VIEWPOINT

Attenuated Psychosis Syndrome Should Be Moved to the Main Section in *DSM-5-TR*

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Introduction

Before the introduction of *DSM-5*, there was discussion on the validity and utility of the clinical high risk (CHR) for psychosis construct. In weighing the pros and cons of including CHR's main syndrome—attenuated psychosis syndrome (APS)—it was ultimately decided to place APS in the section for disorders requiring further study. Ten years have since passed, and developments have occurred that warrant a reevaluation of the status of APS in the *DSM-5*. In this Viewpoint, we review the history of the construct, highlight original points of contention, and discuss developments from research and clinical practice that inform this dilemma. Based on this review, we argue that the balance has shifted in favor of including APS in the main section of the upcoming *DSM-5* text revision.

What Is CHR? Approach to Risk

The CHR construct was created in the 1990s as a psychosis risk syndrome to identify individuals who might be in a putative prodrome of schizophrenia (or other psychoses). CHR includes 3 syndromes based on attenuated psychotic symptoms (included in the *DSM-5* appendix as APS), brief intermittent psychosis, or genetic risk with functional decline. APS is the most common CHR syndrome, characterizing more than 85% of all patients at CHR.[1] The rationale for the development and use of the CHR construct is that by the time of first-episode psychosis, the illness has likely been well underway for several years, with significant social and functional impairment and with motivational, expressive, motor, and cognitive deficits. One analogy for psychosis onset is myocardial infarction. Cardiologists do not wait until the first myocardial infarction but instead identify and treat angina (a risk syndrome for infarction) along with cardiac risk factors, such as obesity, hypercholesterolemia, and smoking. And as with cardiology, a main goal for the psychosis risk syndrome is the prevention of more severe disorder.

Why Is APS in the *DSM-5* Appendix as a Disorder Requiring Further Study?

In 2010, APS was proposed for inclusion in the *DSM-5*. APS met most criteria for a new *DSM-5* category, including substantial evidence for validity, clinical value, and nonoverlap with existing diagnoses. However, the proposal was hotly debated in the mainstream media and in scientific journals in respect to the benefit-to-harm ratio.[2] On one side, there was concern about stigma and antipsychotic exposure, especially for false-positives—individuals who did not go on to develop psychosis. There were also concerns that effective treatments had not been developed and that significant heterogeneity existed within the psychosis risk construct and across outcomes. Proponents emphasized the benefit of the provision of diagnosis and treatment for young people with symptoms and functional impairment, arguing that stigma could be managed and antipsychotics used sparingly. However, there was a critical concern as to whether clinicians could make reliable and valid diagnoses of APS, supported by the finding of indeterminate results in small field trials.[3] Together, these factors led to APS being placed in the section for disorders requiring further study.

Addressing Original Concerns About APS

Stigma, Unnecessary Antipsychotic Exposure, and False-Positives

Concerns relating to stigma and medication exposure in individuals at CHR no longer hold the weight they once did. Research shows that stigma is related more to the symptoms of the CHR syndrome than to a risk or diagnostic label and that stigma can be managed through education.[4] Further, risk of unnecessary antipsychotic exposure has been managed through development of treatment guidelines and professional education. As for false-positives, we now recognize this is a clinically important group to study. Many individuals at CHR who do not develop a psychotic disorder show persistent symptoms, with related distress and functional impairment. A smaller group improves, who may have benefited from early identification and treatment or who hold important clues about resilience. Longitudinal study enables the identification of risk and protective biomarkers for these diverse outcomes—psychosis, persistence, and remission—alone and together in tandem. Thus, a formal diagnosis of APS would serve all individuals who meet these criteria.

