

# Attenuated psychosis and the schizophrenia prodrome: current status of risk identification and psychosis prevention

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## Practice points

- Several reliable and validated instruments exist to assess the presence or absence of psychosis risk states. These assessments should be conducted in conjunction with an evaluation of psychiatric comorbidities as well as an individualized appreciation of relevant risk and protective factors and their social context.
- Interventions should be individualized and consist of:
  - Appropriate treatment of significant psychiatric comorbidity
  - Psychoeducation
  - Careful follow-up and ongoing monitoring
  - Antipsychotics should not be routinely employed even at low doses
  - Targeted and informed treatment of specific symptoms
  - Other treatments are still ‘experimental’
- Although the principal clinical and research focus with regard to this condition has been on developing methods to improve the ability to predict likelihood of developing a full-blown psychosis (‘conversion’ or ‘transition’) and investigation of treatments to reduce the likelihood of conversion to psychosis, other clinical issues are also of great clinical importance:
  - A majority of individuals with a current ultra-high risk (UHR) state have some other current psychiatric comorbidity (frequently depressive or anxiety disorder), which warrants appropriate treatment;
  - Only a minority of UHR individuals transition to psychosis without treatment;
  - A significant proportion of ‘nonconverting’ individuals manifest nonpsychotic psychopathology such as depressive or anxiety disorder;
  - A substantial proportion of UHR individuals do not go on to develop major psychopathology.

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## Practice points (cont.)

- Close follow-up is important and should include:
  - Assessment for conversion to psychosis and early intervention as appropriate;
  - Assessment for development or persistence of other psychiatric conditions (e.g., depression, substance-use disorder and anxiety disorder) and provision of appropriate treatment.
- Attenuated psychosis syndrome is being considered for inclusion as a condition in the DSM-5 either in the main body or in the appendix. Although the outcome is uncertain at present, the final decision will likely impact clinical practice.
- While there is a broad overlap between the UHR state and the schizophrenia prodrome, there is much more to UHR states than the risk of developing schizophrenia and much more to preventing schizophrenia than reducing rates of psychotic conversion among those manifesting UHR syndromes.

**SUMMARY** Recent efforts in the prevention of schizophrenia have focused on defining psychosis-risk syndromes and evaluating treatments that can prevent transition to psychosis in these ultra-high risk groups. In this review, different kinds of prevention approaches are enumerated and necessary conditions for a disease-prevention strategy are summarized. The broad overlap as well as the significant difference between a schizophrenia prodrome and a 'psychosis-risk syndrome' is discussed and the present status of approaches to identify individuals at increased risk for developing psychosis and schizophrenia are critically examined along with evaluations on therapeutic interventions to reduce these risks. Finally, to conclude, recommendations for current best clinical practice and key questions for the future are suggested.

Schizophrenia is a chronic brain disorder that generally begins in late adolescence or early adulthood and affects approximately 0.7% of the population. Schizophrenia is characterized by variable proportions of positive (e.g., delusions, hallucinations and disorganized thinking), negative (e.g., reduced motivation and social drive and restricted affective experience and expression), cognitive and mood symptoms throughout the course of the illness [1]. Despite therapeutic advances over the past half-century, schizophrenia continues to be a debilitating condition with profound lifelong impairments in social and vocational functioning for a majority of affected persons [2,3]. Much of the decline occurs early in the course of the illness and overall outcome is directly correlated with functional ability prior to the onset of psychosis and inversely correlated with the duration of untreated psychosis [3,4]. These facts have provided the impetus to early intervention efforts for those with schizophrenia [5–7]. Reducing treatment delay from the onset of the initial psychotic episode by early diagnosis

and effective treatment has yielded only modest improvements in outcome for individuals with schizophrenia however [8], and this has led to interest in the possibilities for intervention even earlier in the course of the illness (i.e., before the onset of psychosis) [5–7,9,10].

