Published in final edited form as:
Neuropsychiatry (London). 2012 ; 2(4): 345–353. doi:10.2217/NPY.12.36.

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

Neeraj Tandon[*,1], **Jai Shah**[1], **Matcheri S Keshavan**[1], and **Rajiv Tandon**[2]

[1]Department of Psychiatry, Beth Israel Deaconess Medical Center & Massachusetts Mental Health Center, Harvard Medical School, 401 Park Drive, Room 2P12, The Landmark Center, Boston, MA 02215, USA

[2]University of Florida, Gainesville, FL 32611, USA

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

[*]Author for correspondence: Tel.: +1 617 754 1245; Fax: +1 617 754 1250; ntandonbidmc.harvard.edu.

Financial & competing interests disclosure
The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.
No writing assistance was utilized in the production of this manuscript.

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).

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, ω-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 in reducing the rates of transition to psychosis 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].

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].

References

Papers of special note have been highlighted as:

- ■ of interest
- ■■ of considerable interest

1. Tandon R, Keshavan MS, Nasrallah HA. Schizophrenia, ‘just the facts’: what we know in 2008. Part 1: overview. Schizophr. Res. 2008; 100(1–3):4–19. [PubMed: 18291627]
2. Insel TR. Rethinking schizophrenia. Nature. 2010; 468(7321):187–193. [PubMed: 21068826]
3. Tandon R, Nasrallah HA, Keshavan MS. Schizophrenia, ‘just the facts’ 4. Clinical features and conceptualization. Schizophr. Res. 2009; 110(1–3):1–23. [PubMed: 19328655]
4. Marshall M, Lewis SW, Lockwood A, et al. Association between duration of untreated psychosis and outcome in cohorts of first-episode patients. Arch. Gen. Psychiatry. 2005; 62(9):975–983. [PubMed: 16143729]
5. McGorry PD, Nelson B, Amminger GP, et al. Intervention in individuals at ultra-high risk for psychosis: a review and future directions. J. Clin. Psychiatr. 2009; 70:1206–1212.
6. Klosterkotter J, Schultze-Lutter F, Bechdolf A, Ruhrmann S. Prediction and prevention of schizophrenia: what has been achieved and where to go next? World Psychiatr. 2011; 10(3):165–174.
7. Addington J, Heinssen R. Prediction and prevention of psychosis in youth at clinical high risk. Annu. Rev. Clin. Psychol. 2012; 8:1–21. [PubMed: 22035244]
8. Hegelstad WV, Larsen TK, Auestad B, et al. Long-term follow-up of the TIPS early detection in psychosis study: effects on 10-year outcome. Am. J. Psychiatry. 2012; 169(4):374–380. [PubMed: 22407080]
9. McFarlane WR. Prevention of the first episode of psychosis. Psychiatr. Clin. N. Am. 2011; 34:95–107.
10. Tandon R, Nasrallah HA, Keshavan MS. Schizophrenia, ‘just the facts’. 5. Treatment and prevention. Schizophr. Res. 2010; 122:1–23. [PubMed: 20655178]
11. McGorry PD, Edwards J, Mihalopoulos C, et al. EPPIC: an evolving system of early detection and optimal management. Schizophr. Bull. 1996; 22(2):305–326. [PubMed: 8782288]
12. Carpenter WT. Anticipating DSM-V. Should psychosis risk become a diagnostic class? Schizophr. Bull. 2009; 35(5):841–843. [PubMed: 19633215]