Lack of Effective Treatments and Heterogeneity

Another initial concern was the lack of evidence-based treatment. We would argue that treatment development for a syndrome is best served by its inclusion in the *DSM-5* main text, where it gains formal status as a diagnosis that can be studied epidemiologically through review of health records and as a diagnosis to be used for clinical trials and treatment development. Nonetheless, there have been significant advances in psychological treatments for individuals at CHR, such as cognitive behavioral therapy, which improves not only positive symptoms but also mood and anxiety symptoms, and role and social function. Evidence also exists for efficacy of cognitive remediation and aerobic exercise. Together, this treatment research has led the Substance Abuse and Mental Health Services Administration to invest $11 million in stepped evidence-based

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intervention for individuals at CHR at more than 20 sites across North America.[5]

Heterogeneity in the CHR syndrome has also been criticized, although heterogeneity need not be a barrier to inclusion in *DSM-5*, as major depressive disorder has comparable heterogeneity. Nonetheless, heterogeneity provides opportunity, in that our ability to map heterogeneity will lead to promises associated with personalized medicine so deftly used in other fields of medicine, like cancer treatment. The Accelerated Medicines Partnership in Schizophrenia (AMP-SCZ) has as its focus parsing the heterogeneity of CHR (largely APS), in both symptom expression and outcome.[6] AMP-SCZ will enable the characterization of biomarkers and neural mechanisms associated with first-episode psychosis onset, persistence of attenuated symptoms, and even remission. This will guide treatment development and stratification (eg, personalized medicine).

Nonexpert Clinicians and Reliability

The ultimate arbiters of whether a diagnosis is included in the *DSM-5* is the DSM Steering Committee, who have specific criteria for addition of a new diagnostic category to the *DSM-5*.[7] The proposed diagnosis must meet criteria for a mental disorder, have strong evidence of validity, be capable of being applied reliably, manifest substantial clinical value, avoid substantial overlap with existing diagnoses, and have a positive benefit-to-harm ratio.[7] Reliability is a key metric evaluated through the use of field trials in which clinicians conduct unstructured interviews with the same individuals, and their diagnoses and ratings are compared for degree of agreement. In the case of APS, a decade ago, interrater agreement was the same as that seen for schizophrenia. However, as far fewer individuals were involved, the confidence interval for agreement was wider and included the possibility of nonagreement (n = 17; κ = 0.46; 95% CI, 0-0.81).[3] Hence, the criterion for reliability was not met, and APS was placed in the section for provisional disorders.

However, there is now evidence to support that clinicians should be able to reliably diagnose APS. Thousands have been trained and certified in the administration of the Structured Interview for Psychosis Risk (SIPS). The National Institute of Mental Health (NIMH) funds several case-finding grants to identify individuals with subthreshold psychotic symptoms, with proven success in educating community clinicians. Interrater reliability in diagnosis of CHR is easily achieved in the research context,[8] which suggests likely success in training clinicians.

A Call to Arms

Evidence has accumulated for the validity of the APS syndrome.[9] A positive benefit-to-harm ratio is evident, given that stigma and unnecessary medication exposure can be managed, treatments have been developed and implemented, and heterogeneity in symptoms and outcome are a focus for the NIMH and its partners in AMP-SCZ, moving the field toward personalized prevention. What remains is the need to establish reliability in diagnosis by clinicians. Our call now is to invest in broader education of clinicians as to attenuated psychotic symptoms. Too many mental health professionals, even psychiatrists, see psychosis as basically dichotomous—either you have it or you do not. Therefore, there may not be a spontaneous groundswell of felt need from clinicians for APS as a formal *DSM-5* diagnosis. But in our experience, when clinicians hear about CHR and APS, they are eager to find out more and seek training in diagnosis and in provision of feedback. Further, there now exists brief online training for the Mini-SIPS, a 30-minute diagnostic interview,[10] which offers a platform for clinician education and adequately powered field trials.

We call on the DSM Steering Committee, Substance Abuse and Mental Health Services Administration, NIMH, and stakeholder partners to help us identify resources to implement large field trials with clinicians trained in this abbreviated clinical diagnostic interview so that the reliability in APS diagnosis can be given its best shot, paving the way for APS to join *DSM-5-TR*. Given the multimillion-dollar investment in AMP-SCZ by the NIMH and its partners, which include individuals with lived experience from the National Alliance on Mental Illness and OneMind, as well as pharmaceutical companies aiming to develop therapeutics, we believe it is now time to revisit the status of CHR's main syndrome—APS—in the *DSM-5-TR*.

ARTICLE INFORMATION

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