Hopkins Brain Wise
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JOHNS HOPKINS MEDICINE
FALL 2019

Esketamine: A New Approach for Patients with Treatment-Resistant Depression

One thing almost all psychiatrists can agree on," says psychiatry researcher **Adam Kaplin**, "is this: We need antidepressants that work more quickly and for more people."

Indeed, the serotonin selective reuptake inhibitors (SSRIs) that aim to strengthen the brain's circuits and neurotransmitters normally take seven to 14 days to begin to reduce symptoms. That delay poses an increased risk of suicide for people with treatment-resistant depression, says Kaplin.

Now, after three years of studying how the drug esketamine — a more potent form of ketamine — might relieve symptoms in these patients, Kaplin and his colleagues are hopeful. "What's really important about this drug," he says, "is that it's the first to work for treatment-resistant depression with immediate effect. It also appears to reduce suicidal ideation."

Kaplin's research, part of a multisite, international trial, investigated the biological basis of depression and usefulness of intranasal esketamine to treat it. Johns Hopkins will soon begin offering the FDA-approved intranasal treatment to patients with intractable depression in a supervised clinic setting (see sidebar).

Collectively, across all sites participating in the trial, the response rate was between 53% and 69% during the first month of treatment.

The reason esketamine is so effective, explains Kaplin, is that it's delivered not only through a different receptor, but via an ion channel — a much faster route to deliver a signal down the neuron highway of the brain. "It targets dozens of brain connections at once, not just one, and manipulates the neurotransmitter glutamate, which many neurons in the brain use to communicate with each other."

Ketamine is not without controversy. Classified as a schedule III controlled substance, it's an analog of phencyclidine (PCP) and became a popular party/club drug, nicknamed "Special K." But Kaplin is quick to defend its reputation.

He notes that in 1970, the FDA approved ketamine for use as an anesthetic in pediatric and adult surgeries because of its high level of safety and immediate response. Used in the recent rescue of 12 young boys and their soccer coach from a flooded cave in Thailand, the drug is listed on the World Health Organization's list of essential medicines.

"Ketamine has a vital role in surgery," says Kaplin, "and the findings in our trials in patients with treatment-resistant depression have been encouraging." In these studies, he notes, the dose is significantly lower than club use or as an anesthetic.

The esketamine trials also suggest an anti-inflammatory effect, notes Kaplin, who serves as psychiatric consultant for the Johns Hopkins multiple sclerosis and transverse myelitis centers of excellence. "That's good news for my patients with MS and other autoimmune diseases," he says, pointing out that 50% of patients with MS suffer from depression. Suicide from depression is the third leading cause of death in patients with MS across their lifespan.

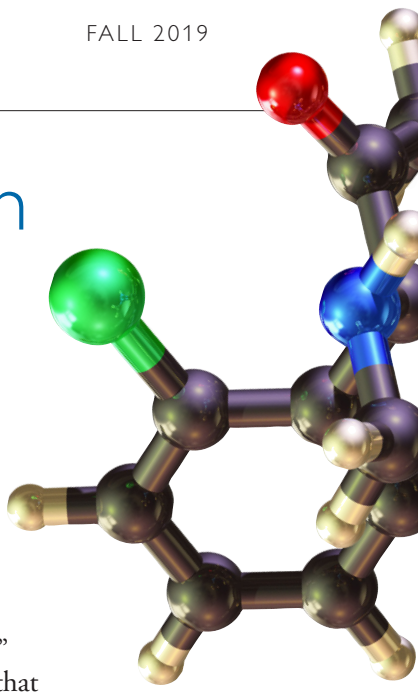


Illustration of a ketamine molecule.

So far, Kaplin says, electroconvulsive therapy has offered the best approach for treatment-resistant psychotic depression. But it's not without side effects. These include confusion, memory loss, nausea and headaches. Ketamine, too, has possible side effects, including mild nausea, dizziness and confusion, but patients are closely observed for at least two hours after treatment to ensure their safety, after which the side effects are gone.

Seeing the positive effect of esketamine on patients, says Kaplin, "has been like watching the World Cup. It's kind of an end goal for us: It's not perfect, but for patients who don't respond to other treatments, esketamine can provide immediate relief from despair." ■

"Unlike other antidepressants, esketamine targets dozens of brain connections at once."