13. Carpenter WT, van Os J. Should attenuated psychosis syndrome be a DSM-5 diagnosis? Am. J. Psychiatr. 2011; 168:460–463. [PubMed: 21536700] ■ Succinct debate about the pros and cons of including attenuated psychosis syndrome as a diagnostic entity in the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition.
14. Corcoran CM, First MB, Cornblatt B. The psychosis-risk syndrome and its proposed inclusion in the DSM-V. A risk–benefit analysis. Schizophr. Res. 2010; 120(1–3):16–22. [PubMed: 20381319]
15. Drake RJ, Lewis SW. Valuing prodromal psychosis: what do we get and what is the price? Schizophr. Res. 2010; 120(1–3):38–41. [PubMed: 20417060]
16. Woods SW, Walsh BC, Saksa JR, McGlashan TH. The case for including attenuated psychotic symptoms syndrome in DSM-5 as a psychosis-risk syndrome. Schizophr. Res. 2010; 123(2–3): 199–207. [PubMed: 20832249]
17. Caplan, G. Principles of Preventive Psychiatry. Basic Books, NY, USA: 1964.
18. Lee C, McGlashan TH, Woods SW. Prevention of schizophrenia. Can it be achieved? CNS Drugs. 2005; 19:193–206. [PubMed: 15740175]
19. Mrazek, PJ.; Haggerty, RJ. Reducing Risks For Mental Disorders: Frontiers For Preventive Integration Research. Washington, DC, USA: National Academy Press; 1994.
20. Mojtabai R, Malaspina D, Susser E. The concept of population prevention: application to schizophrenia. Schizophr. Bull. 2003; 29(4):791–801. [PubMed: 14989415]
21. Sullivan SH. The onset of schizophrenia. Am. J. Psychiatr. 1927; 6:105–134.
22. Chapman J. The early symptoms of schizophrenia. Br. J. Psychiatr. 1966; 112:225–251. ■ Lucid, if somewhat dated, review of the early course of schizophrenia.
23. Huber G, Gross G, Schuttler R, Linz M. Longitudinal studies of schizophrenia. Schizophr. Bull. 1980; 6:592–605. [PubMed: 7444391]
24. Hafner H, Maurer K, Loffler W, et al. Hafner H, Gattaz WF. Onset and early course of schizophrenia. Search for the Causes of Schizophrenia III. 1995Berlin, GermanySpringer:43–66. ■Outstanding study of the early stages of schizophrenia.
25. Gross, G.; Huber, G.; Klosterkotter, J.; Linz, M. Bonn Scale for the Assessment of Basic Symptoms. Berlin, Germany: Springer; 1987.
26. Yung AR, Yuen HP, McGorry PD, et al. Mapping the onset of psychosis: the comprehensive assessment of at-risk mental states. Aust. N. Z. J. Psychiatry. 2005; 39:964–971. [PubMed: 16343296]
27. Miller TJ, McGlashan TH, Rosen JL, et al. Prodromal assessment with the structured interview for prodromal syndromes and the scale of prodromal symptoms: predictive validity, inter-rater reliability and training to reliability. Schizophr. Bull. 2003; 29(4):703–715. [PubMed: 14989408]
28. Klosterkotter J, Hellmich M, Steinmeyer EM, Schultze-Lutter F. Diagnosing schizophrenia in the initial prodromal phase. Arch. Gen. Psychiatry. 2001; 58:158–164. [PubMed: 11177117]
29. Yung AR, Phillips LJ, Yuen HP, et al. Psychosis prediction: 12-month follow-up of a high-risk (prodromal) group. Schizophr. Res. 2003; 60(1):21–32. [PubMed: 12505135]
30. Cannon TD, Cadenhead K, Cornblatt B, et al. Prediction of psychosis in youth at high clinical risk: a multisite longitudinal study in North America. Arch. Gen. Psychiatr. 2008; 65:28–37. [PubMed: 18180426]
31. Woods SW, Addington J, Cadenhead KS, et al. Validity of the prodromal risk syndrome for first psychosis: findings from the North American prodrome longitudinal study. Schizophr. Bull. 2009; 35(5):894–908. [PubMed: 19386578]
32. Simon AE, Velthorst E, Nieman DH, et al. Ultra high-risk state for psychosis and non-transition: a systematic review. Schizophr. Res. 2011; 132(1):8–17. [PubMed: 21784618]
33. Schlosser DA, Jacobson S, Chen Q, et al. Recovery from at-risk state: clinical and functional outcomes of putatively prodromal youth who do not develop psychosis. Schizophr. Bull. 2012 (Epub ahead of print).
34. Keshavan MS, De Lisi LE, Seidman LJ. Early and broadly defined psychosis risk states. Schizophr. Res. 2011; 126:1–10. [PubMed: 21123033]
35. Fusar-Poli P, Bonoldi I, Yung AR, et al. Predicting psychosis: meta-analysis of transition outcomes in individuals at high clinical risk. Arch. Gen. Psychiatry. 2012; 69(3):220–229. [PubMed:

22393215] ■■ Recent systematic review of the rates of conversion to psychosis among individuals identified as being at high clinical risk.

