Pioneering Solutions for Depression and Bipolar Disorder
The Stanford Mood Disorders Center
“Never before have we been so close to breakthroughs that will transform our approach to mood disorders, delivering advanced solutions for sufferers, their families, their friends, and their communities. For the first time, we have the ability to understand brain processes and transform new knowledge, rapidly and efficiently, into new therapies and technologies. Stanford is leading the way.”

Alan F. Schatzberg, MD
THE KENNETH T. NORRIS, JR. PROFESSOR AND CHAIR EMERITUS, STANFORD DEPARTMENT OF PSYCHIATRY AND BEHAVIORAL SCIENCES

Pioneering Solutions for Depression and Bipolar Disorder
The Stanford Mood Disorders Center

At some time in our lives, one in five of us will develop a mood disorder, such as depression or bipolar disorder. Its impact will reverberate far beyond any individual’s life. Families, friends, communities, economies—all are affected by these diseases. By 2020, depression will rank second in morbidity among all illnesses worldwide; bipolar disorder will rank fifth. Tragically, suicide, often triggered by a mood disorder, takes more than one million lives worldwide every year.

Although the incidence and impact of mood disorders are undeniably on the rise, at Stanford University, hope for solutions has never been higher. Through the Stanford Mood Disorders Center and Research Program, scientists and physicians are building on Stanford’s traditions of excellence, healing, and innovation. They are leveraging new knowledge of genetics and the brain’s molecular processes, and drawing on new techniques for imaging and healing the brain. Merging Stanford’s expertise across disciplines—psychiatry, biology, engineering, and a myriad of other fields—they are translating laboratory discoveries into breakthrough treatments.

For the past 15 years, Stanford has led the quest for new knowledge and therapies for mood disorders. Today, the center is expanding its reach and mobilizing Stanford’s diverse expertise toward a powerful shared mission: to overcome mood disorders—one of the most widespread, misunderstood, and stigmatized health issues we face—through innovation and compassion.
THE STANFORD ADVANTAGE: AN INTERDISCIPLINARY APPROACH
Stanford’s comprehensive, interdisciplinary approach to mood disorders integrates deep basic research with innovative clinical care and training for future physician-scientists.

In doing so, 30 senior faculty members from eight Stanford departments, including some of the most respected basic scientists in the world, conduct research, clinical care, and education in these areas:

- PSYCHOLOGY
- PSYCHIATRY
- BIOLOGY
- RADIOLOGY
- NEUROLOGY
- GENETICS
- NEUROSURGERY
- BIOENGINEERING

The Mood Disorders Center leverages this interdisciplinary strength to:

- Understand disease mechanisms through genetics, genomics, and proteomics
- Improve imaging techniques that enable us to understand disease by “looking into the brain” and monitoring and measuring its functions
- Pioneer a holistic approach beyond traditional psychiatry—integrating social factors, a deeper understanding of brain mechanisms, and a growing range of diagnostic and treatment techniques, including genetics, imaging, psychotherapy, acupuncture, and behavioral therapy
- Leverage pharmacological and other approaches to improve outcomes for today’s patients
- Create new therapies using innovative techniques, including next-generation drugs, targeted brain stimulation, and light therapy

Alan F. Schatzberg, MD, the Kenneth T. Norris, Jr. Professor and chair emeritus, Stanford Department of Psychiatry and Behavioral Sciences, heads the Stanford Mood Disorders Center.
Cutting a wide swath across all communities and cultures, major depression is more common in women and is characterized by a variety of psychic and physical signs that persist over several weeks or longer, including lowered mood, decreased energy, sleep disturbances, poor concentration, and chronic pain. Bipolar disorder affects men and women equally and is characterized by episodes of mood highs and lows each lasting at least one week. Although the median ages of onset of both disorders are in adulthood, children can also be affected.

TRACING GENETIC ROOTS

What causes mood disorders? Scientists now understand that these illnesses occur when biological or genetic vulnerability intersects with untoward environmental stress. Stanford experts are in the process of unraveling these interactions using unprecedented discovery techniques made possible by the mapping of the human genome and other genomes over the past decade.

In 1996 the Pritzker family established the Pritzker Network for the Study of Depression, a collaborative forum that brought together researchers from three universities (Stanford University, the University of Michigan, and Cornell University) to study the root causes of depression and to improve treatment for the disorder. Another key Stanford collaboration is occurring with four other universities to identify genes that contribute to bipolar disorder.

To explore the genetic origins of mood disorders, Stanford is also investigating these diseases across generations—for example, collecting data on families in which both adults and children have depression or bipolar disorder. Using the latest in genetic analytic technologies, these studies promise to reveal which genes connote increased risk for developing one or more mood disorders.

Scientists once thought they would be able to attribute mood disorders to a single genetic alteration in a single neurotransmitter system. We now know that the genetics of these disorders is complex. Genes may have an impact on many different functions that can all feed into depression or bipolar disorder—for example, by affecting how our brains respond to stress, modulate mood, or maintain cognitive performance. One Stanford effort explores gene activity in postmortem brain tissue, enabling scientists to look at a large number of
genes simultaneously in specific regions and circuits of the brain. Combined with similar preclinical examinations, these studies will determine which circuits and structures in the brain play key roles in mood disorders—the first step in developing novel, better directed, more effective treatments.