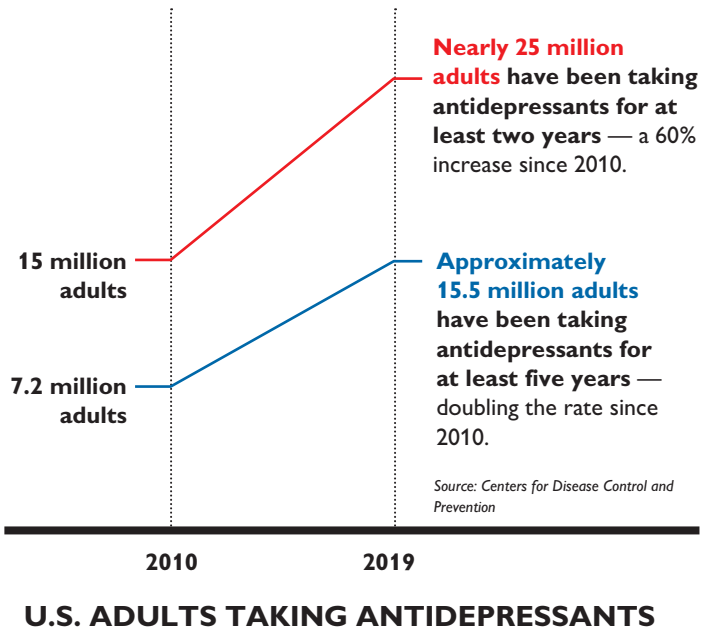
— ADAM KAPLIN

Johns Hopkins Esketamine Clinic Among First in the U.S.

Soon patients with treatment-resistant depression may be eligible to receive esketamine nasal spray treatments.

- The treatment is for patients with at least two failed antidepressant regimens.
- Each nasal spray container provides exactly two doses.
- Administration is medically supervised.
- Patients are monitored by a health care provider for at least two hours.
- Each patient is informed about serious adverse outcomes and need for monitoring.
- Patients are enrolled in a registry to further characterize risks and support.
- Esketamine is used alongside an antidepressant.

To learn more: 410-502-0622



U.S. ADULTS TAKING ANTIDEPRESSANTS

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

Of Grants, Innovation and Clinical Support

As the leaves turn toward brilliant colors, I thought I'd let you know about some things that are turning out well in the department. In the research arena, the hottest areas for federal funding are the opioid crisis and Alzheimer's disease. So, it's not surprising that our biggest recent grants involve the opioid field, with three federal grants worth a total of $16 million. They will cover areas such as better ways to use buprenorphine and strategies to treat withdrawal so that patients in detox stick with it rather than drop out.

A major National Institutes of Health grant also came in for Alzheimer's disease, to psychologist **Quincy Samus**, to fund MEMORI (Making Engagement Meaningful Through Organized Routine Interaction) Corps — a novel way to support dementia patients and their caregivers in the home environment.

We also received private grant funding of $17 million to create the Johns Hopkins Center for Research on Psychedelics and Consciousness, led by professor **Roland Griffiths**. This will allow us to initiate projects examining the potential of psilocybin to treat conditions such as anorexia nervosa and post-traumatic stress disorder.

On the education front, *U.S. News & World Report* has a new ranking of medical schools for their educational quality in psychiatry, and we come in at #2 in the country. This is a wonderful validation of the caliber of our program, which will be further strengthened by a substantial gift to enhance opportunities on the clinician-educator track within the residency.

The big clinical news is that the school of medicine has created a clinical faculty track. Johns Hopkins has always had only a single track throughout its 125 years, and we were the last medical school to maintain that approach. The new track gives us greater opportunity to reward clinically oriented faculty, which should help with recruitment and retention. This is a very positive turn of events for our department, especially given that clinical excellence has always been central to our identity. The response of many of our leading faculty: "Brilliant!"

Lab Studies Dive Headfirst into Pathways Touched by Schizophrenia

A series of complementary studies that Johns Hopkins psychiatrist **Thomas Sedlak** and colleagues completed on animals and people sheds light on a potentially novel approach for schizophrenia treatment targeting metabolic pathways in the brain. The studies further characterized the chemical imbalances in the brains of people with schizophrenia relating to the antioxidant glutathione, and they showed that using sulforaphane — a natural compound derived from broccoli sprouts — can tweak glutathione levels.

