR criteria achieved remission from their initial UHR status. Thus, it appears that about a third of people with ARMS convert to psychosis, another third do not convert but remain symptomatic and functionally impaired, whereas the last third recover symptomatically and functionally. Among the nonconverters who meet ARMS criteria are the “false positives” who do not convert, the “false negatives” who remit, the “false-negative negatives” who would have converted if they had not received treatment, those with “outpost syndromes” who recover initially only to develop psychosis after several years, people who are partially symptomatic and dysfunctional, and those who develop affective or neurotic disorders.

The low conversion rates have also provided the impetus for studies attempting to increase the predictive power of high-risk criteria. At least three different approaches have been used: one that relies on more than one UHR criteria; another combining UHR and BSs criteria, and approaches utilizing other predictors of conversion to psychosis. The last approach has been helped by a large body of literature on structural and functional imaging, neurocognitive, social, and emotional cognitive deficits in familial high-risk, ARMS, and first-episode participants, all of which show that impairments in these parameters predict transition to psychosis. Several studies have, thus, used multivariate models of prediction based on these predictors of psychosis and have been able to predict conversion to psychosis with 70%-80% accuracy, a predictive power which equals or even betters predictions of heart disease or dementia. The latest in this series of studies, which has come up with a “psychosis calculator,” is from the NAPLS. In these studies, the presence of UHR criteria along with unusual thought content, decline in social functioning, neurocognitive impairments, and young age have been able to predict psychosis with a 71%-79% accuracy rate.

Another remarkable development in the field has been the decline in transition rates to psychosis observed in the more recent studies. Several studies and meta-analyses have shown that there is a significant decrease in reported transition risks over the years from above 50% in the early studies to rates as low as 10%-15% in some recent studies. Explanations offered for this decline have suggested that because of the increasing proliferation and awareness of early intervention services, people with ARMS are being detected at a very early stage. Therefore, they do not convert in the short periods, for which they are followed up lowering transition rates. Early detection is often followed by early treatment, which also prevents conversion. However, the final explanation is that these services are picking up a broader, heterogeneous group of people who have a range of outcomes other than conversion to psychosis. It has been proposed that some of these people are healthy participants or those with nonpsychotic disorders who have subthreshold psychotic symptoms or “psychotic-like experiences” (PLE). It has been estimated that 4%-8% of the general population have PLE associated with distress and help-seeking behavior. However, PLE is generally transient, and only a small proportion (8%-10%) evolve into psychotic and nonpsychotic disorders each year. Accordingly, there appears to be slowly developing consensus that the ARMS should not be considered as a risk factor for only psychosis, but as a much broader at-risk state, which increases the chances of converting to both psychotic and nonpsychotic disorders.
Attenuated Psychosis Syndrome in the Diagnostic and Statistical Manual of Mental Disorders-5

Another outcome of the burgeoning research on the ARMS has been the inclusion of a new category called the “Attenuated Psychosis Syndrome” in the appendix of DSM 5. However, this attempt to encourage clinicians to identify and treat patients with ARMS has attracted a great deal of criticism on methodological and ethical grounds and on uncertain efficacy of current treatments.

**Advantages of having a new category**

- May make clinicians more likely to identify and treat individuals with this syndrome
- Although most such patients would not transit to psychosis, the purpose of treatment is not solely to delay transition but also ameliorate distressing symptoms and improve functioning. Early treatment can improve the outcome of the disorder
- The category could prove the impetus for further research efforts

**Criticisms of the new category**

**Flawed evidence**

Majority of the research is based on help-seeking populations; sample sizes are small and follow-up short in many instances; outcomes are biased toward positive symptoms and psychotic conversions ignoring negative symptoms and social functioning; the high rates of nonconversion and declining rates of conversion compromise validity and utility.

**Ethical concerns**

Lowering the threshold of diagnosis or “diagnostic creep;” concerns about treating people who may not be ill; the stigmatizing effect of the diagnosis of psychosis; the possibility of harm caused by antipsychotic treatment; conflicts of interest that arise when such research is funded by pharmaceutical companies.

