

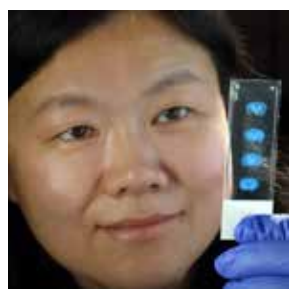
Genetic Model Offers New Insights into Bipolar Disorder

Psychiatry researchers at Johns Hopkins have developed the first robust genetic mouse model of bipolar disorder.

In work directed by research associate **Shanshan Zhu** in the lab of psychiatrist and neuroscientist **Christopher Ross**, investigators genetically engineered mice by knocking out the gene coding for the protein ankyrin-G in neurons in the forebrain, beginning in adolescence. The gene was chosen because it has consistently emerged in human genetic studies as a risk factor for the human disorder. In numerous tests of the animals' behavior, this alteration led to hyperactive and less fearful conduct, akin to human mania. "Remarkably, these behaviors could be reversed by treatment with lithium and valproic acid—the same medications used to treat people with bipolar disorder," Ross says.

The work, published online in the *Proceedings of the National Academy of Sciences*, also demonstrated that the genetically altered mice showed extra susceptibility to a depression-like state after stress, again like humans with the disorder.

"The knockout mice look the same as the controls, but they are super-active and much more willing to escape," says Zhu. "Our animal technician could tell which mice were knockouts compared with controls by holding them in her hand."



course of bipolar disease."

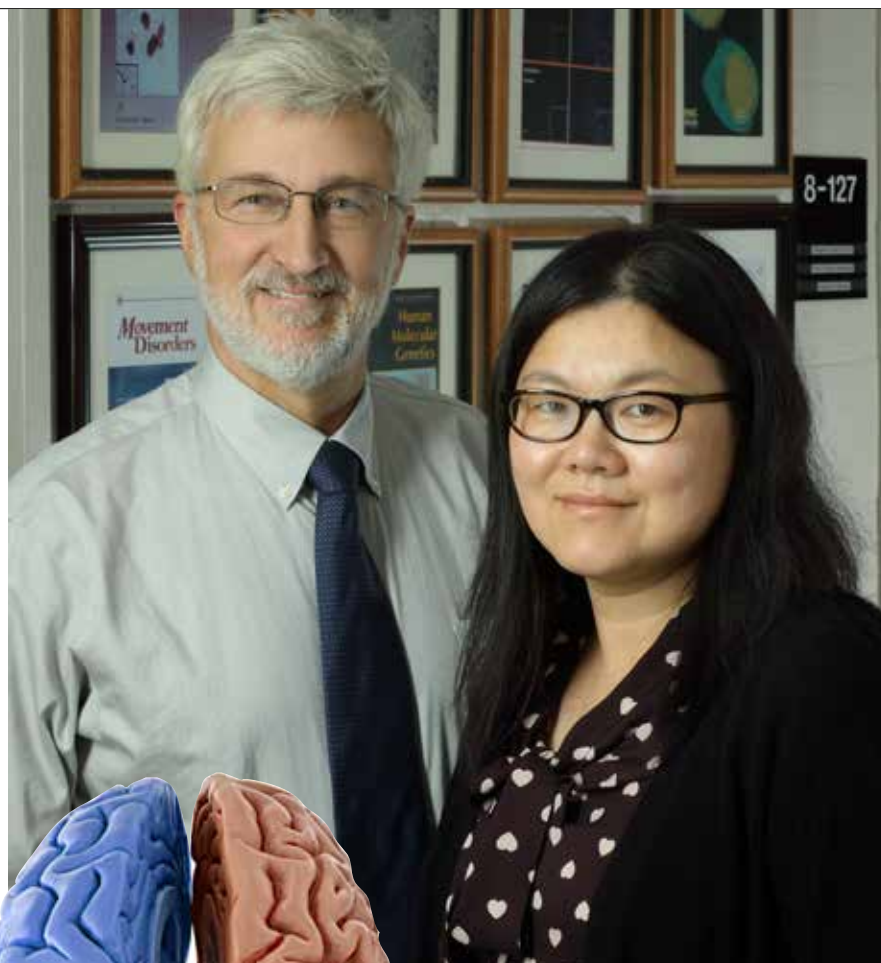
The study, says Zhu, offers "great hope that treatments could be developed to alter the

Ankyrin-G is important for specifying some of the key machinery in brain cells for cell signaling, Ross says: "It's involved in organizing other proteins in its region of the neuron, and thus in controlling synaptic connectivity. We've uncovered alterations in the microcircuitry in how neurons connect with each other with the cerebral cortex; they lose the ankyrin-G, and they also lose their inhibitory synaptic inputs." These kinds of changes have long been thought to underlie psychiatric disorders, but have been very hard to identify and study in the past, he says.