A January 2019 study in *JAMA Psychiatry* demonstrated that people with psychosis averaged 4% less of the neurotransmitter glutamate (a building block of glutathione) and 3% less glutathione in the brain, compared with healthy controls. A February 2019 study in the *Proceedings of the National Academy of Sciences* showed that glutamate neurotransmitter could be derived from the antioxidant molecule glutathione. Sulforaphane was also found to turn on a gene that increased glutathione in rat neurons. A third pilot study, in the April 2018 issue of *Molecular Neuropsychiatry*, found that healthy volunteers who took sulforaphane capsules for a week had a 30% rise in glutathione levels in their white blood cells, with smaller increases suggested in the brain.

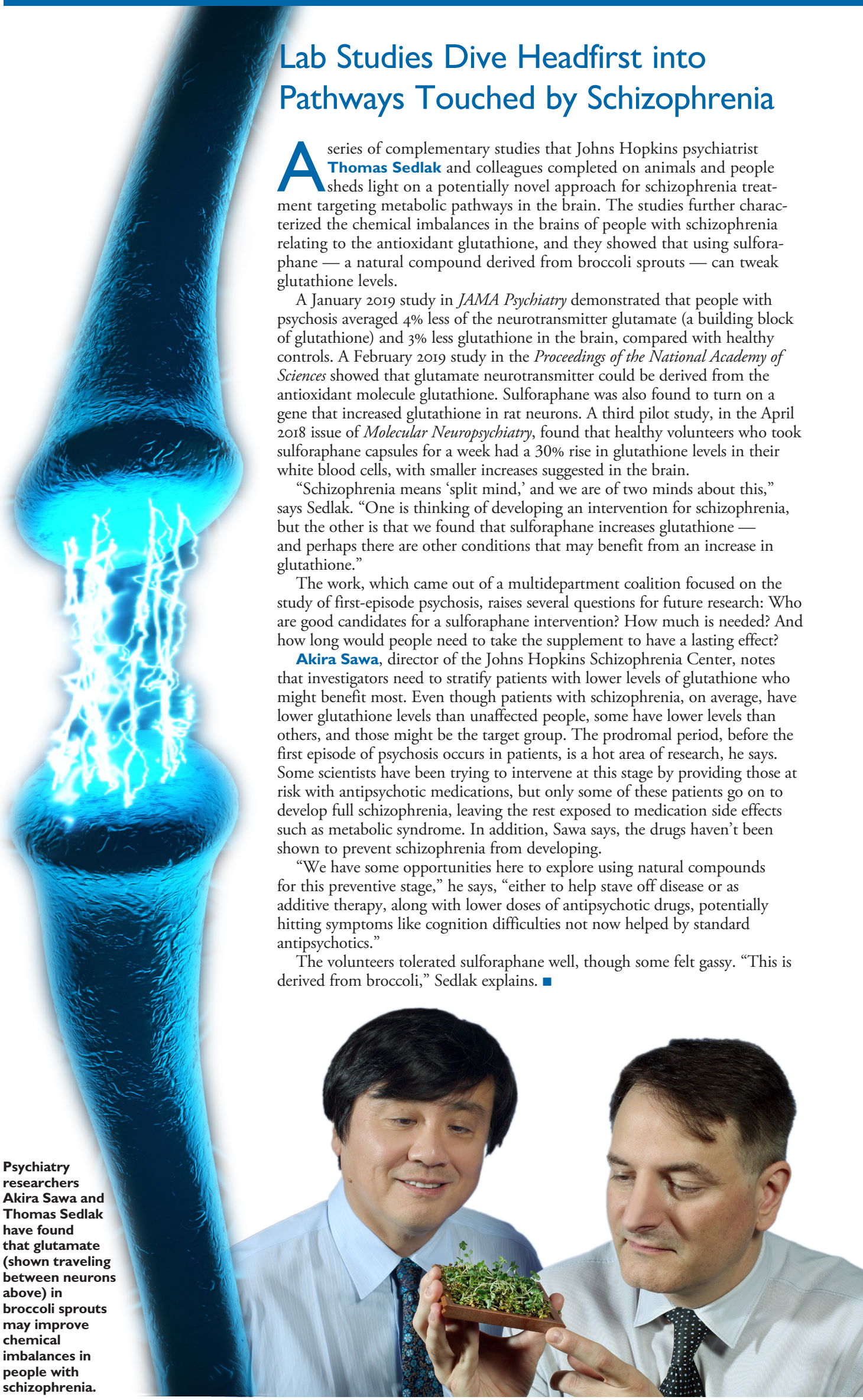
"Schizophrenia means 'split mind,' and we are of two minds about this," says Sedlak. "One is thinking of developing an intervention for schizophrenia, but the other is that we found that sulforaphane increases glutathione — and perhaps there are other conditions that may benefit from an increase in glutathione."