**Doubtful efficacy of current interventions**

Few treatment trials of the ARMS, many of which were underpowered, with flawed designs, heterogeneous samples, and short duration of follow-ups; uncertainty about adequate duration of treatment.

Early Intervention in First-episode Psychosis and At-risk Mental State Phase

A comprehensive review of the considerable amount of research on early intervention is beyond the scope of this review; therefore, only the major developments will be briefly reviewed. First, early intervention consists of two distinct components including early detection of those already psychotic or in the prodromal phase who have not yet received adequate treatment and phase-specific treatment, which is a treatment developed or modified specifically for use in early stages.

The overarching goals of early intervention are preventing distress due to current symptoms, reducing disability, improving outcome, and delaying conversion to psychosis in participants with ARMS. Accordingly, the time points of intervention are in the early or late prodromal stage, reducing DUP before onset of psychosis, treating first-episode psychosis, and treatment during the first 3–5 years following onset of psychosis. This has been referred to as the “critical period” when the maximum deterioration occurs and subsequently reaches a plateau. The essential components of management are coordinated, specialty care with a mix of services and pharmacological and psychosocial strategies, comprehensive assessment, therapeutic engagement, embracing diagnostic uncertainty, and treatment in the least restrictive settings using least restrictive alternatives.

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**Box 4: The Attenuated Psychosis Syndrome category in Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition**

| Advantages of having a new category |
|-----------------------------------|
| May make clinicians more likely to identify and treat individuals with this syndrome |
| Although most such patients would not transit to psychosis, the purpose of treatment is not solely to delay transition but also ameliorate distressing symptoms and improve functioning |
| Early treatment can improve the outcome of the disorder |
| The category could prove the impetus for further research efforts |

| Criticisms of the new category |
|-------------------------------|
| Flawed evidence - majority of the research is based on help-seeking populations; sample sizes are small and follow-up short in many instances; outcomes are biased toward positive symptoms and psychotic conversions ignoring negative symptoms and social functioning; the high rates of nonconversion and declining rates of conversion compromise validity and utility |
| Ethical concerns - lowering the threshold of diagnosis or “diagnostic creep;” concerns about treating people who may not be ill; the stigmatizing effect of the diagnosis of psychosis; the possibility of harm caused by antipsychotic treatment; conflicts of interest that arise when such research is funded by pharmaceutical companies |
| Doubtful efficacy of current interventions - few treatment trials of the ARMS, many of which were underpowered, with flawed designs, heterogeneous samples, and short duration of follow-ups; uncertainty about adequate duration of treatment |

ARMS: At-risk mental state
The efficacy of early intervention in first-episode psychosis is supported by several RCTs showing robust gains, large-scale real-world trials of such patients, meta-analyses of relapse prevention, and documentation of cost-effectiveness. However, contrary evidence has been presented by several other reviews, which have concluded that the evidence for early intervention was insufficient and largely inconclusive despite some evident gains.

Controlled trials of intervention for participants with ARMS have also been undertaken. These have been mainly conducted in the late prodromal stage though psychosocial interventions have also been tried in the early prodromal stage. Pharmacological treatments have included antipsychotics, occasionally antidepressants, and more recently neuroprotective agents notably omega-3 fatty acids. Psychosocial treatments have included cognitive behavioral treatment (CBT), case management, family treatment, and integrated psychological treatment. About 11–12 trials have been conducted till date and others are in progress. Meta-analytic reviews show that there is about a 35%–50% reduction in the risk of conversion to psychosis. Consistent efficacy has been documented for CBT followed by omega-3 fatty acids, integrated treatment, and the least evidence for antipsychotics. Considerable heterogeneity and design problems have been noted for most trials.

**Conclusion**

Research on early intervention and indicated prevention has grown very rapidly over the past 30 years and provided sufficient evidence in favor of early detection and treatment of patients at high risk of developing psychosis. Several issues regarding identifying and managing such patients still remain unexplored. In addition, similar research efforts in other conditions such as mood disorders and research from developing countries are scarce. It can be hoped that in the coming years, these deficiencies will be addressed so that prevention of severe mental disorders becomes a reality.

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**Conflicts of interest**

There are no conflicts of interest.

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