

How should we intervene in psychosis risk syndromes?

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Summary: Research diagnostic instruments such as the Structured Interview for Prodromal Syndromes (SIPS) are now able to reliably identify individuals with different types of psychosis risk syndromes (PRS). About one-third of individuals with PRS convert to a diagnosable psychotic disorder within three years of the initial assessment. Currently available randomized controlled trials of interventions aimed at reducing the rate of psychotic conversion of PRS are promising, but they are too small and too short in duration to provide definitive conclusions about effectiveness. Given the high level of false positives (i.e., most individuals with PRS do not progress to frank psychosis) and the lack of definitive evidence about effectiveness, we recommend a staged approach to intervention in PRS that only uses antipsychotic medication after other, more benign approaches have been tried. At present the best approach appears to be to develop high-quality case-management systems for individuals with PRS that provide close follow-up, psychoeducation and psychosocial support to patients and family members, and, possibly, psychotherapeutic and pharmacological treatments (with antipsychotic medications or neuroprotective agents). The effectiveness of these proposed interventions needs to be tested in large randomized controlled trials that follow up subjects for at least three years.

1. What are psychosis risk syndromes (PRS)?

The occurrence of schizophrenia, affective psychotic disorders and other psychotic conditions are traumatic for both affected individuals and their families. With a peak age of onset of 18 to 30 years, psychotic illnesses often interrupt development during the transition from adolescence to adulthood.^[1] Following the examples set with chronic physical illnesses such as diabetes and heart disease, the scientific focus on psychotic illnesses has increasingly shifted to early intervention. The goals of this new approach are to reduce illness progression and morbidity and, in time, to develop viable preventive interventions.^[2] As part of this scientific reorientation, there is a growing body of work focused on populations at 'clinical high risk' for psychoses and on adolescents and young adults in the putative prodromal phase of a first psychotic episode – at which time there is illness-related deterioration in the functioning of the brain and in neurocognitive, social and role functioning.^[3,4]

In the past decade, research diagnostic instruments such as the Comprehensive Assessment of At Risk Mental States (CAARMS)^[5] and the Structured Interview for Prodromal Syndromes (SIPS) have been used to identify high-risk individuals and to distinguish different types of psychosis risk syndromes (PRS).^[6,7] The SIPS

classifies three types of psychotic risk syndromes: Brief Intermittent Psychotic Syndrome (BIPS); Attenuated Positive Symptom Syndrome (APSS); and Genetic Risk and Deterioration Syndrome (GRDS). The transition of PRS individuals to diagnosable psychosis has been of particular interest to researchers;^[8] the largest meta-analysis available^[9] reports an average transition rate of about 20% over the first year of follow-up and of about 35% over the first three years of follow-up. Therefore, populations with PRS provide an important opportunity to develop a systematic scientific strategy for the earlier intervention and possible prevention of psychosis.

2. Potential benefits and risks of intervening in PRS

Interventions for PRS, which target subjects with minimally detectable symptoms falling below the threshold of a psychotic disorder, can be considered a form of secondary or targeted prevention. The major aims of clinical intervention in PRS are: a) to reduce prodromal symptoms and related problems such as social withdrawal and academic difficulties; b) to reduce the risk of the subsequent onset of frank psychosis; and c) to minimize treatment delay for the subgroup of PRS subjects that do develop a first episode of psychosis.

However, the use of such preventive interventions has

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elicited ethical concerns. Identification as an individual with PRS can be associated with stigma and heightened anxiety, and the interventions themselves have potential short- and long-term side effects.^[10] For instance, low-dose antipsychotic treatments – the cornerstone of the first wave of interventions for PRS – have been associated with neurotoxic effects in some animal studies.^[11-13] Moreover, most persons with PRS do not subsequently develop frank psychosis (false positives), so there are important cost-benefit considerations in recommending that all persons with PRS be referred for treatment.

This raises the question of how to stage treatments to maximize prevention while minimizing harm. Some authors recommend phase-specific interventions that match the symptomatic presentation of PRS and that include more benign options before progressing to pharmacological treatments.^[14,15] Psychosocial interventions should be a component of all interventions for individuals with PRS. They include crisis intervention, assistance in maintaining social functioning, psychoeducation for patients and their family members, and general social support. These basic psychosocial interventions can be augmented by other psychotherapeutic and psychopharmacological interventions depending on the specific needs of the patient. Cognitive-behavioral therapy has been shown to be superior to the simple monitoring of PRS patients over time,^[16,17] but it may not be better than less structured supportive counseling.^[18] Potential psychopharmacologic interventions for PRS have recently been broadened to include non-antipsychotic medications. In the critical phase during the first emergence of a psychotic disorder apoptotic processes might play a key role, so agents with preclinical or clinical evidence for neuroprotective properties that can reduce cell death^[19,20] (including antidepressants^[21,22] and omega-3-fatty acids^[23]) have been considered as candidates for PRS interventions.