Over the past two decades, several centers around the world have developed early psychosis detection and treatment programs to investigate their utility [6,7,11]. In the DSM-5, the addition of a new category of 'Psychosis Risk Syndrome' [12] or 'Attenuated Psychosis Syndrome' [13] is under consideration to describe a clinical condition associated with a significantly increased risk of conversion to schizophrenia or other psychotic disorders. This is a controversial proposal, however, because a sizeable majority of individuals with this condition will not go on to develop a psychotic disorder [13–16]. Furthermore, as there are few established interventions thus far that consistently reduce the risk of conversion to psychosis, the clinical utility of such a diagnostic entity also remains in question.

In this article the elements of, and necessary conditions for, effective prevention strategies in the context of schizophrenia and related psychoses are discussed. The authors distinguish between concepts of ‘schizophrenia prodrome’ and a ‘psychosis-risk syndrome’ and critically examine the present status of approaches aimed at identifying individuals at increased risk for developing psychotic disorders such as schizophrenia. Therapeutic interventions aimed at reducing the risk of subsequently developing a psychotic disorder are evaluated. Finally, recommendations for current best practice and a summary of the key questions for the future are proposed.

### Primary, secondary & tertiary prevention of psychotic disorders

Methods to prevent diseases or reduce their negative impact are usually classified into primary, secondary and tertiary categories [17,18]. Primary prevention denotes methods to protect healthy individuals from developing the disease, secondary prevention refers to efforts to reduce the progression of disease among those with serious risk factors for the disease or with early disease, and tertiary prevention signifies approaches to reduce the impact of extant disease by rehabilitation to restore function and prevent disease-related complications. The focus here is on primary and secondary prevention as these are relevant to the topic at hand. Effective primary prevention requires knowledge of disease risk factors and the availability of methods to reduce the occurrence of these risk factors in the general population (e.g., methods to reduce cigarette smoking to prevent coronary artery disease) or specific general population-level interventions to block these risk factors from leading to disease (e.g., fluoride supplementation to prevent dental caries). Successful secondary prevention requires either the ability to identify groups of people at high risk for developing a disease along with the availability of safe and efficacious treatments that can specifically reduce their likelihood of developing the disease or the ability to reliably diagnose early stages of a disease linked with the availability of specific, effective treatments that can prevent or slow disease progression.

The Institute of Medicine utilizes a different three-layered model of disease prevention that dovetails with the above schema [19]. Universal prevention refers to efforts directed at the entire population to reduce the occurrence of the disease, selective prevention denotes approaches directed

at specific high-risk populations to reduce the occurrence of the disease and indicated prevention describes methods to reduce the progression and impact of the disease among those exhibiting early signs of it. Whereas universal prevention maps onto primary prevention in the previous model, selective and indicated prevention map onto secondary prevention. All these approaches have relevance to the prevention of schizophrenia [6,20], with specific requisites for their application to primary and secondary prevention (**Box 1**).

### The schizophrenia prodrome & the psychosis-risk syndrome: the distinction

It has long been known that the onset of frank psychotic symptoms in schizophrenia is preceded by a variable period of mood changes, perceptual and cognitive changes and social decline that can last weeks to years [21–24]. The prodrome of schizophrenia refers to the period from these first noticeable but nonspecific symptoms or deficits to the appearance of prominent and persistent psychotic symptoms in individuals meeting criteria for schizophrenia. The positive, negative, mood, motor, disorganization and cognitive clusters of symptoms observed in the prodromal phase of the illness fairly map on to the observed psychopathological dimensions of schizophrenia [3], with full-blown psychosis being preceded by depressive, negative and cognitive symptoms by an average of 2–5 years and subthreshold positive symptoms by an average of 1 year [24]. It should be emphasized, however, that the term schizophrenia prodrome can only be applied retrospectively (i.e., after the individual has gone on to develop a full-blown psychotic illness of sufficient length to meet the criteria for a DSM-IV diagnosis of schizophrenia).

