New Treatments for Mood and Anxiety Disorders

Researchers have made significant advancements in basic neuroscience during the last decade, but little has been done to translate these findings into effective therapies for mood and anxiety disorders.

The Department of Psychiatry at The Mount Sinai Hospital is addressing these challenges through innovative proof-of-concept trials. We are part of a team that recently received funding from the National Institute of Mental Health (NIMH) to conduct two clinical trials on new interventions for patients with mood and anxiety disorders. The studies are being coordinated by Massachusetts General Hospital and Duke University Medical Center.

Both NIMH contracts incorporate experimental medicine design elements that increase the chances of successfully identifying a new target.

The first study, Rapidly Acting Treatments for Treatment-Resistant Depression (RAPID), conducted at Mount Sinai by Dan Iosifescu, MD, Associate Professor of Psychiatry and Neuroscience and Chief of the Mood and Anxiety Disorders Program, will develop quick-acting interventions for treatment-resistant depression. The research will address the important clinical problem of delays in treatment efficacy with current antidepressants.

The second study, Fast-Fail Proof-of-Concept Studies for Mood and Anxiety Spectrum Disorders (FAST-MAS), in which I serve as Mount Sinai's site Principal Investigator, will identify new molecular targets for mood and anxiety disorders and test the clinical efficacy of drugs interacting with such targets.

Novel and repurposed pharmacological compounds will be rapidly tested in the clinical setting and analyzed for mechanistic brain effects that reflect engagement of the putative brain targets. This can include evidence that the compound engages its molecular target—via PET receptor occupancy data—or affects clinically relevant neurocircuits as shown by fMRI. FAST-MAS will examine changes in dimensions of psychopathology, such as cognition, positive valence, and reward rather than traditional DSM-based categories.

Advancing the Diagnosis and Treatment of Psychosis

The Department of Psychiatry at The Mount Sinai Hospital recently opened a new Psychosis Research Program that will advance the diagnosis and treatment of psychosis through innovative research. The program, housed within the Division of Psychiatric Genomics, is being led by Sophia Frangou, MD, PhD, a pioneer in the use of neuroimaging as a diagnostic and evaluation tool for psychosis.

The program will explore the genetic, molecular, and neural pathways associated with risk and resilience to psychosis, and with overt disease expression, progression, and treatment response. These research findings will then be translated into new tools that improve diagnoses and offer individualized assessment, treatment, and support.

“The bench-to-beside philosophy underpins all aspects of the program,” explains Dr. Frangou. “We aim to advance our understanding of the causes of psychosis and to explore innovative treatments through translational investigations and clinical trials.”

Prior to joining Mount Sinai, Dr. Frangou was Professor of Psychiatry and head of the Section of Neurobiology of Psychosis at King's College London. During her tenure, Dr. Frangou led two research programs—Vulnerability Indicators for Psychosis and Vulnerability Indicators for Bipolar Disorders—at the Institute of Psychiatry in London that examined biological markers associated with the diagnosis and genetic risk within and between mood disorders and psychosis.
Uncovering the Roots of Psychiatric Diseases

Under the leadership of Schahram Akbarian, MD, PhD, Professor of Psychiatry, scientists in the Division of Psychiatric Epigenomics at The Mount Sinai Hospital are studying whether the roots of psychiatric diseases lie in the epigenome, the cellular material that sits on top of the genome, rather than in the DNA itself.

The epigenome contains epigenetic marks, which are responsible for gene expression and the myriad chemical reactions that occur within the human body. Researchers think these epigenetic marks allow environmental factors such as diet, stress, or toxins to turn genes on or off, and ultimately change the way our bodies act. Dr. Akbarian’s team is studying autism, Alzheimer’s disease, and mood and psychosis disorders within this context.

“Understanding how the epigenome of neurons and other brain cells are regulated during the course of normal development, and how they may be altered in disease, is the key to developing the next generation of therapies to treat neurological and psychiatric diseases,” says Dr. Akbarian. “I expect that our approaches will help uncover novel avenues for treatment, and help us understand the similarities and differences in the epigenetic regulation of the genome inside the brain cells of mice, monkeys, and humans.”

In a study on autism spectrum disorder, for example, Dr. Akbarian’s team created an epigenetic risk map of the prefrontal neurons by examining the post-mortem brains of autism patients. They isolated and characterized small snippets of chromatin fibers—located in the nucleus of the cell—from neurons in the prefrontal cortex and other brain regions. Then they compared those tissues with control subjects and charted for genetic modifications such as DNA and histone methylation markings, which define chromatin structure and function. Their work was published in the Archives of General Psychiatry.

“Our study is the first clear evidence gained exclusively from nerve cells pointing to a link between epigenetic changes and known genetic risk sites for autism,” says Dr. Akbarian.

Neuropsychoimaging of Addiction and Related Conditions

The Neuropsychoimaging of Addiction and Related Conditions (NARC) Research Program at The Mount Sinai Hospital uses neuroimaging and neuropsychological tools to gain a better understanding of why some individuals have impaired ability to control their behavior.

In this endeavor, NARC has produced several highly cited studies. One study using functional magnetic resonance imaging (fMRI) found that particular areas of the brain—that automatically tag stimuli as salient—respond strongly when cocaine-addicted individuals are presented with drug-related words. Another study, using Positron Emission Tomography (PET) to measure the activity of the enzyme monoamine oxidase A (MAO-A) in the brains of adults, found that individuals who have less activity of this enzyme also have high scores on personality measures of aggression.

“Our laboratory focuses on understanding self-regulatory processes dependent on the prefrontal cortex—one’s ability to evaluate and change one’s actions—and how they differ between healthy individuals and individuals suffering from substance use disorders or intermittent explosive disorder,” says Rita Z. Goldstein, PhD, Professor of Psychiatry and Co-Chief of the NARC Program at The Mount Sinai Hospital.

Nelly Alia-Klein, PhD, Associate Professor of Psychiatry at The Mount Sinai Hospital, and Co-Chief of NARC, adds, “With a better understanding of this process, we may be able to develop and tailor therapies that could help individuals control disadvantageous impulses, and minimize or even prevent their risk of relapse.”

Using pharmacological fMRI, the NARC group has discovered that oral methylphenidate, a mild stimulant commonly used in patients with Attention Deficit Hyperactivity Disorder, can improve self-control and normalize function in the prefrontal cortex of individuals addicted to cocaine. Going forward, the lab plans to expand upon these findings by including cognitive behavioral training with methylphenidate, and by testing the efficacy of neurofeedback to reduce disadvantageous behaviors and strong negative emotions.

NARC also investigates the effects of withdrawal and abstinence in addicted individuals. Findings show that short-term withdrawal may be associated with increased problems in emotional processing, while longer-term withdrawal may be associated with decreased cognitive function and information processing.