36. Yung AR, Nelson B, Yuen H, et al. Long-term outcome in an ultra high risk (‘prodromal’) group. Schizophr. Bull. 2011; 37:22–23.
37. Schultze-Lutter F, Ruhrmann S, Berning J, Maier W, Klosterkotter J. Basic symptoms and ultra high risk criteria: symptom development in the initial prodromal state. Schizophr. Bull. 2010; 36(1):182–191. [PubMed: 18579555]
38. Werbeloff N, Drukker M, Dohrenwend BP, et al. Self-reported attenuated psychotic symptoms as forerunners of severe mental disorders later in life. Arch. Gen. Psychiatry. 2012; 69(5):467–475. [PubMed: 22213772]
39. Koutseleris N, Meisenzahl EM, Davatzikos C, et al. Use of neuroanatomical pattern classification to identify subjects in at-risk mental states of psychosis and predict disease transition. Arch. Gen. Psychiatry. 2009; 66(7):700–712. [PubMed: 19581561]
40. Sun D, Phillips L, Velakoulis D, et al. Progressive brain structural changes mapped as psychosis develops in ‘at risk’ individuals. Schizophr. Res. 2009; 108:85–92. [PubMed: 19138834]
41. Smieskova R, Fusar-Poli P, Allen P, et al. Neuroimaging predictors of transition to psychosis – a systematic review and meta-analysis. Neurosci. Biobehav. Rev. 2010; 34(8):1207–1222. [PubMed: 20144653]
42. Fusar-Poli P, McGuire P, Borgwardt S. Mapping prodromal psychosis: a critical review of neuroimaging studies. Eur. Psychiatry. 2012; 27(3):181–191. [PubMed: 21940151]
43. Ruhrmann S, Schultze-Lutter F, Klosterkotter J. Intervention in the at-risk state to prevent transition to psychosis. Curr. Opin. Psychiatr. 2009; 22:177–183.
44. Correll CU, Hauser M, Auther AM, Cornblatt BA. Research in people with psychosis-risk syndrome: a review of the current evidence and future directions. J. Child Psychol. Psychiatry. 2010; 51(4):390–431. [PubMed: 20214698] ■ Comprehensive review of the psychosis-risk syndrome.
45. Bird V, Premkumar P, Kendall T, et al. Early intervention services, cognitive-behavioral therapy, and family intervention in early psychosis: systematic review. Br. J. Psychiatry. 2010; 197:350–356. [PubMed: 21037211]
46. Preti A, Cella M. Randomized-controlled trials in people at ultra high risk of psychosis: a review of treatment effectiveness. Schizophr. Res. 2010; 123:30–36. [PubMed: 20727717]
47. Liu P, Parker AG, Hetrick SE, et al. An evidence map of interventions across premorbid, ultra high-risk, and first episode phases of psychosis. Schizophr. Res. 2010; 123(1):37–44. [PubMed: 20558043]
48. Marshall M, Rathbone J. Early intervention for psychosis. Cochrane Database Syst. Rev. 2011; 6 CD004718.
49. Phillips LJ, McGorry PD, Yuen HP, et al. Medium term follow-up of a randomized controlled trial of interventions for young people at ultra high risk of psychosis. Schizophr. Res. 2007; 96:25–33. [PubMed: 17611080]
50. Yung AR, Phillips LJ, Nelson B, et al. Randomized controlled trial of interventions for young people at ultra high risk for psychosis: 6-month analysis. J. Clin. Psychiatry. 72:430–440. [PubMed: 21034687]
51. Morrison AP, French P, Stewart SLK, et al. Early detection and intervention evaluation for people at risk of psychosis: multisite randomised controlled trial. BMJ. 2012; 344:e2233. [PubMed: 22491790]
52. Cornblatt BA, Lencz T, Smith CW, et al. Can antidepressants be used to treat the schizophrenia prodrome? Results of a prospective, naturalistic treatment study of adolescents. J. Clin. Psychiatry. 2007; 68(4):546–557. [PubMed: 17474810]
53. Gonzalez-Pinto A, de Azua SR, Ibanez B, et al. Can positive family factors be protective against the development of psychosis? Psychiatry Res. 2011; 186(1):28–33. [PubMed: 20627207]
54. Dragt S, Nieman DH, Veltman D, et al. Environmental factors and social adjustment as predictors of a first psychosis in subjects at ultra high risk. Schizophr. Res. 2011; 125(1):69–76. [PubMed: 20884179]

