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Time for New Schizophrenia Rx

LAST MONTH, THE BATTLE AGAINST FOUR MAJOR DISEASES RECEIVED SOME GOOD NEWS. THE U.S. National Institutes of Health (NIH) and 10 of the world's largest pharmaceutical companies decided that instead of working ineffectively in silos, they would work together to discover therapies for Alzheimer's disease, type 2 diabetes, rheumatoid arthritis, and lupus. This initiative—the Accelerating Medicines Partnership (AMP)—recognizes that progress toward new therapies for common chronic diseases increasingly requires large-scale collaborative efforts that range from the need to grapple with heterogeneous polygenic disease phenotypes to the validation of biomarkers in large populations. What is disappointing is that, at least for the time being, the consortium dropped schizophrenia from its list, despite vast unmet medical need and substantial, albeit still recent, scientific advances. Was schizophrenia deemed too risky to pursue? If innovative partnerships such as the AMP are not willing to take on common and serious but otherwise neglected disorders such as schizophrenia, then the scientific community will have to find new ways of pooling intellectual and financial resources to address them.

Schizophrenia is a severe and disabling brain disorder that also creates enormous costs and challenges for caregivers and for society. Antipsychotic drugs that partially treat hallucinations and delusions were discovered in the early 1950s but have serious side effects and leave entirely untreated schizophrenia's characteristic cognitive impairments and "negative" symptoms such as blunting of emotion, loss of motivation, and impoverishment of thought and speech. The past six decades have witnessed many commercially successful antipsychotic drugs, but no new mechanisms of action and no gains in efficacy since the early 1960s. Cognitive behavioral therapies show promise, but even when combined with current medications, individuals with schizophrenia live with profound limitations resulting from diminished control over thought, emotion, and behavior. Many pharmaceutical companies have exited psychiatry in recent years because of high failure rates in clinical trials, only rudimentary understanding of disease mechanisms, and the lack of treatment biomarkers. Under these circumstances, patients and families would have scant hope for the arrival of better drug treatments.

Much about this grim scientific picture has changed in the past 5 years. New genomic technologies, combined with global collaborations to identify study participants and collect samples, have permitted the identification of a large and rapidly growing number of alleles associated with schizophrenia, bipolar disorder, and autism. Molecular pathways involved in neuronal function are emerging from the data and are beginning to suggest drug targets. Animal and in vitro models in which to investigate hundreds of gene variants of small effect remain works in progress. However, promising tools have emerged here too. For molecular and cellular analyses, stem cell technologies make possible the generation of human neurons in vitro. When combined with remarkable new genome engineering tools, these approaches permit the study of individual risk alleles, multiple alleles in molecular pathways, and the correction of risk alleles in neurons derived from patient samples. Studies at neural circuit levels are yet more challenging, but one can even envision transgenic nonhuman primate disease models with the genome engineering tools at hand. Proposals to the AMP have focused on advancing the genetic analysis of schizophrenia; improving in vitro human neuronal models to study disease-associated alleles; and a project to identify biomarkers, modeled on the early stages of the successful Alzheimer's Disease Neuroimaging Initiative.

Perhaps recent exits by companies from psychiatry made schizophrenia too great a reach for the AMP, despite continued strong support from NIH leadership. It is precisely when new knowledge opens challenging but real possibilities to make major advances in health that partnerships such as the AMP seem most warranted. The scientific community, including industry, academia, patient groups, and government, must find ways of sharing financial risk while developing effective and well-governed partnerships. Otherwise, important basic science investments will go untranslated while patients and society continue to bear painful and costly burdens.

– Steven E. Hyman

10.1126/science.1252603

Published by AAAS