SEEING AND HEALING THE BRAIN
Can stress damage the brain and make it more vulnerable to mood disorders? What portions of the brain are affected by depression and bipolar disorder? And how do antidepressants affect the brain? To answer these questions, scientists must be able to study the living brain in real time. And scientists at Stanford are global experts in exploring and developing innovative technologies that reveal mood disorders on a biological level and promise to transform the way we diagnose and treat brain disorders.

Among the advanced technologies developed by Stanford scientists is a new form of functional Magnetic Resonance Imaging (f-MRI) technology that can monitor activity in a deep, difficult-to-image brain region—the subgenual cortex—thought to be associated with deep depression. Other scientists are focusing on high-risk children of women with depression and are combining f-MRI explorations with genetic studies to determine how particular genes, and the neuronal circuits they affect, might influence emotional regulation.

Several teams are using f-MRI to explore how changes in emotion are associated with activation of neuronal circuits in various parts of the brain. They correlate these changes with specific genes to understand the complex regulation of emotions. Some are investigating how neurotransmitters respond to current therapies. Others are looking at how certain hormones affect parts of the brain associated with severe depression.

Another novel technique under preclinical investigation will image, precisely and in real time, the brain’s response to antidepressants. This landmark work will enable us to test novel compounds before exposing humans to them.

NEXT-GENERATION TRAINING
With its highly regarded undergraduate, graduate, and postgraduate programs, Stanford is well positioned to prepare tomorrow’s psychologists and neuroscientists to continue the Mood Disorders Center’s innovative, collaborative work. Center faculty teach undergraduates in human biology as well as honors students in multiple majors, including psychology. The mentorship continues among medical students. Psychiatry residents rotate through the center’s inpatient units and specialty clinics, and postdoctoral fellows, including those in psychology, are trained in our NIMH-funded programs. Students and fellows from multiple disciplines—basic neuroscience, cognitive neuroscience, bioengineering, physics, endocrinology, experimental psychology—also receive training through the center.

Ian Gottlib, PhD, professor of psychology, is using functional Magnetic Resonance Imaging (f-MRI) to explore emotional processing in children of mothers with depression, who are thought to be at increased risk of developing the disorder. His studies combine genetic characterization with innovative brain imaging techniques.

Natalie Rasgon, MD, PhD, professor of psychiatry and behavioral sciences, directs the Stanford Center for Neuroscience in Women’s Health, which studies the connections among women’s reproductive hormones, mood disorder, and cognitive health. Rasgon has been at the forefront of the effort to uncover the links between hormones and brain function.
Synaptic modifications in the brain’s reward circuitry play a critical role in both the development and treatment of depression (mood disorders). The Nancy Friend Pritzker Laboratory of Behavioral Neurochemistry, led by Robert Malenka, MD, PhD, the Nancy Friend Pritzker Professor of Psychiatry and Behavioral Sciences, is a world leader in studying the molecular mechanisms by which stressful events or ingestion of drugs modifies the function of synapses in this key brain area. Such work will lead to the identification of novel targets for the development of new medications for these devastating disorders.

In collaboration with Mood Center director Alan Schatzberg, MD, Allan Reiss, MD, the Howard C. Robbins Professor of Psychiatry and Behavioral Sciences, is using imaging technology to study the relationship between measures of cortisol, a stress-marker hormone, and a key area of the brain—the amygdala. Data to date confirm the theory that a smaller amygdala is associated with increased stress responses and increased risk of developing psychotic thinking, a feature of the most severe form of depression. Collaborating with them, Vinod Menon, PhD, associate professor of psychiatry and behavioral sciences, and Michael Greicius, MD, MPH, assistant professor of neurology and neurological sciences, have developed new f-MRI technology that can image brain circuits at rest. The technology will enable scientists to study the subgenual cortex, an area of the brain where activity is increased in depressed patients, which, without this technology, is difficult to see.

LEADING CLINICAL CARE
Stanford Hospital & Clinics has developed one of the premier clinical programs in psychiatry, ranked by U.S. News & World Report in the top 10 of U.S. psychiatry programs for the past five years. Delivering the highest standard of clinical care, the Mood Disorders Center offers inpatient and outpatient services, and operates both adult and child outpatient clinics for depression and bipolar disorder.

IMPROVING OUTCOMES FOR TODAY’S PATIENTS
Psychiatrists today rely on a combination of pharmacologic agents and psychotherapy to treat patients with depression or bipolar disorder. Stanford scientists are actively exploring which strategies, based on existing drugs and psychotherapeutic techniques, are most successful. At the same time, they are also developing new approaches that boost the effectiveness of these therapies.