55. Yung AR, Nelson B, Thompson A, Wood SJ. The psychosis threshold in ultra high risk (prodromal) research: is it valid? Schizophr. Res. 2010; 120(1–3):1–6. [PubMed: 20378314]
56. Addington J, Cornblatt BA, Cadenhead KS, et al. At clinical high risk for psychosis: outcome for nonconvertors. Am. J. Psychiatry. 2011; 168:800–805. [PubMed: 21498462]
57. Ziermans TB, Schothorst PF, Sprong M, van Engeland H. Transition and remission in adolescents at ultra-high risk for psychosis. Schizophr. Res. 2011; 126(1–3):58–64. [PubMed: 21095104]
58. Simon AE, Velthorst E, Nieman DH, et al. Ultra high risk state for psychosis and non-transition: a systematic review. Schizophr. Res. 2011; 132(1):8–17. [PubMed: 21784618]
59. Ruhrmann S, Schultze-Lutter F, Klosterkotter J. Probably at-risk, but certainly ill- advocating the introduction of a psychosis spectrum disorder. Schizophr. Res. 2010; 120(1–3):23–37. [PubMed: 20400269] ■ Excellent overview, in which the current clinical needs of individuals with ‘at-risk mental syndrome’ are discussed.
60. Rosen JL, Miller TJ, D’Andrea JT, McGlashan TH, Woods SW. Comorbid diagnoses in patients meeting criteria for the schizophrenia prodrome. Schizophr. Res. 2006; 85:124–131. [PubMed: 16650735]
61. Andriopoulos I, Ellul J, Skokou M, Beratis S. Suicidality in the ‘prodromal’ phase of schizophrenia. Compr. Psychiatr. 2011; 52:479–485.
62. Tandon R, Keshavan MS, Nasrallah HA. Schizophrenia, ‘just the facts’. What we know in 2008, 2. Epidemiology and etiology. Schizophr. Res. 2008; 102(1–3):1–18. [PubMed: 18514488]
63. Tandon N, Montrose D, Shah J, et al. Early prodromal symptoms can predict future psychosis in familial high-risk youth. J. Psychiatr. Res. 2012; 46(1):105–110. [PubMed: 22056319]
64. Gill M, Donahoe G, Corvin A. What have the genomics ever done for the psychoses? Psychol. Med. 2010; 40:529–540. [PubMed: 19818200]
65. The International Schizophrenia Consortium. Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. Nature. 2009; 460:748–752. [PubMed: 19571811]
66. Stefansson H, Ophoff RA, Steinberg S, et al. Common variants conferring risk for schizophrenia. Nature. 2009; 460:744–747. [PubMed: 19571808]
67. McGrath J, Saha S, Welham J, et al. A systematic review of the incidence of schizophrenia: the distribution of rates and the influence of sex, urbanicity, migrant status, and methodology. BMC Med. 2004; 2:13. [PubMed: 15115547]
68. Matheson SL, Shepherd AM, Laurens KR, Carr VJ. A systematic meta-review grading the evidence for non-genetic factors and putative antecedents of schizophrenia. Schizophr. Res. 2011; 133(1–3):133–142. [PubMed: 21999904]
69. McGrath JJ, Lawlor DA. The search for modifiable risk factors for schizophrenia. Am. J. Psychiatr. 2011; 168:1235–1238. [PubMed: 22193665]
70. Duncan LE, Keller MC. A critical review of the first ten years of candidate gene-by-environment interaction research in psychiatry. Am. J. Psychiatr. 2011; 168:1041–1049. [PubMed: 21890791]
71. Welham J, Isohanni M, Jones P, McGrath J. The antecedents of schizophrenia: a review of birth cohort studies. Schizophr. Bull. 2009; 35:603–623. [PubMed: 18658128]
72. Tarbox SI, Pogue-Geile MF. A multivariate perspective on schizotypy and familial association with schizophrenia: a review. Clin. Psychol. Rev. 2011; 31(7):1169–1182. [PubMed: 21855827]
73. Lawrie SM, McIntosh AM, Hall J, et al. Brain structure and function changes during the development of schizophrenia: the evidence from studies of subjects at increased genetic risk. Schizophr. Bull. 2008; 34(2):330–340. [PubMed: 18227083]
74. McIntosh AM, Owens DGC, Moorhead WJ, et al. Longitudinal volume reductions in people at high genetic risk of schizophrenia as they develop psychosis. Biol. Psychiatry. 2011; 69(10):953–958. [PubMed: 21168123]
75. Peters BD, Blaas J, de Haan L. Diffusion tensor imaging in the early phase of schizophrenia: what have we learned? J. Psychiatr. Res. 2010; 44(15):993–1004. [PubMed: 20554292]
76. Diwadkar VA, Wadehra S, Pruitt P, et al. Disordered corticolimbic interactions during affective processing in children and adolescents at risk for schizophrenia revealed by functional magnetic resonance imaging and dynamic casal modeling. Arch. Gen. Psychiatr. 2012; 69(3):231–242. [PubMed: 22393216]

