# Researchers suggest new direction for development of psychotropic drugs

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Leading brain and behavior researchers called today for a new direction to develop innovative psychotropic drugs to treat mental illness at the annual meeting of the American College of Neuropsychopharmacology. The panel of academic, industry and government representatives concluded that several factors have impeded the development of novel treatments for mental illness including: incomplete understanding of the impact of mental illness on the brain; continued skepticism of results from animal models for certain disorders; an outdated paradigm of treatment and the industry preference toward so-called "me-too" drugs.

"We need to do better when treating major mental illness, and right now that means we need groundbreaking new research that will result in new medications that are both more effective and have fewer side effects than drugs currently on the market," noted Dennis Charney, MD, Dean of Academic and Scientific Affairs for Mount Sinai School of Medicine and Professor, Department of Psychiatry, Neuroscience and Pharmacology & Biochemistry.

The findings come in the wake of considerable debate in the academic and clinical communities as to whether newer drugs (particularly anti-psychotic medications) represent significant improvement over treatments that have been available for nearly half a century, as well as a greater recognition of the disease burden resulting from mental illness. Currently, mental disorders cause more disability than any class of illness in Americans 15 – 44 years, and the suicide rate in that age group is higher than annual mortality from homicide, AIDS and most cancers.

"There is near universal agreement that we've had only modest progress in developing drugs for schizophrenia and affective disorders in the past several decades. This panel discussion is part of a broader effort to determine why new drug development has been such a historically inefficient process," explained Dr. Bryan Roth, Professor of Pharmacology at UNC Chapel Hill and Director of the NIMH Psychoactive Drug Screening Program at the National Institutes of Health. Affective disorders include bipolar, depressive and anxiety disorders.

The group, reviewing over a decade of psychotropic drug-development research from industry, government and academia, identified several factors that have contributed to the slow progress in developing new treatments.

Review of past clinical research highlighted that a "single disease model" of schizophrenia and mood disorders has prevailed. Increasingly, clinicians and researchers have begun to understand that a combination of several key symptom modalities may need to be addressed separately. "Some early studies are suggesting that we are looking at the wrong targets for mood disorders. Until we have treatments that make it into the clinical setting, we won't fully know the usefulness of single target treatments," added Husseini Manji, MD, FRCPC, Chief, NIMH Laboratory of Molecular Pathophysiology.

The most promising new direction for CNS (central nervous system) drug development appears to be focusing on treatments that act on more than one molecular target. "We typically have used the 'silver bullet' approach (currently the prevailing practice in industry) designed to hit one molecular target at a time. This analysis shows that drugs with more complex action (or utilizing more than one drug at a time) have a greater potential for positive treatment outcomes," concluded Roth.

This shift may be most noticeable when addressing schizophrenia, a disease in which psychosis has long prevailed as the dominant symptom. Now, notes Carpenter, additional attention is being paid to other important symptoms that may have a greater impact on long-term functionality, including cognitive impairment and depression in people with schizophrenia.

Because of limitations in animal models of complex psychiatric disorders like schizophrenia, investigators were often not discouraged by negative results in key tests, particularly if other data seemed encouraging. Roth was surprised by his own findings: "When reviewing this data, we found that animal models were actually quite good at predicting results in human subjects."

However, the overall effectiveness of animal models for mood disorders is still unknown. "Some of these novel molecular targets may be much better than existing ones, but we won't know anything for sure until we have large scale clinical trials," said Manji.

Evaluating decades of research that failed to yield its intended results has provided investigators with insights on how to do better, the researchers believe. Several panel participants expressed the belief that past theories and practices that have been standard practice in new drug development for several decades must change, and new paradigms of mental illness should be embraced to guide future medication development and treatment practice.

"One of the primary reasons we have encountered such difficulty in developing treatments for schizophrenia and mood disorders is a lack of understanding of the diseases themselves," explained William Carpenter, MD, Director of the Maryland Psychiatric Research Center and Professor of Psychiatry at the University of Maryland School of Medicine. "We now have a better understanding of the complex nature

of these illnesses, which affect multiple targets in the brain."

"What is different now is that we have the power of molecular biology combined with improved animal models to identify targets for the development of novel treatments for mood disorders and schizophrenia," noted Charney.

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