The work, which came out of a multidepartment coalition focused on the study of first-episode psychosis, raises several questions for future research: Who are good candidates for a sulforaphane intervention? How much is needed? And how long would people need to take the supplement to have a lasting effect?

Akira Sawa, director of the Johns Hopkins Schizophrenia Center, notes that investigators need to stratify patients with lower levels of glutathione who might benefit most. Even though patients with schizophrenia, on average, have lower glutathione levels than unaffected people, some have lower levels than others, and those might be the target group. The prodromal period, before the first episode of psychosis occurs in patients, is a hot area of research, he says. Some scientists have been trying to intervene at this stage by providing those at risk with antipsychotic medications, but only some of these patients go on to develop full schizophrenia, leaving the rest exposed to medication side effects such as metabolic syndrome. In addition, Sawa says, the drugs haven't been shown to prevent schizophrenia from developing.

"We have some opportunities here to explore using natural compounds for this preventive stage," he says, "either to help stave off disease or as additive therapy, along with lower doses of antipsychotic drugs, potentially hitting symptoms like cognition difficulties not now helped by standard antipsychotics."

The volunteers tolerated sulforaphane well, though some felt gassy. "This is derived from broccoli," Sedlak explains. ■



Psychiatry researchers Akira Sawa and Thomas Sedlak have found that glutamate (shown traveling between neurons above) in broccoli sprouts may improve chemical imbalances in people with schizophrenia.

Low-Cost Intervention Reduces Risk of Opioid Overdose

Kelly Dunn and colleagues Cecilia Bergeria and Andrew Huhn have developed an online, self-paced tutorial that improves knowledge and reduces risky behaviors around opioids. It emphasizes risk factors for and symptoms of overdose and explains what to do when an overdose happens.

Psychiatry associate professor and researcher **Kelly Dunn** is taking aim at a serious problem: the opioid overdoses that claim about 130 American lives every day.

We saw a gap in the way people were thinking about addiction and overdose," says Dunn, who has been studying the opioid epidemic since 2011. Until now, she says, much of the prevention effort has focused on people who use opioids illegally and not on patients treated for pain.

What's more, she says, prevention "was really about giving (overdose-reversing medication) naloxone, but there was little available to empower people to prevent them from getting to the point of overdosing and needing it."

Now, Dunn and colleagues **Cecilia Bergeria**, postdoctoral fellow in the Behavioral Pharmacology Research Unit; and **Andrew Huhn**, assistant professor of psychiatry, have created an intervention they believe can prevent some of those overdoses from happening in the first place.

They developed an online, self-paced tutorial about opioids, risk factors for and symptoms of overdose, and what to do when someone overdoses. The intervention improves knowledge and reduces risky behaviors — such as mixing opioids with alcohol or taking them when alone — among pain patients as well as those who use the drugs illegally.

With just a few words each on 33 slides, the intervention provides straightforward information and dispels potentially deadly misconceptions, such as the popular myth that injecting someone with saltwater will stop an overdose.

A study, authored by Bergeria, Dunn and Huhn, in the journal *Preventive Medicine,* examines the effects of web-based interventions on three groups of opioid users: people who are prescribed opioid medication for acute pain, patients prescribed opioids for chronic pain and people without pain who take opioids illicitly.

The research shows that the intervention is effective for all three groups. What's more, all three showed improved opioid knowledge immediately, as well as 30 days later. The researchers found that the acute pain group had the least opioid knowledge before the intervention.

The authors say their investigation is the first to show "meaningful and sustained increases in opioid overdose knowledge and to simultaneously target three unique populations of people exposed to opioids who may be at heightened risk of overdose."

They are now working to make the intervention available to clinicians and patients. "We like this approach because staff members are very busy and don't necessarily know how to teach interventions," says Dunn.

The study also looked at two formats for the intervention: a "mastery" style, with periodic quizzes that require correct answers in order to continue; and a "presentation" style, without the quizzes.

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New Psychiatry Residency Tracks: **More Mentorship and Career Development**

Since its 1913 origins, Johns Hopkins' Department of Psychiatry and Behavioral Services has been known for providing trainees with a clinically rigorous program and cutting-edge academic opportunities. The department has trained leading psychotherapists such as **Irving Yalom** and eminent neuroscientists like **Solomon Snyder**. But a changing landscape because of factors such as medical documentation demands has meant less time for residents to pursue scholarly efforts and career development.