77. Piontkewitz Y, Arad M, Weiner I. Tracing the development of psychosis and its prevention: what can be learned from animal models. Neuropharmacology. 2012; 62(3):1273–1289. [PubMed: 21703648]

Website

101. American Psychiatric Association. DSM-5 Progress. 2012www.dsm5.org. ■■ The current status of the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition proposals are provided on this site and regular updates are provided. Currently, ‘Attenuated Psychosis Syndrome’ is slated to be included in section three or the appendix of the manual, as a condition needing further study.

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.
- 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.

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

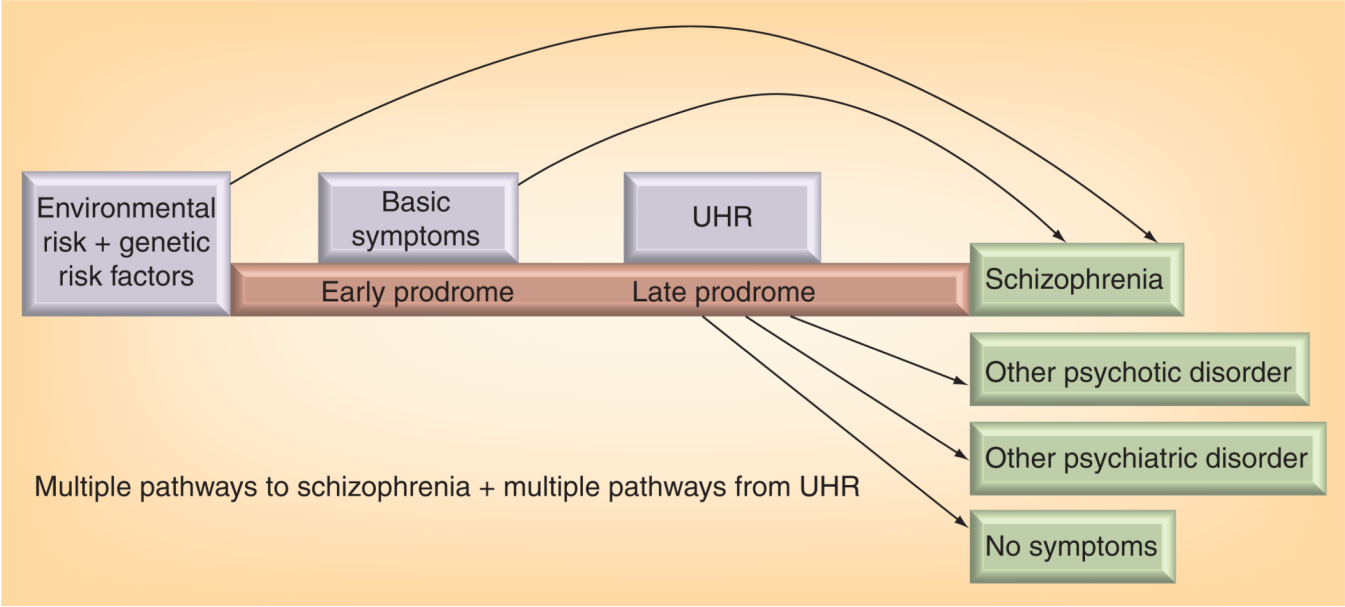

Figure 1. Schizophrenia prodrome and ultra-high risk states

Multiple pathways to schizophrenia and multiple outcomes of UHR states.
UHR: Ultra high-risk.