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Psychosis Risk: What Is It and How Should We Talk About It?

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Abstract

Schizophrenia and other psychosis spectrum disorders do not develop *de novo* but emerge from prodromal stages that are named and operationalized differently depending on the research group or consortium and its theoretical orientation. As a result, a complex lexicon now exists for characterizing individuals' risk of subclinical symptoms converting to psychosis. Researchers aim to develop instruments and methods to identify people at risk of psychosis, better understand their risks, and offer preventative treatments to arrest conversion to psychosis; ethical and policy questions loom large with each of these projects. In this paper, we canvass the lexical complexities of the at-risk status for psychosis and then consider ethical and policy challenges that researchers and clinicians face in disclosing, preventing, and treating psychosis risk.

The Costs of Psychosis

Schizophrenia and schizoaffective disorder, among other psychotic disorders, can be devastating illnesses and pose serious public health challenges. Typically developing in young people between the ages of 18 and 25, schizophrenia affects about 1 percent of the population. Of patients with schizophrenia, 5 to 6 percent die from suicide, with the majority of deaths occurring in patients between the ages of 18 to 34 [1]. There are also significant financial costs of treating and supporting patients with schizophrenia—estimated to be over $60 billion annually in the US—including costs associated with comorbid substance use disorders found in half the affected population, a proportion that is well above that of the general population [2-5]. Efforts to reduce these human and financial costs focus on early detection and intervention.

The idea that psychotic illness does not emerge *de novo* from an otherwise healthy brain—and therefore that prevention might be possible—is long-standing [6, 7]. Kraepelin and Bleuler recognized premorbid cognitive impairment and "characteristic peculiarities in the manner of their being" of persons with schizophrenia [3]. The promise of early detection and prevention originates from clinical observations and retrospective studies of attenuated psychotic symptoms in patients who later developed psychotic illnesses [8, 9]. Retrospective and prospective investigations into the clinical,

physiological, and genetic factors leading to psychosis reveal a high-risk prodromal stage [10-12].

Psychosis Risk: A Complex Lexicon

Yung et al. identified three prodromal syndromes typically associated with psychotic illness: brief frank psychosis, attenuated psychotic symptoms, and functional decline with genetic risk [13, 14]. Researchers now describe the state referred to by these alternate terms as "high risk," "clinical high risk," "ultra-high risk," or "at-risk mental state (ARMS)." Some have advocated for a "psychosis risk syndrome" or "attenuated psychosis syndrome (APS)" as the diagnostic penumbra under which high-risk patients should be classified for research purposes [15]. Although APS was nearly codified within the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-5*) [16], it was instead included in the appendix devoted to conditions for further study, due in large part to concerns about the limitations of current evidence and the broader implications of labeling persons in a putative prodromal phase [17], which we discuss. Others have advocated making "psychosis spectrum disorder" part of *DSM-5*'s research criteria [18]. The term "psychosis spectrum," which we prefer, is a broader construct that does not require recent symptom onset or significant impairment and includes negative symptoms not necessarily captured in other constructs [19].

This conceptual and lexical complexity is a result of decades of independent research consortia working across three regions (Oceana, Europe, and North America) [20]. We believe that prevention will ultimately require clarifying and harmonizing the many theories, definitions, and assays used to detect emerging psychotic symptoms, recognizing that psychiatric categories are fluid and spectral, not static and discrete.

Detecting Psychosis Risk

There are at least 22 instruments used to detect psychosis risk that can be grouped into three categories [21]. The first category aims to assess attenuated psychotic symptoms and highlight clear precursors of psychosis. The second category tracks basic symptoms (i.e., subtle, subjective deficits) and first phases of subjective alterations in experiences that occur early in the development of psychosis. The third category aims to incorporate features of both attenuated symptoms and early subjective experiences; the comprehensive assessment of at-risk mental states (CAARMS) is one such instrument. Instruments also vary in how they measure and categorize genetic risk and how they categorize positive symptoms (such as visual or auditory hallucinations, disorganized speech, and delusions), timing of onset, persistence of symptoms, and self-report of disturbances [22].