In their study, investigators placed the mice in an empty box, called an "open field" test. While typical mice tend to hug the walls, the knockouts spent much more time in the center, venturing out more than 20,000 times per hour, compared with 7,000 times per hour for typical mice. Knockout mice were active for up to 17 hours a day, compared with 12 hours for typical mice. Another test exposed the mice to different, bigger, aggressive mice, which led them into a depressive-like state.

"They could switch back and forth between states reminiscent of mania and depression, similar to a patient with bipolar disorder," Ross says.

Some psychiatric diseases, such as schizophrenia and autism, are believed to be caused by



Christopher Ross and Shanshan Zhu have successfully altered mice genetically so that they exhibit signs of mania and show heightened susceptibility to a depression-like state after stress. Alterations in how neurons connect with each other emerged, shedding new light on synaptic changes.

In a given year, **bipolar disorder affects** about 5.7 million American adults, or about 2.6 percent of the U.S. population 18 and older, according to the National Institute of Mental Health.

neurobiological alterations that occur during embryonic or early development stages, Zhu says: "By contrast, in our mouse model, the bipolar-like behavior was related to synaptic changes happening in adolescence or adulthood. This offers great hope that treatments could be developed to alter the course of the disease, and even to prevent future episodes."

Ross explains that while this is an initial study, the team hopes to use the model to understand the biology of bipolar disorder, to learn how lithium works, and potentially to develop new drugs for the disorder. ■

Learn more about the study: bit.ly/modelbpdisorder.



Jimmy Potash, M.D., M.P.H.

The Power of Patient Care, Discovery and Generosity

Our department is one of the few places in the nation that both delivers state-of-the-art patient care and makes discoveries that advance the state of the art. Our care of those with substance use disorders and obsessive-compulsive disorder (OCD), for example, is provided by clinicians who are among the nation's best. In this issue, you will read about efforts to develop new methods to treat opioid withdrawal and to zero in on the roots of OCD.

We know the future lies in understanding what happens in the brain to give rise to mental illness. We need to know what is broken to be able to fix it. We have treatments that are good for about two-thirds of patients. But this excludes many who cannot benefit from what we have to offer. We need to do better. That will require figuring out what sets these illnesses in motion and how they unfold in the brain. Only then can we create better conventional drugs as well as newer gene-based treatments.

As for how illnesses unfold in the brain, we are interested in molecular neuroscience—the molecules of the mind. We can put a known bipolar disorder gene into a mouse brain and see whether the animal behaves in ways reminiscent of the human illness, and what changes in its brain function. This is what Professor Chris Ross has done with a bipolar disorder gene, as described in our cover story. The approach lets us test potential new medications in these animals to determine whether they can correct the problematic behaviors.

There is enormous promise in all these new developments from our department. They move us toward making a difference for patients—both within our four walls and around the globe.

Much of the impact we make is built not only on the talent and energy here, but also on the generosity of our friends and partners. To see just how that plays out, be sure to read about grateful mom and donor Katherine Warren, whose teenage son we were able to help. I want to thank her, and thank all of you for taking the time to learn more about what we do.

Probing the Seeds of Doubt in OCD

It's not uncommon, says psychiatrist **Gerald Nestadt**, to hear someone joke over cocktails, "I'm so OCD," implying that the person is exceedingly fastidious about everything. But obsessive-compulsive disorder, which affects some 3 percent of the world's population, is no laughing matter.

Over the past 30 years, Nestadt, who trained as a psychiatric epidemiologist, has studied and treated scores of patients with OCD. He's found compelling evidence for a biological basis for OCD, noting that obsessions and compulsions are common in such medical conditions as Huntington's chorea, Parkinson's disease, Tourette disorder and schizophrenia. He's also found that serotonin reuptake inhibitors and selective serotonin reuptake inhibitors have proven effective in controlling OCD symptoms. Nestadt helped conduct the first trial of a medication to dampen OCD patients' obsessive impulses, persistent, intrusive and repetitive thoughts.

