See article by Torrey et al

NIMH Supports Evidence-Based Treatments for Schizophrenia: A Response to Torrey et al

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I appreciate the concerns raised by Torrey and colleagues about the decrease in the number of medication trials for schizophrenia as outlined in their commentary "NIMH Drug Trials for Schizophrenia."[1] Serious mental illnesses, including schizophrenia and other psychotic disorders, affect millions of people in the United States each year.[2] As the lead federal agency for mental health research, the mission of the National Institute of Mental Health (NIMH) is to transform the understanding and treatment of mental illnesses through basic and clinical research, paving the way for prevention, recovery, and cure. Addressing the needs of those affected by serious mental illness is inherent to this mission. NIMH remains devoted to supporting novel approaches to reduce the tremendous burden shouldered by individuals and families living with serious mental illnesses, and the vast impact this burden has on our society.

Accordingly, the NIMH continues to actively support drug discovery efforts in schizophrenia across the development pipeline, including first-in-human and early efficacy trials.[3] The NIMH Drug Discovery and Clinical Therapeutics Program funds research to design and develop novel therapeutic agents for the treatment of mental illnesses. For example, NIMH-supported researchers are examining the potential for 3 novel muscarinic receptor positive allosteric modulators to improve cognition in people with schizophrenia. Two of these compounds are at the stage of safety and tolerability testing in humans.[4,5] To further stimulate innovative research on potential therapeutic compounds, the NIMH Psychoactive Drug Screening Program provides researchers with broad screening capabilities in the form of pharmacologic and functional assays. Through these and other lines of research, NIMH strives to improve neurocognitive dysfunction, a hallmark of schizophrenia and a significant contributor to disability associated with schizophrenia. This research is critically important because currently approved medications do not target this core symptom of schizophrenia.

Torrey et al correctly note that NIMH now insists that NIMH-funded clinical trials include target identification and validation components. This is a direct outgrowth of the experience of the clinical trials industry as a whole—both public and private—over the past several decades, during which many promising compounds failed to prove effective in clinical testing after years of preliminary research. In consultation with numerous experts in the extramural and pharmaceutical industry communities, NIMH recognized the need to ensure that trials with negative outcomes were as informative as those with positive ones. Requiring investigators to show that their intervention affected the intended target ensures that tests of novel drugs don't just examine the efficacy of a particular chemical compound (at a particular dose, frequency, etc), they also test the relevance of the underlying mechanism, ensuring that, regardless of the result, the trial contributes to our knowledge base and moves science forward. Notably, however, we do not require that targets be genes or circuits; any target that informs a mechanistic understanding is an acceptable target.

We call this focus on mechanistic targets the "experimental therapeutics" approach. Within the context of the experimental therapeutics approach, we welcome applications testing novel drugs for efficacy in schizophrenia, particularly ones that follow on novel insights such as those linking schizophrenia to neuroimmune dysfunction as discussed by Torrey et al. We will insist that these studies be rigorously designed, and this rigor includes the need to confirm engagement of the appropriate target. Ironically, drugs that alter immune function, neurohormones, or the microbiome, as suggested in the commentary, would all be ideally suited to the experimental therapeutics approach, since targets are readily identifiable and measurable. Thus, we remain staunchly committed to the experimental therapeutics approach.

NIMH also remains firmly devoted to the crucial research we support that uses methods other than medication to improve the lives of those suffering from schizophrenia and other serious mental illnesses. Thanks to such research, thousands of patients suffering from psychosis are now getting evidence-based care at over 250 clinics across the country.[6,7] All of these clinics are dedicated to coordinated specialty care for first episode psychosis; none of these clinics existed 5 years ago. To build on these successes, the NIMH supports the Advanced Laboratories for Accelerating the Reach and Impact of Treatments for Youth and Adults with Mental Illness (ALACRITY) Research Centers, which aim to improve the effectiveness, delivery, and

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quality of evidence-based services in diverse settings for individuals with serious mental illness, including psychotic disorders.[8–10] In addition, the NIMH supports research to help patients function better through efforts that improve medication adherence, medication monitoring, and the use of technologies to enhance interventions.[11–15]

These crucial research topics are direct responses to the recommendations of NIMH partners such as the Interdepartmental Serious Mental Illness Coordinating Committee (ISMICC), the National Alliance on Mental Illness, and numerous other partners who work with us to achieve our common mission. These partners have helped us forge a collaborative approach to solving the problems faced by those suffering from mental illnesses. Collectively, we share a deep commitment to improving the lives of those affected by schizophrenia and other psychotic disorders. I encourage others in the mental health advocacy and policy community to join us as we work together to speed toward achieving our common mission.

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