Education leaders felt it was time for a change.

Starting this academic year, the psychiatry residency program will offer four scholarly tracks with dedicated faculty mentors: public mental health, led by **Jin Joo**; child psychiatry, by **Esther Lee** and **Hal Kronsberg**; research, by **Christopher Ross**, **Kellie Tamashiro** and **Russell Margolis**; and clinician-educator, by **Karen Swartz**.

Residents will be given dedicated time each year to pursue independent activities: one month in the first year, two months during the second and third years, and seven months during the fourth year. The goal is for residents to develop an area of expertise and produce a scholarly product — such as a research paper or educational curriculum — by graduation. Each resident is paired with one or more mentors.

"We have tried to emphasize to applicants and residents that the first two years are exploratory," says **Graham Redgrave**, director for residency education. "We want them to meet a ton of people in the department, do a lot of reading and have a lot of short- and longer-term exposures to help them make decisions, so during the second two years they can start building toward a project."

A big part of the program is peer mentorship, he adds. As third- and fourth-year residents' projects come to fruition, those residents can help peers who are earlier in their training. Also built into the tracks are monthly meetings during which residents can meet faculty, discuss their interests and ongoing work, and receive feedback.

The program was rolled out during the 2018–2019 academic year, with interns given elective time. All four residency classes will have protected time for scholarship this academic year. Trainees have used the time to develop research projects, finish papers begun in medical school with the help of Johns Hopkins mentors, and pursue adolescent mobile treatment, among other opportunities, Redgrave says.

"We've gotten a lot of very positive feedback," says **Jimmy Potash**, director of the psychiatry department. "The residents are really quite excited about it for all kinds of reasons. For one thing, they really like the closer mentorship experience with faculty. We want the residency to be a place where we train the future leaders in the field of psychiatry, and we see the tracks as a vehicle for helping make that happen." ■

Four new scholarly tracks offer dedicated mentorship for residents as they develop projects, says residency education director Graham Redgrave.

Low-Cost Intervention Reduces Risk of Opioid Overdose

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They found that the mastery format caused more participants to drop out, without leading to any advantage in improved knowledge as compared to the presentation format.

"The presentation version of this intervention may be of particular value because it is brief, user-friendly, well-accepted and recommended by participants, low-burden and scalable," the researchers wrote.

"It could have significant public health impact by reducing opioid overdose risk in people who are managing their acute or chronic pain with an opioid prescription, or who have no pain and are using opioids illicitly." ■

Access the intervention at **bit.ly/opioidEd**

"There was little available to empower people to prevent them from getting to the point of overdosing and needing naloxone."

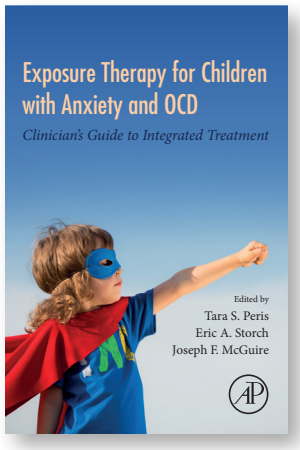
— KELLY DUNN

NEW BOOKS BY FACULTY

Exposure Therapy for Children with Anxiety and OCD
Clinician's Guide to Integrated Treatment
Edited by Tara Peris, Ph.D., Eric Storch, Ph.D. and Joseph McGuire, Ph.D.

Academic Press

Release date January 2020



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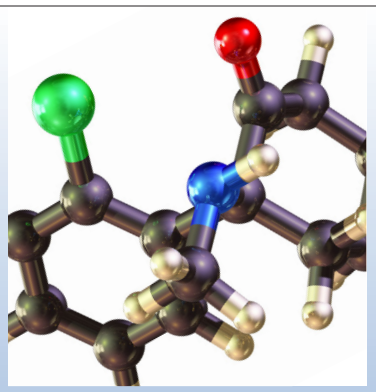

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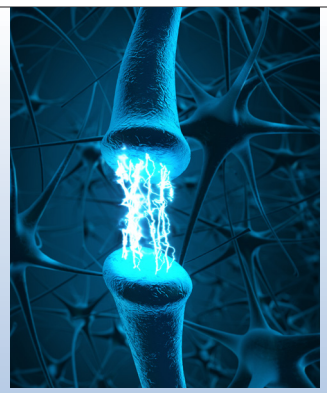

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