VIEWPOINT

Attenuated Psychosis Syndrome or Pharmacologically Attenuated First-Episode Psychosis?
An Undesirably Widespread Confounder

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Preempting the risk of transition of a subclinical liability into a full-blown disorder is a central tenet of preventive medicine. In psychiatry, although incipient psychosis may be difficult to detect, this strategic goal has inspired and given momentum to the breadth of prodromal/ultrahigh risk (UHR) research and its clinical translations. Such a research stream has in turn tangibly contributed to an overarching, prevention-oriented re-envisioning of the field of clinical psychiatry.[1] Indeed, with the ultimate aim of reducing chronicity and attenuating the burden of its consequences, the timely identification of individuals at high risk of developing psychosis has become a catalyst for developmentally oriented understanding of illness trajectories, personalized risk prediction, and service innovation.[2] In this perspective, the meta-analysis by Salazar de Pablo and colleagues[3] provides an important, timely overview of the validity of *DSM-5* attenuated psychosis syndrome (APS) as well as an interesting photograph of some major blind spots in the field.

DSM-5–APS and the Meta-analytical Radiography of Its Clinical Validity

The findings by Salazar de Pablo and colleagues,[3] which are based on a cumulative sample of 2376 individuals pooled from 23 prospective cohort studies, are in line with a 2016 meta-analysis on individuals at UHR[4] and reveal a similar risk of transition to psychosis over a follow-up period of 6 to 36 months (ie, 11% vs 10% at 6 months, 15% vs 16% at 12 months, 20% vs 19% at 24 months, and 23% vs 21% at 36 months for *DSM-5*–APS[3] compared with its specific UHR homologue [ie, APS subgroup[4]]). Tested against evidence-based antecedent, concurrent, and prognostic validators, *DSM-5*–APS reveals convincing concurrent and prognostic validation, substantially echoing previous UHR psychometric research in the field.

However, in these meta-analyses,[3,4] most included studies overlooked the potential confounding role of ongoing antipsychotic treatment at baseline in mitigating the clinical presentation and modulating the later outcome trajectory.[5] Persons diagnosed with APS while being already treated with antipsychotic medication may not reach at follow-up the formal psychometric threshold for psychosis because of the ongoing antipsychotic treatment and—at baseline—might surreptitiously be equated to antipsychotic medication–naive APS while they are actually to be regarded as having antipsychotic medication–attenuated equivalents of first-episode psychosis.

The magnitude of this systematically overlooked confounder reverberates on current prognostic estimates and reduces the precision of contemporary prediction models. Therefore, estimating the proportion of patients with APS already taking antipsychotic therapy (ie, attenuated equivalents of first-episode psychosis) among all patients with APS is an essential step forward.

A Deeper Meta-analytical Look

Pending on the source of the study cohorts included in the meta-analysis by Salazar de Pablo and colleagues[3] (see the Baseline Treatments section in eTable 6 in the Supplement), 5.5% to 57.1% of enrolled individuals with APS were already prescribed antipsychotic medication at baseline inclusion. On the basis of the raw data of the subgroup of studies (n = 12) that actually reported antipsychotic medication exposure, the meta-analytic prevalence of patients with APS already taking antipsychotic treatment at baseline is substantial: of 1438 patients with APS, the pooled prevalence of patients taking antipsychotic therapy at baseline was 20.6% (95% CI, 18.5-22.8) in the fixed-effects model and 23.6% (95% CI, 16.4-31.6) in the random-effects model.

These data suggest that at least 1 of 4 or 1 of 5 patients enrolled as having APS are actually already taking antipsychotic medication at the baseline inclusion, with intuitive cascading confounding the effect on the correctness of prospective risk estimation. Indeed, the patients with APS already taking antipsychotic treatment are unlikely to have the same risk trajectory of antipsychotic medication–naive patients with APS for the mere reason that their presentation is presumably already pharmacologically attenuated. In this respect, the original UHR model, in addition to the criterial transition to psychosis based on psychometric scores on positive symptoms, explicitly mentions a functional equivalent of transition, that is, the threshold at which antipsychotic treatment would probably be commenced in common clinical practice.[6] Far from being clinically arbitrary, such a threshold is based on the identification of a mental state in urgent need of antipsychotic medication by collegial decision of the treating staff and obviously offers a nonnegligible index of clinical severity, signaling "the threshold for onset of a psychotic episode."[6] Indeed, on a convergent line, the start of the first antipsychotic treatment is typically considered the end point of the duration of untreated psychosis (also known as *duration of untreated psychosis*).[7]

Clearly, taking seriously the notion of antipsychotic treatment in patients with APS as a functional equivalent of transition is a critical step to improve the precision of current risk modeling and a very much-needed correction to the overall transition rates

reported in the literature. Thanks to the systematic work of Salazar de Pablo and colleagues,[3] it is now evident not only that transition outcomes are underestimated (since basically most of the studies merely report criterial, ie, psychometric, transitions and neglect the functional ones[5]) but also that baseline rates of APS are overinflated due to inclusion of patients with APS taking antipsychotic treatment.

Learning From Mistakes and Amending Unintended Consequences

On the basis of the comprehensive summary of the field emerging from recent meta-analyses,[4,5] some general considerations are mandatory to optimize the translational implications of current UHR research and further corroborate the clinical validity of *DSM-5*–APS.

First, by neglecting the original UHR notion of functional equivalent of transition to psychosis,[6] it looks like a nontrivial fraction of help-seekers with a clinical equivalent of first-episode psychosis (ie, mental state severe enough to require antipsychotic medication) are overinclusively labeled as having APS.

Second, mainstream prediction models (and meta-analyses) that include both antipsychotic medication–naive patients with APS (ie, those truly with APS) and antipsychotic medication–treated patients with APS (ie, those with pharmacologically attenuated first-episode psychosis) together under the same APS category plausibly underrate natural course transition rates, because transition risks are expected to be different for antipsychotic medication–naive patients and antipsychotic medication–exposed patients with APS. This widespread clinical and conceptual flaw could also affect the rate of benign outcomes other than psychosis and might contribute to the surface-level phenomenon of dilution effect of criterial transition rate (ie, a progressive decline of transition rates to psychosis, especially evident in recent cohorts compared with earlier samples).[6]

Third, a reanalysis of antipsychotic medication exposure in available data sets is imperative, and a new wave of UHR studies with transparent and systematic ways of reporting antipsychotic medication exposure at baseline and follow-up is mandatory in the field.

Finally, although antipsychotic medications are used in community practice in a variety of ways[8] (sometimes to the detriment of interventions with lower adverse effect burdens[9]), it is worth reiterating that available treatment guidelines for individuals at risk of psychosis[10] do not consider their prescription appropriate unless the symptoms are severe and progressive and not adequately mitigated by other first-line interventions.

Conclusive Remarks and Pragmatic Recommendations for the Advancement of the Field

Therefore, to increase transparency and make a necessary step forward toward precision psychiatry in the field of early detection, the following issues need adequate appraisal:

A. With respect to the *DSM-5*–APS definition, ongoing antipsychotic medication exposure at baseline should be a motivated exclusion criterion for the diagnosis.
B. In line with the original UHR concept, antipsychotic medication exposure at follow-up should be regarded as a functional equivalent of conversion to psychosis even when positive symptoms remain below the psychometric severity threshold.
C. A more detailed reporting about antipsychotic treatment at baseline and follow-up is mandatory.

ARTICLE INFORMATION

Published Online: July 8, 2020. doi:10.1001/jamapsychiatry.2020.1634

Conflict of Interest Disclosures: None reported.

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