

# NewYork-Presbyterian Advances Psychiatry

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NewYork-Presbyterian  
Psychiatry ranks #3  
in the nation.

## Research Highlights: Targeting Challenges in Mental Health

Each and every day, NewYork-Presbyterian researchers and clinician-scientists are advancing knowledge in virtually every medical specialty. At Weill Cornell Medicine and Columbia University Vagelos College of Physicians and Surgeons, faculty are targeting some of today's most formidable health challenges, pushing scientific discoveries forward and applying research breakthroughs to improving the lives of patients everywhere. In this issue of *Advances*, we share several of our recent investigations in behavioral health.

### Online Databases: A Prescription for the Opioid Epidemic

Drug overdoses took the lives of some 64,000 Americans in 2016, a 22 percent rise over the previous year. The majority of these deaths were linked to opioids, including heroin, prescription painkillers, and the powerful synthetic drug fentanyl, which together killed more people than gun violence or even car accidents.

The growing crisis has alarmed officials at the highest levels, and in October, President Donald Trump directed the Department of Health and Human Services to declare the nationwide epidemic of opioid abuse a public health emergency. "It is a huge problem," says **Jonathan Avery, MD**, Director of Addiction Psychiatry, NewYork-Presbyterian/Weill Cornell Medical Center, and an Assistant Professor of Clinical Psychiatry at Weill Cornell Medicine. "When I started here in 2009, it wasn't even on many doctors' radar."

"Historically, there was no way for a physician to check to see if a patient had a history of being on the medication or was actively getting it from someone else."

— Dr. Jonathan Avery

In recent years, however, New York City has seen a staggering number of fatal overdoses – nearly 1,400 in 2016, a 46 percent increase over the previous year, according to the city's health department. Says Dr. Avery, "We're seeing a lot of death everywhere."

### Tracking Prescriptions

Solutions have remained elusive, but according to Weill Cornell Medicine researchers, one of the most effective ways to prevent overdoses may be as simple as keeping better track of prescriptions. People who have developed opioid use disorders or are illicitly sharing pills with others often go to several doctors, either to get multiple prescriptions or to get a new prescription after being refused a refill. "Historically," says Dr. Avery, "there was no way for a physician to check to see if a patient had a history of being on the medication or was actively getting it from someone else." While some doctors may unscrupulously prescribe inappropriate drugs for profit, many well-intentioned practitioners are simply unaware that their patients have been prescribed opioids by another clinician.

But according to **Yuhua Bao, PhD**, Associate Professor of Healthcare Policy and Research, that is changing thanks to the advent of prescription drug monitoring programs. With these statewide online databases, pharmacies are required to log each opioid prescription they fill, and physicians and pharmacists can check whether a particular patient has already been prescribed one by another practitioner. Forty-nine states (all except Missouri) and the District of Columbia now have such programs – up from 11 in 2003, the year the federal government began offering grants to fund them.

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## Online Databases: A Prescription for the Opioid Epidemic (continued from page 1)

Dr. Bao has spent the past few years studying the effectiveness of these programs. In 2016, she led a team that found that when a state creates one, it lowers the likelihood that a pain patient will be prescribed Schedule II opioids (a category that includes Percocet and OxyContin) by 30 percent, a result that Dr. Avery, who was not involved with Dr. Bao's study, says demonstrates their "huge" potential to curb addiction. While it is not clear that all the eliminated prescriptions would have been unnecessary, Dr. Bao says, it does indicate that monitoring programs make doctors more circumspect about prescribing the most addictive drugs.

"We found the effect of a state implementing a monitoring program to be immediate," Dr. Bao says of the work, published in 2016 in the journal *Health Affairs*. "It might be because of rising awareness of an opioid misuse problem, or because physicians feel like they're being watched."

In some states, physicians' use of databases is voluntary, while in others, doctors have a legal obligation to at least register with the system. In a 2017 study, also published in *Health Affairs*, Dr. Bao and colleagues reported that the requirement simply to register can trigger a drop of as much as 10 percent in the number of opioid prescriptions filled by Medicaid patients, presumably by raising physicians' awareness of the monitoring system and the potential for drug misuse.

