

• Forum •

Treatment of prodromal schizophrenia

Is pharmacological intervention necessary in prodromal schizophrenia?

Jingping ZHAO*, Hailong LV, Xiaofeng GUO

In 2009 the American Psychiatric Association (APA) proposed including Attenuated Psychosis Syndrome (APS) in Section III of DSM-5, the section reserved for mental disorders that require further research before they can be included in the main text of the diagnostic manual. The rationale for this recommendation was that extensive research – including structural and functional brain imaging studies, neurocognitive studies, genetic studies and other types of studies – had identified several potential risk factors for serious psychiatric disorders. The belief was that the identification of APS as a clinical entity could help physicians in the early detection and treatment of individuals who are at a high-risk of developing severe mental illness.^[1,2] APS, which can be viewed as a prodromal form of schizophrenia, has also been called Psychosis Risk Syndrome (PRS). The proposed DSM-5^[3] diagnostic criteria for APS are as follows:

- A. *Characteristic symptoms: At least one of the following in attenuated form with intact reality testing, but of sufficient severity and/or frequency that it is not discounted or ignored: (1) delusions; (2) hallucinations; (3) disorganized speech.*
- B. *Frequency/currency: symptoms in Criterion A must be present in the past month and occur at an average frequency of at least once per week for the past month.*
- C. *Progression: symptoms in Criterion A must have begun or significantly worsened in the past year.*
- D. *Distress/disability/treatment seeking: symptoms in Criterion A are sufficiently distressing and disabling to the patient and/or parent/guardian to lead them to seek help.*

E. *Symptoms in Criterion A are not better explained by any DSM-5 diagnosis, including substance-related disorder.*

F. *Clinical criteria for a psychotic disorder have never been met.*

The main goal of adding the diagnosis of APS to DSM-5 is to give clinicians the opportunity to provide preventative treatment to these high-risk individuals. The primary intervention for persons with a diagnosis of APS would be to regularly meet with them and their family members, to systematically monitor their symptoms, and to periodically reevaluate whether or not the risk is high enough to justify the use of antipsychotic medications. There are three main reasons for considering preventive pharmacological treatment.

First, persons who meet the diagnostic criteria for APS are in a prodromal stage of a psychiatric disorder, experiencing mild psychotic symptoms and a clear decline in their functioning. Based on results from the Global Assessment of Functioning (GAF) scale, they have moderate to severe impairments in their daily functioning (GAF scores in the range of 40 to 60).^[4,5] Compared to controls their cognitive functioning is impaired.^[6] Many of them seek medical treatment (or their relatives bring them for treatment) due to concern about these symptoms.^[7,8]

Second, the risk for persons with APS developing a mental illness (primarily schizophrenia) is 400 times higher than that in unselected community members.^[9] The most recent meta-analysis shows that for persons with APS, 18% progressed from APS to a psychotic disorder within six months, 22% within one year, 29% within two years and 36% within three years.^[10] In some of these studies individuals with APS who took antipsychotic medications were less likely to develop a psychotic disorder than those who

did not take antipsychotic medications. Thus, even though it is not yet possible to predict which persons with APS will progress to a full-criteria mental illness, failure to provide them with preventative treatment may increase their risk of developing a full-blown psychotic disorder. Other studies report that 80 to 90% of patients with schizophrenia have a relatively long prodromal period before they meet the full criteria for the disorder.^[11] Early intervention during this prediagnostic prodromal period can shorten the duration of untreated psychosis (DUP), reduce chronic deterioration and improve prognosis in individuals with schizophrenia. Based on these findings, some researchers recommend that early intervention should be provided to all high-risk individuals who meet the criteria for APS.

Third, there is emerging evidence that early intervention for persons with APS is safe, can improve symptoms and functioning, and can reduce the risk of developing a psychotic disorder.^[10,12,13] One meta-analysis reported that the one-year psychotic conversion rates of intervention group subjects and control group subjects were 11.0% and 31.6%, respectively (relative risk 0.36), and that the three-year psychotic conversion rates were 25.8% and 42.0%, respectively (relative risk 0.64).^[12] Currently, the main preventive measures being tested in clinical trials include monotherapy with olanzapine, risperidone with adjunctive individual psychological therapy, and cognitive behavioral therapy without antipsychotic medication.^[14-16] A recent 2010 study also found that the use of omega-3 fatty acids without any adjunctive antipsychotic medications can prevent or delay the development of psychotic disorders in persons with APS.^[8] Given the goal of minimizing exposure of individuals with APS to unnecessary antipsychotic treatment, antipsychotics should be used conservatively; if possible, the potential usefulness of omega-3 fatty acids and cognitive behavioral therapy for the patient should be assessed before starting low-dose antipsychotic medication.

Some researchers^[17] oppose the inclusion of APS in DSM-5 and the use of early preventative interventions for the following reasons. Currently the evidence supporting the effectiveness of interventions for persons with APS remains relatively weak: prodromal symptoms alone are not a good predictor of whether or not a person will develop schizophrenia and most persons with APS do not subsequently develop a psychotic disorder, so incorrectly labeling them as having a mental disorder and exposing them to antipsychotic medications will result in unnecessary psych distress and can lead to stigma and discrimination. Moreover, treating individuals who have APS with medications that they may not need exposes them to unnecessary side effects, and treating them using psychotherapeutic methods of uncertain effectiveness is time consuming and expensive.

Clearly, the benefits and risks of pharmacological and other types of interventions for persons with APS need to be more rigorously assessed and compared. To this end, the authors' research group is conducting a multicenter cohort study – the 'Early Diagnosis, Prevention and Intervention in Prodromal Schizophrenia' (EDPIPS)^[18] – that should help to clarify these issues. The project, which will be completed in three years, is assessing diagnostic tools for use during the prodromal period, characterizing the progression of APS to psychotic disorders (or not), identifying factors that predict different prognoses, and comparing different treatment approaches.

Until such definitive studies are available, I believe that the potential benefits of pharmacological intervention for persons in the prodromal stage of schizophrenia are greater than the potential risks. The majority of persons with APS are adolescents whose family members seek treatment because the individual has exhibited distressing psychological symptoms and experienced deteriorating social functioning. In this situation, it is justified to provide low-dose antipsychotic medication because this conservative intervention has relatively few side effects, can reduce symptoms and improve functioning, and may lower the risk of developing a severe mental disorder.

Conflict of interest

The authors report no conflict of interest related to this manuscript.

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Professor Jingping Zhao received his bachelor's, master's and doctorate degrees in medical science from Hunan Medical University and is currently the Vice-Director of the Mental Health Institute of the Second Xiangya Hospital of Central South University. He is the former president of the Chinese Society of Psychiatry, and a current council member of the Asian College of Neuropsychopharmacology, the International Society of Bipolar Disorders, and the Schizophrenia International Research Society. He is also the Editor-in-Chief of the Chinese Journal of Psychiatry and of the (Chinese) International Journal of Psychiatry as well as being on the editorial boards of more than ten other journals. His main research interests are genetic and pathological mechanisms of major mental disorders and the pharmacological and psychosocial treatment of schizophrenia and autism.