Now he's digging deeper to understand another component of the disorder: doubt. "I've been fascinated by its clinical relevance," Nestadt says. "Doubt is not based on insufficient knowledge to make decisions. It's a behavioral trait." In the context of OCD, he theorizes, doubt demonstrates a "lack of confidence in one's own memory, attention and perception necessary to reach a decision."

Nestadt gives the example of patients who feel compelled to keep checking their front door to ensure that it's closed. "They check it with their own eyes, but yet still need to go back and jiggle the lock to be sure," says Nestadt. He suspects a genetic basis for this behavior, though environment also plays a role.

In a recent study published in *Comprehensive Psychiatry*, Nestadt and his colleagues report an investigation of 1,182 adults with OCD who were assessed to evaluate the relationship between doubt and OCD's clinical features. "It's the first investigation of the clinical significance of the doubt construct in OCD," says Nestadt.

Doubt was assessed with the following questions: After you complete an activity, do you doubt whether you performed it correctly? Do you doubt whether you did it at all? When carrying out routine activities, do you feel you don't trust your senses—i.e., what you see, hear or touch? Cases were categorized as mild, moderate, severe or extreme on a "doubting" scale.

The study found that doubt in patients with OCD was strongly related to the number of checking symptoms and, to a lesser extent, to the number of contamination/cleaning and hoarding symptoms patients experienced.

The findings, says Nestadt, suggest that doubt has important implications for understanding the nature of OCD. For one thing, the severity of doubt was distributed in the sample such that many cases were rated as severely burdened with doubt, whereas a sizeable proportion were rated as having no or little doubt. "This suggests that doubt may not be a core feature of all OCD cases, but rather a frequently occurring symptom of, or related to, the disorder," says Nestadt.

The biggest surprise, he adds, was the finding that "the more doubtful you are, the more dysfunctional you are; 80 percent of the doubters were extremely



"Doubt is not based on insufficient knowledge to make decisions. It's a behavioral trait."

—GERALD NESTADT

dysfunctional." Most likely, explains Nestadt, these symptoms emerge "from a neurocognitive vulnerability in the mental life of the individual, which has a basis in neurophysiology."

So, what can provide relief for these patients? "Typically, 60 to 70 percent of people respond to cognitive-behavioral therapy," says Nestadt. "But in patients with severe doubt, only about 35 percent respond. That's where antidepressants come in."

Next up, Nestadt and his colleagues are developing a multi-item instrument to assess doubt dimensionally in clinical and nonclinical samples. "With greater understanding about the neuroscience behind decision-making in patients with OCD," he says, "we can further our understanding of the vulnerability to doubt that underlies the disorder." ■

Learn more about the study: bit.ly/OCDdoubt.

DELIRIUM AND ALCOHOLISM

Why Doctors Must Be More Vigilant About Diagnosing and Treating Wernicke's Encephalopathy

Abnormal eye movements. Unsteady gait. Delirium. For over a century, physicians have used this triad of symptoms to diagnose Wernicke's encephalopathy (also called Wernicke-Korsakoff syndrome), a neurological condition caused by a deficiency in B vitamins such as thiamine.

Those with alcohol use disorders or who are malnourished are at the greatest risk for developing

the condition, says **Karin Neufeld**, clinical director of psychiatry at Johns Hopkins Bayview Medical Center, who recently gave a Grand Rounds lecture on the topic. But physicians today need to think beyond the triad and suspect Wernicke's in any at-risk patient presenting with one or more of the symptoms. Quick treatment with high-dose thiamine infusions can reverse the symptoms, she says: "If there is delirium in the setting of alcoholism, suspect Wernicke-Korsakoff syndrome." The presentation can include a broad array of symptoms, including hearing loss; difficulty swallowing; fatigue and apathy; memory and mood disturbances such as amnesia, irritability or psychosis; arousal disorders, including sleep apnea and drowsiness; polyneuropathy; hypothermia; hyperhidrosis and lactic acidosis.

"It's probably safe to say that we're missing cases that present in the acute hospital setting and beyond,"

Tramadol: A Viable Detox Alternative?

