Whither the Attenuated Psychosis Syndrome?


1Orygen Youth Health Research Centre, Centre for Youth Mental Health, University of Melbourne, Australia; 2Department of Psychiatry, PRIME Research Clinic for the Psychosis Risk Syndrome, Yale University, New Haven, CT; 3Department of Psychiatry and Psychotherapy, University Hospital of Cologne, Germany; 4Department of Psychiatry, University of Toronto, Canada; 5University Hospital of Child and Adolescent Psychiatry, University of Bern, Switzerland; 6Division of Psychiatry Research, The Zucker Hillside Hospital, North Shore—Long Island Jewish Health System, Glen Oaks, NY; 7Center for Psychiatric Neuroscience, The Feinstein Institute for Medical Research, North Shore, Long Island Jewish Health System, Manhasset, NY; 8Hofstra North Shore-LIJ School of Medicine, Hempstead, NY; 9Department of Child & Adolescent Psychiatry, Medical University of Vienna, Vienna, Austria; 10School of Psychology, University of Birmingham; 11Department of Psychiatry, University of Basel, Basel, Switzerland; 12Department of Psychology, Yale University, New Haven, CT; 13AMC, Academic Psychiatric Centre, Department Early Psychosis, Amsterdam, the Netherlands; 14School of Psychological Sciences, University of Manchester; 15Greater Manchester West Mental Health NHS Trust, Manchester; 16Department of Psychology, King’s College London, Institute of Psychiatry, London; 17Beth Israel Deaconess Medical Center and Massachusetts Mental Health Center, Harvard Medical School, Boston, MA; 18Department of Psychiatry, Seoul National University College of Medicine, Seoul, Korea; 19Department of Neuropsychiatry, Toho University School of Medicine, Tokyo, Japan; 20University Psychiatric Clinics, Center for Gender Research and Early Detection, c/o Universitätsspital Basel, Switzerland; 21Department of Psychiatry, University of Turku; Psychiatric Clinic, Turku University Hospital, Finland; 22Department of Neuropsychiatry, University of Toyama Graduate School of Medicine and Pharmaceutical Sciences, Toyama, Japan; 23VU University and EMGO Institute, Amsterdam and Parnassia Psychiatric Institute; The Hague, the Netherlands

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After 4 years of debate, a decision has been made. The attenuated psychosis syndrome (APS) will not be a coded diagnosis in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). Formerly known as the psychosis risk syndrome, the proposed diagnosis was based on criteria developed in the mid-1990s that were informed by a comprehensive review of retrospective studies on the prodromal phase of nonaffective psychoses. These criteria aimed to identify prospectively people in the prodrome of schizophrenia and other psychotic disorders and have been variously titled “ultra high risk (UHR),” “clinical high risk (CHR),” “at risk mental state (ARMS),” and the “prodromal stage,” and included a group with attenuated (subthreshold) positive psychotic symptoms. The criteria are associated with rates of onset of psychotic disorder substantially higher than in the general population and other clinical populations. A recent meta-analysis reported the rate of onset of a psychotic disorder to be 36% after 3 years. About 73% of those developing a psychotic disorder fulfill criteria for schizophrenia spectrum psychoses. It should be noted that these data are from treated samples consisting of patients referred to specialist clinical services.

Despite the consistent finding that there is a high risk of developing a psychotic disorder associated with the APS group, there has been considerable controversy around the idea of formally codifying it into a DSM5 diagnosis. Indeed, we, the authors of this communication, all active researchers in the area, have had differences in opinion about the merits of including APS as a new diagnosis in the DSM.

One issue debated was the tension between the possibility of early intervention to prevent progression of disorder vs potential unnecessary diagnosis and treatment of what might be a self-limiting phase. The possibility of stigma and discrimination was also raised. Some speculated that a formal diagnosis would be assumed to equate to an indication for antipsychotic medication and so increase the likelihood of antipsychotic prescription. Others argued that the absence of an APS diagnosis has led to some clinicians using the term psychosis NOS (not otherwise specified), which may lead to antipsychotic prescription. The APS as an alternative to this diagnosis could then actually reduce antipsychotic prescribing. Importantly, an APS diagnosis will enable evidence-based treatments to be developed, including...
psychological therapies, and could therefore decrease antipsychotic use.13

Ultimately, the decision to exclude APS as a coded diagnosis was made not in response to any of the above issues or in the light of data addressing the principal disputes but because data on the diagnostic reliability of APS in clinical practice were limited and inconclusive.

Following this decision, some critics have been quick to denounce the whole APS/ultra high-risk/clinical high-risk/prodromal concept.13–15 We, therefore, feel it is timely, as a group involved in high-risk (prodromal) research, to document some points of consensus between us and highlight areas for future research.

Points of Consensus

Attempts to recognize the prodrome of schizophrenia prospectively have been active for nearly 20 years.2 Many samples of persons meeting high-risk criteria have been seen and evaluated. A strong consensus exists that individuals meeting APS criteria (which includes a criterion for help-seeking) are symptomatic and in need of clinical care.16–18 People meeting the criteria do in fact fulfill the broad definition of mental disorder: “a clinically significant behavioral and psychological syndrome or pattern … that is associated with present distress … or disability … or with a significantly increased risk of suffering death, pain, disability, or an important loss of freedom,”119 (p. xxi). Thus, treatment is clearly justified, regardless of the justification of reduction of risk or prevention. We agree that this treatment should include the APS as a category in its recommendation to include the APS as a category in the appendix (Section 3) of DSM-5 as a condition for further study.