One team is investigating whether a specific form of psychotherapy in combination with medication is more effective than aggressive pharmacologic treatment in patients with chronic depression. Rachel Manber, PhD, is studying optimal psychosocial treatments for reducing insomnia in major depression and exploring whether these treatments can improve depression as well.

Other researchers, looking at recurrent depression, are comparing the long-term effectiveness of serotonin-based drugs to that of therapies that combine serotonin with norepinephrine. One novel study, conducted across three medical centers, is looking at how a dopamine-based agent now used for restless leg syndrome might improve a patient’s response to antidepressants.

Stanford scientists are also looking at whether genetic variations can predict which of today’s antidepressants will work best for particular patients. So far, this project has yielded several genetic tests that are available through the clinical laboratories of the Mayo Clinic. Over time, it may be possible to develop a series of genetic markers to help doctors identify the most promising treatment for each patient.

Bipolar disorder often requires a combination of mood stabilizers and antidepressants to bring relief to patients. However, some commonly used medications are associated with insulin resistance and diabetes. In collaboration with a national research network, one Stanford team is combining novel brain imaging and endocrinology techniques to explore risk factors for the development of these complications. These studies promise to yield methods to reduce risk of diabetes and overcome insulin resistance.
Creating New Therapies

Although most people with mood disorders eventually respond to treatment, many must try several therapies before they find one (or a combination) that works. And some therapies are associated with considerable side effects. To usher in a new era of mood disorder care—more effective, faster acting, better tolerated—Stanford is taking the lead in developing groundbreaking treatment approaches.

One of the most severe forms of depression, delusional depression has a high mortality rate due to physical causes or suicide. People with the disorder often receive electroconvulsive therapy, one of the most effective treatments available. Researchers at Stanford are working to reduce and in some cases eliminate the memory loss which can be a side effect of this treatment. Following up on a number of studies that reveal elevated cortisol as an indicator of delusional depression, Stanford research has led to the use of a fast-acting alternative medication that blocks a specific cortisol receptor in the brain. This medication is now being studied in a Phase III trial by a biotechnology company.

Meanwhile, other Stanford teams are investigating which areas or circuits of the brain are potentially overactive in depression in order to develop new treatments that provide electrical stimulation to targeted areas of the brain. So far, these therapies stimulate the surface of the brain through the scalp. However, some key areas associated with mood disorders lie deep within the brain. In collaboration with other researchers, Stanford plans to explore deep brain stimulation—implanting electrodes into specific regions, such as the subgenual cortex, guided by imaging—as part of a national multicenter project.

Stanford is also pursuing new, alternative techniques to stimulate deep brain regions. One approach focuses stimulation on these regions using 3-D telemetry and magnetic or radiosurgical stimulatory techniques. Other Stanford researchers are exploring acupuncture—a safer alternative for pregnant women with depression—mindfulness techniques, and dialectic behavioral therapy.

A National Network of Excellence

Bringing leaders together in breakthrough collaboration, Stanford has worked on the development of a network of National Designated Depression Centers in cooperation with the original center at the University of Michigan. Like previous movements to establish national networks for cancer and heart disease, the effort seeks to establish centers of excellence in treatment, research, and training related to depression and bipolar disorder. These centers promise to improve the productivity and efficiency of mood disorder research, speed the development of new therapies, and share new treatment guidelines widely—an important step in removing the stigma associated with depression and bipolar disorder.
Robert Sapolsky, PhD, is the John A. and Cynthia Fry Gunn Professor of Neurology and Neurological Sciences. He is a professor of biology, neurosurgery, and neurology and neurological sciences. The scientists at his laboratory are working on novel methods for gene therapy in brain tissue.

The Stanford Mood Disorders Center and Research Program is building on Stanford’s tradition of excellence, healing, innovation and collaboration to offer new hope, diagnostics, and therapies to those who suffer from these life-altering diseases.

New drugs represent another important frontier in the treatment of mood disorders—an area Stanford is actively pioneering. Postmortem measurement of gene activation in the brain is laying the groundwork for novel targets for new medications that affect specific systems in the brain. Several new targets are being screened already.

**RALLYING THE RESOURCES TO LEAD**

What will it take to usher in a new era in the treatment of mood disorders—an era in which we understand the biological and genetic roots of depression and bipolar disorder, wield technologies that enable us to see and heal the brain in real time, optimize the effectiveness of current tools, and turn next-frontier ideas into high-impact therapies? It will take both innovation and compassion, proven expertise and a constant hunger for new knowledge, and groundbreaking ideas and collaborative spirit. Inspired by The Stanford Challenge—and by the enormous potential of research now under way at Stanford—we can rally these resources to realize the mission of the Stanford Mood Disorders Center: delivering solutions, cultivating understanding, and transforming lives.

**CONTACT US**

For more information, please contact:

William Gray  
Associate Director of Development  

Stanford University  
Office of Medical Development  
2700 Sand Hill Road  
Menlo Park, CA 94025  
T (650) 234-0668  
F (650) 234-0644  
bgray@stanford.edu  
thestanfordchallenge.stanford.edu