3. Current evidence of effectiveness of interventions for PRS

Several randomized control trials with follow-up times of 3 to 12 months have assessed the effectiveness of different types of interventions for PRS.^[24-26] Cognitive behavioral therapy either on its own^[17,18] or in combination with risperidone^[25] and ethyl eicosapentaenoic acid (ethyl EPA)^[23] have been shown to significantly reduce PRS transition rates. Cognitive behavioral therapy^[16] and olanzapine^[27] have been shown to significantly reduce the severity of the psychopathological symptoms of PRS. However, few studies followed up patients after the acute treatment phase, and those that do have long-term follow-up data^[17,25,28] found that the reduced risk for transition in the active treatment group is not maintained over time. The one exception is the 2008 study of ethyl EPA by Amminger and colleagues^[23] which reported that 2.5 to 3.5 months of acute treatment

produced a sustained reduced risk of transition for nine months after stopping the active treatment.

There are also several ongoing randomized controlled trials with non-antipsychotic medications including ethyl EPA, D-serine, and sarcosine (see: www.clinicaltrials.gov) and with family-based interventions.^[29] It is too early to come to a definitive conclusion, but the weight of the evidence suggests that pharmacological and non-pharmacological interventions can significantly reduce transition rates in PRS, perhaps by as much as two-thirds (i.e., from 30 to 10%).^[30]

4. The study of PRS in Shanghai

In collaboration with the Beth Israel Deaconess Medical Center at Harvard Medical School, we evaluated the reliability and validity of the Chinese version of the Structured Interview for Prodromal Symptoms (SIPS) and used it to assess the prevalence of PRS in individuals treated at the Psychological Counseling Center of the Shanghai Mental Health Center. The SIPS was translated in standard fashion from English to Chinese and back-translated from Chinese to English. The resulting instrument had excellent inter-rater reliability when used by Chinese psychiatrists with 38 patients (ICC=0.96).^[31]

Over a 10-month period, we screened 2078 patients, directly interviewed 1444 patients, and identified 104 (5.0%) who met PRS criteria. These 104 cases included 68 (65.7%) subclassified with attenuated positive symptom syndrome (APSS) and 23 (22.4%) with genetic risk and deterioration syndrome (GRDS); the overall prevalence is similar to western samples though the proportion of GRDS is somewhat higher than elsewhere. Routine treatment by the outpatient clinicians (who were blind to the results of the SIPS assessment) included the prescription of antidepressants for 33 of these individuals and antipsychotic medications for 22 of them; the 53% (55/104) rate of pharmacological treatment for PRS is comparable to the rate reported in the North American Prodrome Longitudinal Study.^[32] Naturalistic follow-up of these individuals six months after the initial assessment for PRS found that 49 (47.1%) never returned to the clinic, a possible reflection of the limited psychosocial intervention and support provided to persons with PRS in China. Among the 86 individuals followed up by the research group, 5 (5.8%) met SIPS criteria for a psychotic episode; this six-month transition rate is lower than the 18% rate reported in western studies.^[9] The reasons for the lower rate of transition are unclear, but it could be related to the higher proportion of the GRDS subtype of PRS and the relatively high age (maximum 45 years old) in our sample.

5. Summary and conclusions

Individuals with PRS can be reliably identified using clinical diagnostic tools such as the SIPS. Simply

monitoring PRS subjects for the first signs of frank psychosis might be an effective means of reducing the delay between the onset of the first episode and the start of antipsychotic treatment for the subgroup of patients who might need it. The use of pharmacological and psychological interventions during the prodromal phase may decrease the severity of the PRS presenting symptoms and reduce the rate of transition to frank psychosis, but the clinical trials that have assessed these interventions have been under-powered and have not followed up patients long enough to provide a definitive answer about this crucial question. Further research is needed to determine whether initial treatment effects can be maintained.

Chinese clinicians are now starting to pay attention to the early recognition and prevention of psychotic illnesses, particularly schizophrenia. As they identify and diagnose more individuals with PRS it is important that they expand their usual pharmacological approach to psychosis and include more benign interventions such as high-quality case management, psychoeducation, family treatment, and cognitive behavior therapy. Large randomized clinical trials that rigorously exam the long-term effects of these interventions are needed both in China and elsewhere. This effort will require expanding the range of personnel who provide supportive care to individuals with PRS, training clinicians in the skills needed to provide community-based case management services, and mobilizing the administrative support and funding needed to conduct large, long-term studies.

Conflict of interest

The authors report no conflict of interest.

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