The most widely accessed treatment for opioid use disorder is medically supervised withdrawal, or detoxification. To help their patients, physicians primarily prescribe one of two medications to manage opioid withdrawal, but each has its challenges, says psychiatry researcher **Kelly Dunn**.

Buprenorphine is commonly used, but because of its potential to be abused, it can be prescribed only by physicians with specialized waivers. Buprenorphine access may be limited as a result, and some physicians are ideologically opposed to using it, says Dunn. Clonidine, used to treat high blood pressure and attention deficit hyperactivity disorder, has been used off-label to manage opioid withdrawal. It doesn't perform as well as buprenorphine, and it's sedating, Dunn says, "but it's easier to give because you don't need special permissions."

Looking for alternatives, Dunn's colleagues recently landed on the extended release form of the analgesic tramadol hydrochloride. It has opiate-like properties but a relatively low potential for abuse—a good candidate to test, they reasoned.

In a double-blinded, randomized clinical trial, Dunn's group compared tramadol-extended release with the other drugs during a seven-day opioid taper as part of a 26- to 28-day medically supervised inpatient detoxification. They enrolled 103 adult patients with opioid use disorder between 2010 and 2015. After their conditions were stabilized with morphine for seven to 10 days, participants were randomly assigned to take either clonidine, tramadol or buprenorphine during tapering, then were followed for an additional week on placebo.

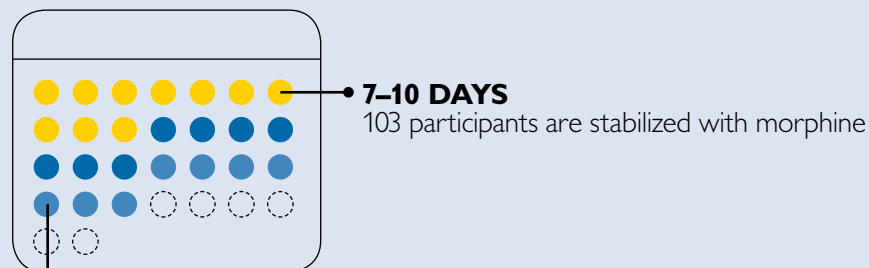
The results, published this summer in *JAMA Psychiatry*, found that tramadol was more effective than clonidine and comparable to buprenorphine in reducing opioid withdrawal symptoms. Ninety percent of patients taking buprenorphine completed the taper period, compared with 72 percent of those on tramadol and 66 percent of those on clonidine.

The work, says Dunn, "suggests that tramadol does have value as an opiate agonist for the treatment of opioid use disorder and opens up an additional medication that physicians may feel more comfortable prescribing...especially in settings where they were only willing to prescribe clonidine before."

Since study publication, she and her co-authors have received calls from numerous physicians throughout the country asking for advice on how to implement opioid tapers using tramadol. While the Drug Enforcement Administration moved tramadol from an unscheduled drug to a schedule IV controlled substance since the study began, it should still be viewed as a useful alternative, Dunn says: "With the opioid epidemic, the fact that many people are trying to get access to treatments, and that tapering is one of the most accessed treatments, anything that can make that a little bit more successful is of value." ■

Learn more about the study: bit.ly/tramadolJAMA.

7-DAY OPIOID TAPER as part of 26–28 day detoxification

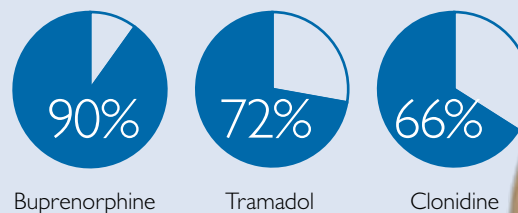


NEXT 7 DAYS + ADDITIONAL WEEK ON PLACEBO

Participants are randomly selected to take

- Buprenorphine
- Clonidine
- Tramadol

RESULTS OF PARTICIPANTS SUCCESSFULLY COMPLETING TAPER PERIOD



"...[the work] suggests that tramadol does have value as an opiate agonist for the treatment of opioid use disorder..."

—KELLY DUNN



"It's probably safe to say that we're missing cases that present in the acute hospital setting and beyond ... In part, it's due to recognition."