Each instrument is constructed upon different concepts of the psychosis spectrum and employed in major research centers and research networks worldwide [23]. Because they aim to measure different things in different ways, these instruments' results

inevitably will vary. This variation might influence how conversion risk is ultimately understood by and described to research participants and patients [24]. There are obvious advantages to researchers and clinicians in having access to a diverse portfolio of screening tools. Comprehensive data sets can be compiled that reveal composite risk factors for an individual. And subtleties can be drawn from analysis of comprehensive data sets that would otherwise be missed by instruments within a single category.

Talking About "It"—Whatever "It" Is

The diversity of assessment methods contributes to conceptual and lexical complexity, with clinical implications for individuals and their families. For example, any attenuated symptoms detected by an instrument designed largely to detect such symptoms might be interpreted as an inevitable cascade of events leading to the full illness, triggering a physician's premature prescription or administration of medication.

Conversely, when instruments are used to detect subtle symptoms, researchers might be wary of disclosing results because of low conversion rates. We see this now: across the many research and clinical centers where psychosis risk research is happening, there is no stated consensus on how best to disclose and discuss the findings of screening instruments [25].

Disclosure methods are ethically important. In one study, healthy research participants anticipated the negative impact of hypothetical psychosis risk to be similar to the hypothetical risk of cancer [26]. A level of distress related to psychosis risk is unavoidable. However, poorly designed or overly pessimistic communication strategies could cause patients and families additional unnecessary distress, anxiety, stigmatization, and feelings of helplessness. These iatrogenic stressors might, in turn, exacerbate the impact of psychotic symptoms. In contrast, overly hopeful messaging could leave patients with the incorrect impression that they are at little-to-no risk of conversion to a psychotic disorder. Given the uncertainty and risks related to psychotic spectrum diagnoses, ethicists have proposed a hybrid disclosure model that balances full and partial disclosure, with caveats [25]. Deciding on the appropriate amount of information to present and how to present that information suitably remains a matter of an individual physician's judgment and experience, as randomized controlled trials on physicians' communication strategies have yet to be conducted [27].

Questions related to autonomy and free will also emerge: if early detection of attenuated psychosis becomes a *bona fide* diagnosis, what expectations should we hold for people with this diagnosis [28]? Early diagnosis also has implications for both public and self-stigma [29], discussed in more detail below.

Implications of the Psychosis Spectrum for Stigma

The debate surrounding the inclusion of attenuated psychosis syndrome in *DSM-5* highlights the need for research into the ways risk assessments can cause or contribute

to stigma [16, 27]. One concern about communicating psychosis risk is that it could lead to stigma and adversely affect children and adolescents for their entire lives, whether they eventually develop schizophrenia or not [30]. But it is unclear whether stigma experiences created by risk-based labels are comparable to those of their corresponding illnesses. In other words, do persons who are at risk for psychosis experience the same kinds of social distancing, marginalization, and discrimination as those with schizophrenia? This is an unanswered empirical question that could be used to stimulate subsequent research.

Intuitively, it seems important to appreciate differences between persons' experience of stigma for risk-based diagnoses and their experience of stigma for a schizophrenia diagnosis. In the former case, public stigma might be less of a concern, because these people typically have yet to exhibit dramatic symptoms that would increase public discomfort. On the other hand, people assigned a risk-based label might have heightened insight into their health risks and experience self-stigma. A recent study by Yang and colleagues seems to bear this out [31]. They demonstrated that the clinical high-risk label is a significant source of stigma. And, as this study suggests, some features of "symptom-based stigma"—for example, heightened shame and discrimination—appear to be more distressing than the stigma experienced by being labeled with a mental illness.

