Rethinking the Psychosis Threshold in Clinical High Risk

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Two decades of research in the context of clinical high risk (CHR) for psychosis has addressed a time-honored value in medicine: early detection and intervention to reduce severity and persistence of illness. Despite validation of the concept including substantial transition rates to full psychosis, CHR has been criticized. Perceived problems include concerns with pathologizing normative behavior, introducing stigma and therapeutics with high risk/benefit profiles by associating CHR with schizophrenia, and the false assignment to psychosis risk of persons whose attenuated psychosis symptoms are presumed to reflect disorders, such as anxiety and depression. These issues have drawn increased attention as reported rates of transition to full psychosis have dropped from about a third of cases in early studies to less than 10% in some more recent reports. In the following text, we address 2 issues in support of the view that secondary prevention of psychosis is feasible and that CHR patients merit clinical care for nonpsychotic psychopathology and impaired functioning.

The Threshold Problem: Natural Course Transitions and Psychometric Conversion to Psychosis

Almost a quarter of a century since the first prototypical conceptualization of the ultra-high risk (UHR) state for psychosis, while the original UHR concept seems to progressively move toward a more extensive revision in an attempt to capture a broader, subsyndromic transdiagnostic risk of severe psychopathology (CHARMS), the essence of the UHR/CHR framework remains its capacity to prospectively identify individuals at increased risk of “transition” to psychosis, mostly defined in terms of “above-threshold” positive psychotic phenomena, such as delusions and hallucinations.

Although the clinical relevance of such “transition” in terms of predicting more long-term functional and bio-psycho-social outcomes is not necessarily superior to the multidimensional impairment in other symptom domains (eg, negative, cognitive, and affective), its empirical value—at least in terms of concept-proofing—the can be hardly disputed. Indeed, advances in the psychopathological characterization and treatment of CHR are presumably greater (and more nuanced) than what is currently revealed by the crude measure of transition to psychosis. Nonetheless, transition rates in treated CHR samples are expected to substantially underestimate the natural course transition rates and obscure the value of treatment as usual in the CHR therapeutic paradigm.

Much of the literature describes the clinical course of persons with CHR. These cases are usually receiving treatment in an expert center or in clinical circumstances familiar with the CHR paradigm. It is likely that clinical care is organized in relation to issues associated with the CHR state, interventions that may be effective at delaying or preventing full transition to psychotic illness. Treatment as usual (TAU) delivered in these contexts is likely to benefit from a more intensive case management leading to lower drop-out rates and improved treatment adherence than in naturalistic, nonresearch-oriented settings or in persons at CHR who are not in clinical care.

A second issue relates to transition rates as currently measured via predefined psychometric cutoffs on psychotic experience items derived from rating scales (eg, CAARMS and SIPS). With this methodology, persons being treated with anti-psychotic medication (AP) may not reach a transition definition because of the AP therapeutics. This is a crucial aspect since AP need is rather frequent in the clinical management of CHR individuals. A tangible example of the impact of this issue emerges from a recent meta-analysis: 7 of the 33 studies included in UHR subjects who were on AP at the baseline
assessment, and more than two-thirds (24 out of 33) report exposure to AP during follow-up. Patterns of AP treatment are varied and do not necessarily indicate psychotic psychopathology. But manifesting attenuated psychotic-like symptoms and/or a worsening of these symptoms may be the basis for AP treatment. In these cases, AP drugs may prevent meeting criteria for transition. Cases on AP mediation at baseline may have already met criteria for psychosis but this is not reflected if currently meeting CHR criteria but not full psychosis. An unknown proportion of the AP prescriptions after the identification of a CHR state is likely to reflect a worsening of the clinical symptoms related to transition to full psychosis as perceived by the treating staff. Notably, the threshold at which AP treatment is commenced in common clinical practice was explicitly considered a functional equivalent of transition to psychosis in the original UHR model. Clinical judgment in this regard reflects a global appreciation of the severity and change in clinical status not necessarily limited to the level of positive symptoms. Psychometric assessments are more specific and uniform across cases, but clinical assessment is far broader in considering changes in psychopathology including social and role functioning. Overall, this clearly indicates that transition rates in treated CHR based on a focused psychometric threshold may substantially underestimate transition rates and thus underestimate potential value for secondary prevention of the CHR paradigm. Adding criteria for transition that includes the onset or dose increase in AP medication may enhance the transition assessment and relate to common clinical practice.

This may offer a more realistic estimate of transition rates in the context of clinical treatment.

The Target Problem: Expanding the Therapeutic Concept

In the above text, we argue that CHR studies to date are underestimating transition rates to full psychosis. There is no data on rates in untreated CHR cohorts and psychometric definitions, while valid, may systematically underestimate transition rates in treated cohorts with failure to utilize a broad clinical perspective. Clinically important (and often prognostically decisive) features of individuals presenting a CHR mental state reside outside the positive symptoms dimension and need full consideration to prevent or mitigate the risk of developing more severe psychopathology. Therefore, a broader range of function and symptom assessment is required to better trace relevant clinical outcomes beyond the psychometric “transition to psychosis” and track treatment benefits. Persons who merit clinical care within the CHR paradigm have multiple psychopathology issues apart from attenuated psychotic symptoms. Issues such as anxiety, depression, negative symptoms, increasing stress sensitivity, and deteriorating social and role function are increasingly being recognized as critical aspects for clinical attention. There are multiple targets for a wider spectrum of interventions. Yes, for secondary prevention of psychosis, but also to address the full range of psychopathology and functional consequences.

Conclusion

CHR criteria and the related conceptual toolbox have been a key factor for the implementation of those early intervention services that have radically transformed the way treatment is delivered to help-seekers at putative risk of developing psychotic disorders. However, the main outcome on which the CHR paradigm has been presented, transition to psychosis, is too narrow. Transition rate from CHR to full psychosis in untreated cohorts is not known. The low rate in treated cohorts is not trivial but is partly based on the psychometric assessment that does not include full clinical assessment or cases where treatment prevented progression. Limiting the focus to the positive psychosis dimension has failed to give emphasis to the multiple aspects of psychopathology and functional consequences associated with the CHR state. Clinical therapeutics have many targets, and secondary prevention is not limited to psychosis. On the contrary, a central strategic focus for secondary prevention based on the CHR paradigm should be the treatment of those symptom domains that substantially contribute to the risk of severe psychopathology in domains relevant for each individual, to prevent deterioration of functions and to reduce the progression to chronicity.

References