—KARIN NEUFELD

Neufeld says. "In part, it's due to recognition. But it may also be that we are seeing more cases of Wernicke's because of more people undergoing surgical procedures for weight loss. Anything that decreases absorption of nutrients is going to put you at greater risk." One of Neufeld's fellows saw a female patient who had been diagnosed by a local neurologist with an Alzheimer's dementia, but she actually had Wernicke's. With treatment,

it reversed. She was someone who had a bowel resection and drank heavily, Neufeld notes.

"What's really cool about Wernicke's is if you have someone with eye findings, those eye findings will go away within hours to a day of giving high-dose thiamine," she says. Problems with gait disappear within days to a week, and even memory problems resolve over time—although this is generally over the course of weeks to months.

"Many untreated Wernicke's patients will end up in nursing homes, so it's critically important that we be more aggressive about treatment."

The brain needs a steady stream of thiamine to work efficiently, Neufeld says, but the body can store just 30 milligrams at a time. While there's no set protocol for thiamine infusions in the U.S., the current thinking, based on United Kingdom protocols, is to give three 500-milligram doses intravenously for two to three days, Neufeld says, followed by 100 milligrams orally three times a day for the remainder of a patient's hospital stay or during outpatient treatment, until symptoms resolve. ■

A Quest for Peace of Mind

More often than not, when 17-year-old Michael swings his tennis racket, everything comes together: focus, breathing and staying ahead of the ball. That takes skill, but at its core is control—something that eluded him several years ago when he experienced a sudden change in character. The Houston native had been having difficulty concentrating and sleeping; he ate either very little or huge amounts; he was oppositional and no longer interested in tennis or other activities he used to love.

It would take weeks before a firm diagnosis of bipolar disorder came to light, a scenario not uncommon in adolescence, when severe mood swings are expected. Michael and his mother, Katherine Warren, credit Johns Hopkins psychiatrist **Lynn Taylor** and the child and adolescent inpatient unit for helping to turn Michael around. Taylor worked with a team of experts who helped determine a medication regime for stabilization and ongoing maintenance that included liquid and fast-dissolving forms.

The inpatient nursing staff went one step further to



Michael, pictured with his mother, Katherine Warren, benefitted from what Katherine calls a “soothing and inclusive environment” at Johns Hopkins’ inpatient child and adolescent psychiatry unit.

encourage Michael to take his medicine by pairing it with palatable foods like Nutella, peanut butter or chocolate pudding, says

Elizabeth Reynolds, a psychologist on the unit. They also set up a system of rewards for positive behavior and participation in group therapy once he was stabilized. The Warrens say they appreciated the unit’s calm, soothing, environment; its patient care and its inclusion of parent participation.

Three years ago, when he first started having symptoms, Michael was admitted to a local mental health system near home, where he was eventually diagnosed with bipolar disorder. But his medications made his heart

race and interfered with his sleep. Michael struggled to stay compliant, resulting in crises that exacerbated his behaviors. A doctor on the team offered to transfer Michael to the inpatient child and adolescent psychiatry unit at Johns Hopkins.

After about four weeks of inpatient care there, the staff members developed a safe step-down plan to the day program for Michael and arranged for a home health aide to spend time with him at a local hotel. When he was ready to head home, they developed a plan for home management and referred him to a local psychiatrist.

In appreciation for Michael’s care, Katherine has made donations to support the needs of the inpatient child and adolescent psychiatry unit. “Everything Hopkins provides is extraordinary. The inpatient unit was like nothing we’d seen and a necessity for an adolescent with a severe mental health disease.”

Michael is now a high school junior and back to playing varsity-level tennis, and just received a referral to an adult psychiatrist in advance of his 18th birthday. Tennis remains a passion for Michael, and he’s proven to be a valuable player on the tennis team. But when he’s off his game, he’s much more likely to have a measured response. ■

Hopkins *BrainWise*

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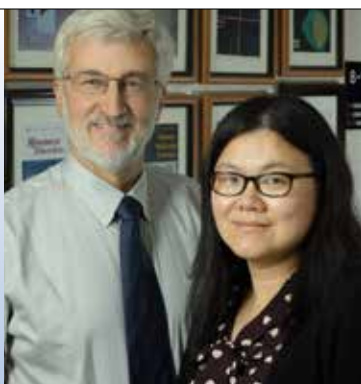
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