#### Box 1. Primary and secondary prevention applications for schizophrenia.

##### Primary prevention

- Knowledge of schizophrenia risk factors
- Availability of methods to reduce the occurrence of these risk factors in the population
- Knowledge of neurobiological pathways mediating effects of various risk factors in causing schizophrenia and availability of specific interventions to block these risk factors from leading to the disease

##### Secondary prevention

- Ability to identify groups of people at high risk for developing schizophrenia
- Availability of safe and effective specific treatments that reduce their likelihood of developing schizophrenia
- Ability to reliably diagnose early stages of schizophrenia
- Availability of specific, effective treatments that can prevent or slow disease progression

Symptoms observed in the schizophrenia prodrome have allowed the construction of definitions of a psychosis-risk syndrome based on combinations of positive, negative, cognitive, disorganization and motor symptoms – these symptoms are relatively mild in severity and/or brief in duration and thereby do not meet criteria for any psychotic disorder. Among commonly utilized instruments [25–27], the Bonn Scale for the Assessment of Basic Symptoms (BSABS) [25] aims to capture the early prodrome to identify individuals who may transition to diagnosable schizophrenia over an average 5-year period [28], whereas the Comprehensive Assessment of ‘At-Risk Mental States’ (CAARMS) [26] and the Structured Interview for Prodromal Symptoms (SIPS) [27] aim to define the late prodrome identifying individuals who may transition to schizophrenia over a 1–2 year period [29,30]. The BSABS assesses subthreshold positive, negative, cognitive and motor symptoms, whereas the CAARMS and the SIPS evaluate multiple risk factors associated with an increased risk of transition to psychosis, identifying three groups of individuals – those with brief periods of threshold psychotic symptoms (i.e., brief limited psychotic symptoms [BLIPS]), individuals with recent-onset subthreshold psychotic symptoms (i.e., attenuated psychotic symptoms [APS]), and those with a schizotypal personality disorder or a first-degree relative with schizophrenia and recent functional decline (i.e., genetic risk plus functional decline). Based on these various definitions, individuals are classified as meeting the criteria for ‘ultra-high risk’ (UHR) [5], ‘clinical high risk’ [30], ‘prodrome’ [31], ‘at-risk mental state’ [26], or ‘psychosis-risk syndrome’ [14] across different centers. While the above terms cover overlapping constructs and are often used interchangeably, their precise definitions and implications differ as discussed below.

In particular, the broad overlap but also the significant distinction between schizophrenia prodrome and the high-risk syndrome (various terms) warrants attention. SIPS and CAARMS criteria do identify individuals with a several 100-fold increase over the general population in the risk of developing a psychotic disorder over the next 1–2 years [29–31]. A significant majority of individuals identified by these definitions of psychosis-risk syndrome do not, however, go on to develop schizophrenia [5–7,32,33] and it can thus be said that they were not experiencing a schizophrenia prodrome. First, the majority of

individuals with a psychosis high-risk syndrome do not develop a psychotic disorder. Second, among those that do develop a psychotic disorder, only approximately half develop schizophrenia [30]. Thus, while prospective identification of individuals in the midst of a schizophrenia prodrome is important – and, indeed, necessary – to allow therapeutic interventions at this stage to improve the future course of the illness [34], the predictive ability of available tools is limited.

### UHR for psychosis or psychosis-risk syndrome

Recent research has uncovered significant variability in the transition from psychosis risk states to psychosis. Conversion to psychosis refers to an increase in severity and/or duration of the attenuated psychotic symptom(s) that allow a diagnosis of a psychotic disorder – examples would include persistence of psychotic symptoms in those with BLIPS or loss of insight and/or greater impact on behavior of a previously attenuated psychotic symptom in those with APS. A recent meta-analysis found conversion rates from the high-risk syndrome to psychosis of 22% at 1 year, 29% at 2 years and 36% at 3 years [35]. Transition rates were found to be moderated by the age of and different treatments received by the participants.

