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# Bending the curve on psychosis outcomes

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Priorities for the development of treatments for psychosis have gradually shifted to early interventions that are designed to soften or even prevent the debilitating course of illness. To "bend the curve"—ie, change the conditions such that individual outcomes improve and societal effects of psychotic disorders are reduced,[1] we must advance our understanding of the neurobiological substrates of their most disabling symptoms, and use this information to guide mechanistic, hypothesis-driven treatment studies.

Although functional outcomes in psychotic disorders are closely linked to the severity of negative symptoms and cognitive impairment,[2] few, if any, pharmacological treatments exist for these disabling symptoms. The need for novel therapeutics that improve function in patients with psychosis is evident in the rates at which these patients are homeless, incarcerated, or reside in long-term residential care facilities. In *The Lancet Psychiatry*, Joshua Kantrowitz and colleagues[3] convincingly show that a rationally selected modulator of the N-methyl-D-aspartate-type glutamate receptor (NMDAR) might substantially reduce negative symptoms in young people at clinical high risk of developing psychosis. The investigators reported that 9 (90%) of 10 individuals treated with D-serine had a reduction in negative symptoms; and across groups, symptom reduction was significantly correlated with a blood-based infl ammatory biomarker (IL-6). These findings support the possibility that early intervention might result in improved outcomes for those at clinical high risk of schizophrenia.

Lessons learned from this important study can inform future large-scale clinical trials. First, studies of this nature are logistically and interpretively complex. This study was done in four world-class academic centres during a 3-year period; in such a design, rigorous standardisation and careful coordination of procedures is needed. A substantial amount of the overall research effort is inevitably dedicated to the outreach necessary to identify, recruit, and retain participants at clinical high risk of schizophrenia in such studies. Even with the laudable efforts of expert study teams at leading academic specialty centers, however, only 21 participants actually completed the trial (ten from the D-serine group, and 11 from the placebo group). This modest sample size underlines the tremendous struggle of

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finding individuals at clinical high risk of schizophrenia who will consistently engage with mental health treatment studies.

Second, despite difficulties in school, the presence of unusual thoughts or perceptions, and social isolation, 75% or more of the so-called basement kids, playing video games alone most of the week and losing interest in the world above ground,[1] will not go on to develop psychosis within 3 years.[4] Thus, altering the progression of a biologically complex disease process in a cohort of transitional age youth, most of whom will ultimately not develop the disease itself or consistently engage in treatment, represents a formidable challenge. Participant attrition in the present study must surely have been exacerbated by the rigorous blood and urine monitoring required by the regulatory oversight of an investigational intervention. This intensive monitoring and its effect on attrition, added to the complexities of risk recruitment and conversion, creates a particularly daunting challenge to future studies of investigational drugs in this population.

Studies of early interventions in clinical high-risk cohorts are also difficult because treatment response varies substantially and is confounded with other factors (eg, genes, neurodevelopment, circuit dysfunction, environmental factors, family dynamics, and external supports). Kantrowitz and colleagues[3] were confronted with a third issue, one that has plagued psychiatric treatment development: a high rate of placebo response. Although, 9 of 10 D-serine participants showed a more than 20% reduction in negative symptoms, so did five of the 11 placebo participants who completed the trial. We have learned from decades of antipsychotic treatment studies that higher rates of placebo response are associated with studies that contain small numbers of participants, younger ages, and shorter durations of illness[5]—unavoidable participant characteristics in clinical high-risk and early illness studies.

Perhaps some of the obstacles to clinical high-risk intervention development could be overcome with even larger-scale multicentre trials. But with the trifecta of challenging participant recruitment, low psychosis conversion, and high placebo response rates, it is reasonable to look to improve the yield of therapeutic development for psychosis. We mention two possibilities here: biomarkers and studies in more readily available participants.

Clinical high-risk samples might be enriched through the use of biomarkers that predict either the likelihood of conversion to chronic psychosis, or the response to preventative or therapeutic interventions.[6] Biomarkers offer the hope that, despite the heterogeneity and multivariate interactions in the pathogenesis of brain disorders, objective measures will identify clusters of individuals that can then be reliably stratified in terms of the cause, course, or treatment sensitivity of a psychotic disorder.[6] For example, mismatch negativity is a robust, reliable,[7] translatable, and mechanistically relevant[8] neurophysiological biomarker that has already been extensively validated for use in large-scale multisite psychosis studies.[9] Mismatch negativity also seems to substantially improve the prediction of which clinical high-risk individuals are most likely to develop psychosis.[10] Biomarkers derived from electroencephalography,[8] blood (eg, IL-6[3,11]), cognitive, or behavioural assessments might allow us to direct our resources to the patients at clinical high risk with the greatest vulnerability to psychosis. Ultimately, objective, laboratory-based biomarkers might be able

to guide individuals towards viable therapies and away from treatments that are not likely to be successful.[6]

Biomarker-guided treatment stratification algorithms are also needed for patients with established illness. Compared with clinical high-risk populations, individuals with established psychotic disorders are much more readily available to participate in treatment studies; as a result, we have identified medications, social skills, and cognitive training interventions with varying degrees of efficacy in these patients.[12,13] In fact, studies of therapeutics for patients with chronic illness might both address the need for improved therapeutics for those already with these disorders, and provide an opportunity to elaborate crucial brain biomarker–treatment associations that can bend the curve on the individual outcomes and societal effect of psychosis.

In summary, Kantrowitz and colleagues[3] show that early intervention in the disabling symptoms of psychotic illness is possible, though not necessarily easy. Further studies targeting persistent negative symptoms and cognitive dysfunction are warranted not only in the prodrome but also in patients with established illness. Ideally, increased use of both neurophysiological and biochemical biomarkers might help either larger-scale or higher-yield clinical trials for transformative therapeutics for psychosis.

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