Commentary

Biological Psychiatry

Classification Is Essential for the Attenuated Psychosis Syndrome

William T. Carpenter

Persons who meet the criteria for clinical high risk (CHR) will also meet criteria for other disorders including some forms of anxiety or depression disorders, borderline and schizotypal personality disorders, and other conditions with diagnostic codes. Debate regarding a new classification for CHR is not new (1–5). This commentary states the case for DSM/ICD inclusion of a diagnostic class that is viewed as a syndrome and used as a temporary placeholder diagnosis. Clinical care is appropriate at an early stage, and clinical trials focused on CHR participants are essential for evidence-based treatment. Over time, a traditional diagnostic category may be determined.

To borrow a phrase from Thomas Jefferson, I hold the following truths to be self-evident:

1. Early detection and clinical intervention are medical imperatives.
2. Symptomatic reduction with early intervention offers the best chance of remission.
3. For progressive disorders, early intervention is the best time to prevent progression.
4. For functional outcomes, early intervention is the best opportunity to maintain social and occupational roles.
5. Existing classification at early intervention does not address heterogeneity or guide therapeutics—the diagnosis of individuals will likely change in a short time frame.
6. Therapeutics are based on specific psychopathology and function in each case and include compensatory and resilience methods.
7. Current diagnoses based on ICD-9 or DSM-5 codes will turn out to be incorrect over time for many or most cases and will be an inadequate guide to therapeutics.
8. Therefore, it is better to have an explicit placeholder diagnosis to capture the early clinical period.

The scientific study of individuals who are at CHR has been a 21st-century growth industry, much of which is substantiated in this special issue of *Biological Psychiatry*. These studies use terminology such as ultra-high risk, CHR, and attenuated psychosis symptoms. Terms such as basic symptom and genetic high risk relate to rather different clinical populations. The CHR concept is represented in section 3 of the DSM-5 as attenuated psychosis syndrome (APS) (6,7). This approach identifies persons for whom clinical attention is warranted. This is early illness, not pre-illness. APS is a clinical syndrome associated with extensive heterogeneity in psychopathology and function with no unifying pathophysiology, as is the case with other clinical syndromes, such as schizophrenia, as stressed in the DSM-5 (7,8).

The risk for progressing from CHR to a psychotic disorder (usually schizophrenia spectrum) is quite substantial—within a broad range of 10% to 30% within 2 years (4). Even 10% is far higher than incident rates in the general population. The transition to full psychosis may be underestimated because the use of antipsychotic medications and other treatments during the CHR stage may prevent progression to full psychosis (9). It has also been suggested that fluctuation in psychotic experiences associated with anxiety and depression disorders may result in false positive designation of a psychotic disorder (5).

While the majority of CHR patients do not progress to full psychosis, functional impairments are observed in most cases. As with most disorders, symptoms, signs, and function in persons at CHR are on a continuum with the general population and vary across the CHR population. As with many other disorders, APS depends on distress, disability, and dysfunction to distinguish clinical cases from the non-ill population. Using APS as a placeholder diagnosis anticipates greater clarity regarding traditional disorders with observation over time. Anxiety and depressive disorders are common in the CHR population, as are schizotypal and borderline personality disorders and a range of psychotic disorders.

Individuals at CHR could simply receive a traditional diagnosis at the outset, with the diagnosis being changed as the presentation and course of psychopathology are clarified over time—so why is a unique and temporary diagnosis advantageous? First, it ensures specific clinical and research attention to facilitate the translation of concepts and research to clinical application. Second, it should be explicit that this is a time-limited diagnosis. Third, it ensures attention to the potential for secondary prevention of full psychosis and functional deterioration. There may also be an advantage in reducing stigma in cases where a psychosis diagnosis is premature.

As with other clinical syndromes, CHR calls attention to multiple aspects of psychopathology that vary across individual patients in the diagnostic class. Anxiety, depression, sleep disturbance, social disruption, paranoia, deteriorating role function, attenuated psychosis symptoms, motor abnormalities, cognition, and other psychopathology and a range of environmental risk factors require individualized clinical attention.

The weakness of using established diagnoses mirrors the advantages of a having formal CHR category such as APS. Traditional concepts of anxiety disorders and major depressive disorder, for example, are not associated with profound vulnerability for schizophrenia, and the need for secondary

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prevention will not be anticipated. The CHR state appears not to have predictive validity for nonpsychotic disorders (10).

Clinical interventions and therapeutics established for existing disorders are not necessarily valid for persons at CHR, are not based on secondary prevention, and do not have a risk/benefit profile for CHR cases. Use of off-label pharmacotherapeutics will be common, and the field needs to establish evidence-based guidelines for all relevant treatments for this stage of illness.

Perhaps most pressing is the expectation that attenuated psychotic symptoms will be associated with antipsychotic drug treatment regardless of diagnostic category. The risk/benefit profile will be adverse for many cases. Clinical trials based on an official diagnostic category that enables translation to clinical practice is the best hope for combatting the already common overuse of antipsychotic drugs in troubled young people.

The above comments lead to the following conclusions:

1. A mental disorder category is essential for advancing knowledge related to therapeutics and secondary prevention for persons at CHR.
2. The criteria need to feature attenuated psychosis symptoms.
3. Implications of clinical syndrome status must be explicit.
4. The disorder must have placeholder status.
5. The diagnostic concept must be anchored in criteria that are reliably applied in general practice.
6. Deconstructing psychopathology and function at the individual level is essential.
7. The section 3 DSM-5 APS should be placed in the main text as soon as reliability data are adequate. Reports in this special issue support the view that CHR data are sufficient to support a consensus view on defining criteria for APS as a diagnosis for the main text in DSM-5.1.

APS is defined in section 3 of the DSM-5 and can be coded as “other specified schizophrenia spectrum” and “other psychotic disorder” (298.8 [F28]) (7). This is an ineffective half measure. Experts in the CHR field should develop a consensus on the criteria and text with modifications if needed. Reliability of the APS must be documented in clinical practice outside expert centers. This should result in a proposal to the DSM-5.1 committee that APS be moved to the main text based on supporting data.

There are implications for treatment development:

1. Clinical trials will be based on agreed concept/criteria.
2. Therapeutic targets will be specified at the level of psychopathology or function.
3. Secondary prevention of psychotic disorders remains relevant.
4. Translation of results to guidelines will be facilitated.
5. Case recognition in nonexpert centers will facilitate evidence-based therapeutics.
6. Opportunity for policy and services must be maximized to support informed integrative therapeutics and reduce the burden of disease.

Here are a few final thoughts for CHR experts: you have created a broad and deep understanding of CHR. It has moved past its origins related to the schizophrenia prodromal phase. You know it is a heterogeneous clinical syndrome. Take the necessary actions to establish a basis for translation of research to clinical practice.

The development of special treatment centers that do not rely on diagnostic codes is aimed at reducing stigma by avoiding diagnostic categories and provide wonderful care—and this is terrific. But these centers will not address the worldwide needs of the millions of persons at CHR who, if they receive clinical care at all, will not have access to expert centers.

Recognize the need for enhancing therapeutic and prevention trials that translate to action in the ordinary clinical settings where most persons at CHR may eventually receive evidence-based care. And accept the DSM-5.1 challenge!

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