Conversion to psychosis does not necessarily imply development of a schizophrenia spectrum disorder (e.g., schizophrenia, schizoaffective disorder or schizophreniform disorder); it may reflect development of a nonschizophrenia spectrum psychotic disorder (e.g., psychotic mood disorder, delusional disorder and substance-induced psychotic disorder, among others). Since most studies do not provide precise details regarding the nature of the psychotic disorder developed by UHR subjects transitioning to psychosis, estimation of the proportion of ‘converting’ high-risk patients developing schizophrenia across studies is difficult, but appears to occur in approximately half the cases [30]. The likelihood of developing schizophrenia over a 1–3 year period among those with a ‘clinical high risk’ or UHR syndrome also needs to be considered in the context of a continuing risk up to 10 years of developing a psychotic disorder among high-risk individuals [36].

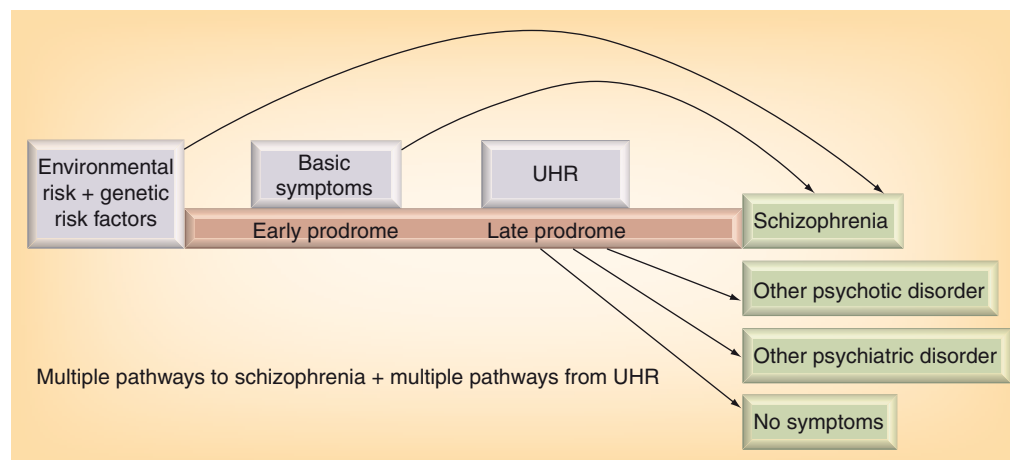
Far fewer prospective studies have evaluated the likelihood of future development of schizophrenia among those with basic prodromal symptoms (defined by the BSABS) [25], but these have noted a conversion rate of up to 70% over

a 10-year period [26]. The notion [34] that basic symptoms represent the early prodrome and routinely progress to attenuated and brief limited psychotic symptoms in the late prodrome and then onto full-blown psychosis is only partially supported by empirical studies [37]; this suggests that the clinical pathway from basic symptoms to schizophrenia may not always progress through BLIPS or APS (Figure 1). Finally, it must be emphasized that all of the above transition rates from basic symptoms, BLIPS or APS to psychosis were observed in help-seeking samples, which might represent a more severely ill subgroup of individuals. By contrast, a recent general population study found a 1% rate of transition to psychosis over a 5-year period among 3343 individuals with self-reported attenuated psychotic symptoms [38].

Neurobiological correlates of increased likelihood of conversion to psychosis among individuals with an ‘at-risk mental state’ are being identified and structural and functional brain changes during the process of psychotic conversion are being elucidated [39–42]. Efforts to enhance the predictive value of clinical criteria by adding brain-imaging markers promise improvement but are still in their early stages of development and do not yet lend themselves to clinical application. Future studies need to consider the possibility that distinct neurobiological pathways may drive risk and differentially modulate the process of conversion to psychosis in various high-risk groups (e.g., genetic high risk versus APS vs BLIPS versus basic symptoms). For indicated prevention strategies to be effectively

employed in schizophrenia, specific interventions that reduce the likelihood of conversion to psychosis and otherwise improve outcome in specific target groups need to be available.