Stigma and its effects can reverberate through the at-risk person's social network. The impact on families is multifaceted. Parents and siblings will need to become well educated about the distinction between at-risk versus disease states. Parents should be careful not to treat their at-risk child as having a psychotic disorder. One worry is that parental confusion or anxiety could exacerbate sub-psychosis symptoms and lead to greater social distancing, diminishing their child's quality of life overall. Although parents might want to rethink priorities, expectations, and adjust their child's plans (e.g., encouraging their child to attend college nearby instead of across the country), they will also likely be challenged to balance protective measures against opportunities for their child's personal growth [32]. Deciding on a reasonable balance will be an individual clinical or family decision and will be complicated by public misunderstandings and stigma. These dynamics require additional research, although clinicians should stand ready to assist families with these challenging choices.

Public Health and Policy Ramifications of Psychosis Spectrum Disorders

Primary prevention of psychosis spectrum disorders based on a theory of gene-environment interplay will have several aims [33]. For example, to decrease the incidence of psychosis, public health interventions aimed at reducing adverse childhood experiences, exposure to environmental toxins, and improvement of prenatal health could be deployed. Tertiary prevention aims to cure or alleviate the severity of schizophrenia; efforts toward this end have been long underway.

Strategies have also been proposed to detect, reduce, or arrest emerging symptoms at the secondary level of prevention, in which schizophrenia is viewed as a neurodevelopmental disorder [6, 25]. For example, by providing educational resources and psychometric instruments to primary care providers, broader public health strategies will aim to enhance overall wellness. The ethical controversies at this level are manifold, resulting in part from the fact that, at present, prediction batteries have considerable false positive rates. A further complication stems from evidence that the at-risk or psychosis spectrum state can itself be associated with functional impairment, comorbid psychopathology, and distress, suggesting that it can be an appropriate intervention target, regardless of eventual conversion to a psychotic disorder [34].

A first important ethical question considers risks and benefits associated with initiating an active intervention—such as psychoeducation, cognitive behavioral therapy, or stress management strategies—or a "wait-and-watch" approach for an individual patient [35]. A second question is whether a patient with elevated risk of conversion to psychosis should be treated with antipsychotic medications. Given the risks of antipsychotic drugs—such as weight gain, diabetes, and adverse cognitive effects on the developing brain—research will be necessary to gain certainty about the probability of conversion to schizophrenia in order to justify the preventative use of such medications [36]. As antipsychotic medications are marketed and used more and more for off-label purposes, clinicians might become increasingly willing to consider prophylactic use of antipsychotics in at-risk patients [37].

Monitoring patients with psychosis spectrum symptoms might be accomplished by any number of methods. Self- and family-monitoring and regular check-ins with primary care clinicians or psychiatrists should be recommended and encouraged. New automated hovering devices and mobile device applications offer means for self-monitoring, medication compliance, and interaction with clinicians without face-to-face meetings [38]. Ethical issues pertaining to patient privacy and concerns about coercion can arise with these technologies, however. Of course, in this population—a group in which some individuals might have a heightened predisposition to paranoid ideation and sensitivity to surveillance—automated hovering and tracking methods should be used with particular care to ensure they do not trigger or exacerbate symptoms.

Conclusion

At-risk states along the psychosis spectrum are not clearly definable disease entities like a microbe or genetic lesion that causes illness. On the contrary, they exist only insofar as the precision of our diagnostic technology and our prognostic confidence increases. Therefore, at-risk states should be understood as pragmatic constructs that will necessarily be refined and reconceived as new evidence is revealed.

In ways similar to the *DSM-5* revision process, it will be important for researchers, clinicians, and other stakeholders—including mental health patients and their advocates—to routinely revisit, refine, and revalidate points along the psychosis spectrum. Inclusive and democratic deliberative processes should be used to ensure that categories reflect both scientific evidence and shared values and priorities of mental health clinicians and patients [39]. These processes could include public meetings and web-based educational materials, conferencing, and open commenting periods. The National Institute of Mental Health (NIMH), for example, seems like the appropriate public institution to lead and facilitate such an important endeavor.

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