That 2017 study relied on 2011-2014 data from the Centers for Medicare and Medicaid Services, which covers a population that is especially vulnerable to opioid misuse and overdose. The reasons for this are complex, but one is that lower-income people often work physical jobs that are more likely to cause injury, which in turn can lead to chronic pain conditions for which doctors may prescribe opioids. Once Medicaid patients receive a prescription for opioids, they may also be more likely

to misuse them, a risk factor linked to the tendency of less affluent people to suffer from more life stressors.

Some of Dr. Bao's future work on drug monitoring programs will involve exploring their potential pitfalls. These include the worry that if doctors fear they'll face negative consequences for prescribing opioids even if patients genuinely need them, they may opt not to prescribe them at all. Also, limiting access to prescription opioids may lead individuals to turn to even more dangerous street drugs, including heroin and fentanyl.

Dr. Bao will also study ways to make monitoring programs more effective, including by sharing data across state lines. "This is especially salient to places like New York City," she explains, "where you may also have patients from New Jersey or Connecticut." And she notes that in addition to saving lives, databases could also reduce costs: The 2017 study found that if every state mandated that prescribers register with the system, Medicaid would save more than \$166 million a year.

*Source: Weill Cornell Medicine*

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## Opioid Overdose Survivors Face Higher Death Rate



Dr. Mark Olfson

Survivors of opioid overdose are at great risk of dying in the year after overdose, but the deaths are not always caused by drug use, according to **Mark Olfson, MD, MPH**, Professor of Epidemiology at Columbia University's Mailman School of Public Health, and lead author on the first study to evaluate causes of death in opioid overdose survivors, recently published in *JAMA Psychiatry*. In addition to succumbing to drug use, the Columbia investigators found that survivors were much more likely to die from respiratory diseases, viral hepatitis, and suicide.

"We found that adults who survive an opioid overdose have an exceptionally high risk of dying from a wide range of medical diseases and suicide," says Dr. Olfson, Professor of Psychiatry at Columbia University Vagelos College of Physicians and Surgeons. "While it was not surprising that adults who survive

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## 'Anxiety Cells' Identified in the Brain's Hippocampus

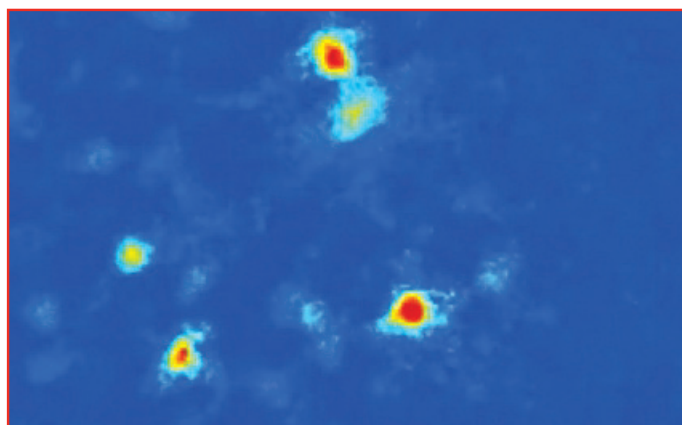
Neuroscientists at Columbia University Medical Center and the University of California, San Francisco, have found in mice that certain brain cells in the hippocampus fire when the animal is anxious, triggering anxiety-related behaviors. While the researchers found the cells in the brains of mice, they believe that the cells probably also exist in humans, notes **Rene Hen, PhD**, Professor of Neuroscience and Pharmacology in Psychiatry at Columbia and one of the study's senior investigators. "We call these anxiety cells because they only fire when the animals are in places that are innately frightening to them," says Dr. Hen. "For a mouse, that's an open area where they're more exposed to predators, or an elevated platform."

The firing of the anxiety cells sends messages to other parts of the brain that turn on anxious behaviors; in mice, those include avoiding the dangerous area or fleeing to a safe zone.

Though many other cells in the brain have been identified as playing a role in anxiety, the cells found in this study are the first known to represent the state of anxiety, regardless of the type of environment that provokes the emotion.

"This is exciting because it represents a direct, rapid pathway in the brain that lets animals respond to anxiety-provoking places without needing to go through higher-order brain regions," says **Mazen Kheirbek, PhD**, Assistant Professor of Psychiatry at UCSF and the study's other senior investigator.

"Now that we've found these cells in the hippocampus, it opens up new areas for exploring treatment ideas that we didn't



Using optogenetics, anxiety cells in the brains of mice light up when the animal is stressed. (Courtesy of Hen Lab)

know existed before," says lead author **Jessica Jimenez, PhD**, an MD/PhD student at Columbia University's Vagelos College of Physicians and Surgeons.