Several pharmacological and psychosocial treatments have been investigated to reduce the risk of transition to psychosis in high-risk individuals [5,43–52]; these include various antipsychotic agents,  $\omega$ -3 fatty acids, glycine, antidepressants, cognitive behavioral therapy, family therapy, psychoeducation and case management. As summarized in a recent Cochrane review, “there is emerging, but as yet inconclusive, evidence that people in the prodrome of psychosis can be helped by some interventions” to reduce transition to full-blown psychosis and “there is a question of whether gains are maintained” [48]. Some effectiveness of both low-dose antipsychotic therapy and cognitive therapy in reducing conversion rates is observed, but these interventions are associated with adverse effects and have thus far not been demonstrated to be significantly more effective than supportive therapy or monitoring [50,51]. These data suggest that such treatment approaches require additional study before they can be recommended for routine clinical use and raise the question of whether supportive therapy and/or routine monitoring may themselves be key ingredients among individuals at UHR for psychosis. A protective family environment and good social adjustment have also been found to decrease the likelihood of conversion to psychosis among individuals at UHR for psychosis [53,54].



**Figure 1. Schizophrenia prodrome and ultra-high risk states.** Multiple pathways to schizophrenia and multiple outcomes of UHR states.

UHR: Ultra high-risk.

The exclusive focus on conversion to psychosis and its prevention among individuals with an UHR syndrome has detracted attention from two other clinically relevant attributes of this condition. First, a significant proportion of UHR individuals experience adverse psychiatric outcomes other than conversion to psychosis [55]. At up to 2 years of follow-up, approximately 40% of 'non-converters' continue to experience one or more attenuated psychotic symptoms, approximately half are diagnosable with an anxiety or mood disorder and the group as a whole continues to exhibit functional and social impairments in comparison with healthy control subjects [56]. Although there is a paucity of data about long-term outcomes of UHR individuals [56–58], it is clear that a majority do not develop schizophrenia or other psychotic disorders: a significant number of nonconverters continue to manifest other psychiatric conditions and yet another substantive proportion do not exhibit any serious psychopathology.

Second, it is important to recognize that individuals with an UHR state (in studies thus far) are help-seeking individuals who present to the clinic for some current psychiatric morbidity with subjective distress and/or impairment [59,60]. They are diagnosed with an UHR state based on the presence of specific psychiatric symptoms and are diagnosed with a range of psychiatric disorders (principally anxiety and depressive disorders). They have immediate risks of adverse psychiatric outcomes such as suicide [61] and could benefit from a range of personalized treatments (e.g., cognitive behavior therapy [51] and antidepressants [52]). This recognition of a current psychiatric need among those with an UHR for psychosis syndrome as opposed to this condition merely representing a risk for future psychosis has led to a reconceptualization in the DSM-5 proposal [101], wherein the designation has changed from psychosis-risk syndrome [12] to attenuated psychosis syndrome [13].

#### **Preventing schizophrenia: risk factors & individuals at risk**

Schizophrenia is a familial disorder caused by an assorted interaction between a number of specific genetic and environmental factors [62]. Whereas the general population risk of developing schizophrenia is approximately 0.7%, first-degree relatives of people with schizophrenia have a 10–15-times greater risk. The latter can be significantly 'enriched' for the likelihood of conversion to psychosis by the addition of clinical criteria [63].

Genetic factors contribute approximately 80% of the overall liability for the illness [64]. After many decades of effort, some specific schizophrenia genes are beginning to be identified [62,64–66], however, these genes collectively explain a very small fraction of all of schizophrenia. A number of specific biological and social environmental factors associated with an increased risk for schizophrenia have also been identified [62,67,68] – these include migration, urbanicity, advanced paternal age, maternal infections and malnutrition during pregnancy, obstetric complications, childhood trauma, late winter/early spring birth, social adversity and cannabis abuse. Whereas their potential modification provides an opportunity for primary prevention of schizophrenia [62,69], little is precisely understood about how these genetic and environmental factors interact to cause schizophrenia [62,70] and what neurobiological pathways mediate these effects.