Collectively, we have devoted many hours into thinking about this condition. Through our research and clinical experience with these patients, we have evolved our thinking and our conceptualization of APS. Initially, the high-risk criteria were developed, as the name suggests, to detect individuals at high risk of psychotic disorder. However, the use of the criteria should not be thought of as identifying and treating an asymptomatic group at risk of a poor outcome, analogous to detecting and treating hyperlipidemia to prevent myocardial infarction (MI). APS patients are symptomatic and distressed. Thus, angina may be a more apt analogy. However, better still is to think of the criteria as detecting chest pain. The condition is distressing, symptomatic, and leads to help seeking. It may indicate the early signs or risk for a serious but noncardiac disease such as MI, a serious but noncardiac disease, such as pneumonia or a benign self-limiting condition such as esophageal spasm or costochondritis. Likewise, APS may indicate the early signs or risk for illnesses such as nonaffective and affective psychotic disorder, presence or risk for a serious but nonpsychotic illness such as severe unipolar depression, or it may indicate something that is not serious and which may resolve, with or without treatments such as psychological support, stress reduction family interventions, and practical help.

This way of conceptualizing APS leads to many different paths for research. Suggestions for the future research agenda follow.

Expanding the Range of Outcomes to Be Studied

Investigation of different outcomes in both the short and long term including psychotic disorders, nonpsychotic disorders, persistence or remission of APS, and social and cognitive functioning is needed. Refining risk factors for these different outcomes is another avenue of research. It may be that added criteria are necessary to enrich the sample for schizophrenia, such as basic and negative symptoms and decline in cognitive and social skills.30,31 Other methods of enrichment for other outcomes can also be studied, including multiple subclinical symptoms plus depression,32 presence of personality disorder, family history of mental disorder, and childhood trauma and adversity.33

Examining recovery and remission of the high-risk state as outcomes is another area that is currently understudied. Searching for predictors of these positive outcomes can then lead to adding such factors to ascertainment criteria as exclusions, which would result in a reduced false positive rate and increased positive predictive power.

Searching for Markers of Different Trajectories

Examining associated neurobiological,34–36 cognitive,37 physiological,38 metabolic,39 and genetic40,41 associations
with the APS and its different outcomes is needed so that subgroups can be more sharply delineated. Longitudinal follow-up is needed to elucidate whether the biological markers that are observed in the APS group are indicative of a trait vulnerability to psychotic disorder or whether they are state markers. Comparison with other psychiatric groups without APS will determine whether biological findings are specific to APS and represent a continuum with psychotic disorders such as schizophrenia or whether they are associated with general psychiatric distress.

Stigma and the Effect of Symptoms and Diagnosis
Research is also needed as to what harms and benefits are associated with an APS diagnosis. This should include assessing any perceived stigma, and comparison made with the stigma, stereotypes, and wish for social distance associated with overt psychiatric symptoms that may occur prior to help seeking and diagnosis. Whether clinical care that provides information, treatment, and hope of a good outcome can minimize stigma should also be studied. The effects of creating a new diagnosis, on patients, their families, and the wider health system, needs to be better understood.

Reliability and Clinical Utility
While reliability of assessment has been demonstrated in previous studies using structured interviews, the clinical utility and reliability of assessment in routine practice needs to be assessed and improved and the impact of the proposed diagnosis on prescribing practice examined. Investigation of factors that lead APS patients to seek help will also be useful. Currently, it is unclear how much of the distress that leads to seeking help is related to the psychotic-like symptoms or to associated nonpsychotic mental disorders, such as depression and anxiety. Little is known about the prevalence of APS in adolescent and adult clinical populations and in the general community and this also needs further study.

Treatment Trials
Further intervention research is also needed. Omega-3 fatty acids have shown promise in reducing symptoms as well as decreasing the risk of transition to psychotic disorder in one study. This requires replication. Other novel treatments such as psychological treatments, vitamin D, glycine, and other neuroprotective agents are also worth testing.

Possibility of a Pluripotent Risk Syndrome
Finally, with increasing the knowledge of risk factors for different outcomes (see above), the APS model could also be extended to a more general a strategy for early intervention in a range of mental disorders. It may be that many disorders develop from initial nonspecific symptoms and syndromes, from a background of specific and nonspecific risk factors (such as genes and early environment). Worsening of symptoms and acquisition of new symptoms may occur, together with progressive neurobiological abnormalities, and related neurobehavioral deficits, until clear-cut recognizable mental disorders appear. Progression of symptoms and neurobiological abnormalities could continue after “threshold” diagnosis, with development of chronic symptoms, relapses, and ongoing functional deterioration. Transition from one stage to the next is not inevitable, either due to different risk and resilience factors or due to nonspecific or specific intervention. Thus, preventive possibilities exist across this spectrum of evolving illness.

This concept of a pluripotent risk syndrome opens up a range of research possibilities. Studying genetic and environmental risk factors and gene and environment interactions for different outcomes, further work on resilience and protective factors, and examination of different trajectories are all future avenues of research. Whether any specific markers for particular course and outcome can be detected early is another area and leads to the possibility of early specific treatments. Novel methods such as multimodal imaging and neurocognitive analysis, single subject methods to predict individual disease course are also possible.

Conclusion
APS concept remains a useful one. It identifies people with significant mental health problems that justify treatment in their own right, as well as having a higher likelihood of developing a psychotic disorder (mostly schizophrenia) within a few years. Research into this group will increase our understanding of psychotic-like symptoms and their trajectories and the emerging phase of psychotic disorders. The APS concept is consistent with the continuum view of psychosis and is probably a reflection of biologic reality. Outcomes other than psychotic disorder are also clearly worthy of study. The placement of APS in the DSM-5 appendix should be a clarion call to the field to focus attention on these patients and families in need.

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