The findings appeared in the February 2018 issue of *Neuron*. "This study shows how translational research using basic science techniques in animal models can elucidate the underlying basis of human emotions and reasons for mental disorders, thereby pointing the way for treatment development," says **Jeffrey A. Lieberman, MD**, the Lawrence C. Kolb Professor and Chair of Psychiatry at Columbia and Psychiatrist-in-Chief at NewYork-Presbyterian/Columbia University Irving Medical Center.

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## Opioid Overdose Survivors Face Higher Death Rate (continued from page 2)

opioid overdoses have high ongoing risks of drug-related death and dying from HIV or viral hepatitis, I was taken aback by their markedly elevated risks of dying from so many other conditions, including circulatory, respiratory, and digestive system diseases. These findings underscore the overall medical frailty of this patient population and show us that instead of just focusing on survivors' drug use, we need to coordinate addiction treatment for survivors with general medical and mental health care."

The researchers analyzed Medicaid records from 45 states to look for causes of death in more than 75,000 adults who were treated for an opioid overdose between 2001 and 2007. More than 5,000 of the adults died within the first year following an overdose – 24 times the death rate found in the general population. The most common causes of death were those related to drug use (25 percent), diseases of the circulatory system (13 percent), and cancer (10 percent). The data show that adults in this population are substantially more likely to die of these causes than adults in the general population.

Compared to the general population, the opioid overdose group was 130 times more likely to die of a drug-use-related cause, 40 times more likely to die of chronic respiratory diseases,

30 times more likely to die of viral hepatitis, and 25 times more likely to die of suicide. Women who survived an opioid overdose were nearly 50 times more likely to die of suicide.

"Some of the mortality in this group likely reflects health risk factors that are common in individuals with opioid use disorders, such as cigarette smoking, which can lead to respiratory diseases, cardiovascular disease, and cancer, and needle sharing, which can lead to hepatitis and HIV," says Dr. Olfson.

Opioid use has greatly increased in all sectors of society since the data were collected. "Given the substantial and diverse mortality risks following opioid overdose, it's critically important that clinicians coordinate addiction treatment, general medical care, and mental health care in individuals with opioid use disorders," adds Dr. Olfson.

### Reference Article

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## 'Anxiety Cells' Identified in the Brain's Hippocampus (continued from page 3)

To understand how things go awry in anxiety disorders, researchers in the Hen lab have been looking at mice to decipher how the brain processes healthy anxiety. "We wanted to understand where the emotional information that goes into the feeling of anxiety is encoded within the brain," says Dr. Kheirbek, who was an Assistant Professor at Columbia before moving to UCSF.

The hippocampus plays a well-known role in the brain's ability to form new memories and to help animals – from mice to humans – navigate through complex environments. But recent research has also implicated the hippocampus in regulating mood, and studies have shown altering brain activity in the ventral part of the hippocampus can reduce anxiety. It's also known that the hippocampus sends signals to the amygdala and the hypothalamus that have also been shown to control anxiety-related behavior.

Using a miniature microscope inserted into the brains of the mice, Dr. Hen's team recorded the activity of hundreds of cells in the hippocampus as the mice freely moved around their surroundings. Whenever the animals were in exposed, anxiety-provoking environments, the researchers noticed that specific cells in the ventral part of the hippocampus were active. And the more anxious the mice seemed, the greater the activity in the cells.

The researchers traced the output of those cells to the hypothalamus, which is known to control behaviors associated with

anxiety, including increased heart rate, avoidance, and secretion of stress hormones. By turning the anxiety cells off and on using optogenetics that allows scientists to control the activity of neurons using beams of light, the researchers found that the anxiety cells control anxiety behaviors. When the cells were silenced, the mice stopped producing fear-related behaviors, wandering onto elevated platforms and away from protective walls. When the anxiety cells were stimulated, the mice exhibited more fear behaviors even when they were in "safe" surroundings.

The discovery of the anxiety cells raises the possibility of finding treatments that target them and reduce anxiety. "We're looking to see if these cells are different molecularly from other neurons," says Dr. Hen. "If there's a specific receptor on the cells that distinguishes them from their neighbors, it may be possible to produce a new drug to reduce anxiety."

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