Certain groups of individuals are found to be at an increased risk of developing schizophrenia. In addition to relatives of people with schizophrenia (discussed above), these include individuals with delay in achieving developmental milestones and/or intellectual disability [71], those with schizotypal personality disorder [72], and those with minor physical anomalies and neurological soft signs. These characteristics are likely to be early manifestations of the disease process rather than representing risk factors for the disease [3]. Finally, as discussed in the previous section, individuals with subthreshold psychotic symptoms are at substantially increased risk of developing a psychotic disorder in the near future. Whereas the annual incidence rate of schizophrenia is approximately 10–40 per 100,000 (0.01–0.04%), the risk of an individual currently with an at-risk mental state developing a psychotic disorder (approximately a half of which may be schizophrenia) over the next year approximates 20% – a several 100-fold increase.

Although the precise neurobiological pathways mediating disease causation by various schizophrenia risk factors remain to be defined, our understanding of the neurobiology of risk and early disease progression in schizophrenia has substantially improved over the past decade. Familial high-risk relatives are found to exhibit a number of structural, neurochemical and functional brain abnormalities observed in individuals with schizophrenia, albeit to a lesser extent [73–76]. Efforts to relate specific genetic and environmental risk factors to particular brain

abnormalities and thereby precisely define neurobiological pathways of schizophrenia causation and progression [77] are, however, in their infancy. For selective prevention strategies to be effectively employed in schizophrenia, such pathways need to be clearly delineated and safe interventions to modify these processes developed.

Currently, primary prevention approaches in schizophrenia would emphasize reduction of risk factors for schizophrenia in the general population (e.g., improving maternal nutrition during pregnancy, improving obstetric care, reducing cannabis abuse and childhood trauma). Although such population-based interventions face challenges of practicality and scalability, they hold the potential to improve overall population health by reducing risk for many disorders other than schizophrenia that may be caused by such factors. Secondary prevention efforts would concentrate on high-risk groups (e.g., those with UHR for psychosis syndrome) and try to prevent progression to psychosis by augmenting protective factors (e.g., improving family environment and enhancing social skills) and addressing current psychiatric needs (e.g., pharmacological and psychotherapeutic interventions for comorbid depression, anxiety, substance dependence and other psychiatric conditions). In addition, secondary prevention efforts would focus on close monitoring and follow-up of such high-risk groups to allow early detection and intervention should schizophrenic psychosis occur, thereby reducing functional deterioration and social decline. In a recent 10-year follow-up study, early detection and intervention was, in fact, found to increase the chances of milder deficits and superior functioning among individuals with schizophrenia [8].

### Conclusion & future perspective

Much progress has been made over the past decade in elucidating the relationship between defined psychosis-risk syndromes and the development of schizophrenia. While there is a broad overlap between UHR (for psychosis) states and the schizophrenia prodrome, there is also a significant divergence (Figure 1). The pathway to schizophrenia does proceed via basic symptoms (early prodrome) through currently defined UHR states (late prodrome) to full-blown psychosis in

many individuals, but there are several other pathways to schizophrenia as well. Similarly, whereas schizophrenia is one possible outcome of UHR syndromes, this occurs in a small minority of people with UHR states. A majority of help-seeking individuals with UHR syndromes have significant other psychiatric comorbidities warranting current clinical attention and a significant proportion progress either to adverse psychiatric outcomes other than development of schizophrenia or show a relative resilience to psychiatric disorder.

The next phase of research in this area needs to focus on the broad overlap as well as the significant divergence between UHR states and pathways to the development of schizophrenia in order to optimally achieve the dual goals of schizophrenia prevention and meeting the clinical needs of individuals with UHR syndromes. The neurobiological underpinnings of the broad overlap as the separate pathways to and from schizophrenia and UHR states require better understanding. Efforts to better define predictors of conversion from UHR states to schizophrenia and evaluate safe and effective interventions to reduce rates of transition need to continue. At the same time, research on other pathways to schizophrenia and specific prevention efforts should separately progress [62,68]. Similarly, more focused research on current and future clinical needs of individuals manifesting the UHR syndromes that go beyond conversion to schizophrenia are needed. In view of the potential importance of UHR states in conjunction with their uncertain nosologic status, we agree with the current recommendation to include 'Attenuated Psychosis Syndrome' in the appendix of DSM-5 as a condition needing further study [101].

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