



Milestone Study Shows Psychedelic Treatment with Psilocybin Relieves Major Depression

Since the early 2000s, psilocybin — a legally restricted Schedule I drug with low toxicity in animals and people — has offered hope for people with intractable depression. Long considered controversial, the naturally occurring psychedelic compound found in so-called magic mushrooms, which evoke hallucinations and a profound change in consciousness, is gaining legitimacy as a safe and viable treatment when medically supervised.

Johns Hopkins Medicine psychiatric researchers have been at the forefront of psilocybin research. In 2016, they first reported that treatment with the compound under psychologically supported conditions significantly relieved severe anxiety and depression in people with a life-threatening cancer diagnosis.

Now, the findings of a small study of adults with major depression, published Nov. 4, 2020, in *JAMA Psychiatry*, suggest that psilocybin may prove effective in a larger population of patients with intractable depression than previously appreciated.

Roland Griffiths, founding director of the Johns Hopkins Center for Consciousness and Psychedelic Research, was both surprised and buoyed by the study's results. "Because there are several types of major depressive disorders that may result in variation of how people respond to treatment," he says, "I was surprised that most of our study participants found the psilocybin treatment to be effective."

Griffiths and his colleagues reported that two doses of psilocybin during medically supervised treatment — supplemented by supportive psychotherapy — produced rapid and large reductions in depressive symptoms. Most of the 24 participants showed improvement, and half of the study's members achieved remission through the four-week follow-up among participants with a long history of depression. The majority of them had experienced persistent symptoms for approximately two years before enrolling in the study. The average age of participants was 39, and 16 were women; 22 identified themselves as white, one person as Asian and one person as African American.

To ensure safe exposure to the experimental treatment, the participants had to taper off any antidepressants prior to the study — with the help of their

personal physician. Each treatment lasted approximately five hours, during which participants laid on a couch wearing eyeshades and headphones that played music, while in the presence of monitors.

Ultimately, of the entire group of 24 participants in the study, 71% showed a more than 50% reduction in depression symptoms at the four-week follow-up, and 56% were in remission at the four-week follow-up — meaning they no longer qualified as being depressed.

Griffiths points out that the major depression treated in this latest study may have differed from the "reactive" form of depression in patients in the 2016 cancer trial. He also says he and his team were encouraged by public health officials to explore psilocybin's effects in the broader population of those with major depressive disorder, "considering the much larger potential public health impact."

Griffiths is especially pleased by the study's outcome because his research on psilocybin — dating back to the early 2000s — was initially met with skepticism and concern for dangerous side effects, such as "bad trips" and hallucinations. Since then, dozens of startups and research labs have followed up with their own research and are actively working to develop marketable forms of psilocybin and related psychedelic substances.

The need for effective treatment for severe depression is greater than ever, adds Griffiths. According to the National Institute of Mental Health, more than 17 million people in the United States and 300 million people worldwide have experienced major depression. The condition puts them at high risk for suicide. A 2018 Centers for Disease Control report documented the number of suicide deaths in the U.S. that year at 48,344.

Griffiths and his colleagues continue to study the effects of psilocybin and other compounds, including esketamine, for a variety of psychiatric disorders at the first-of-its kind psychedelic research center, which opened in September 2019. In addition to expanding research for people with psychiatric disorders, he says the center works to increase studies in healthy volunteers, "with the ultimate aspiration of opening new ways to support human thriving." ■



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

Triumphs Amid the Pandemic

I want to welcome you to the winter 2021 edition of *Hopkins Brain Wise*. Like all of you, we continue to be very careful about COVID-19. Our outpatient services have converted largely to tele-mental health, which has been well received by many who like the ease of getting to their appointments, and our admitted patients are all COVID-tested before they come in to the hospital. In the face of the 2020 challenges, we were quite pleased to be named the #1 psychiatry department for clinical care in the 2020-21 *US News & World Report's* Best Hospitals ranking. The excitement around our new Psychedelic Center probably gave an additional boost to our reputation. But our fundamental strength rests on our comprehensive and systematic approach to patient care, rooted in the *Perspectives* framework.

A “viewpoint” appeared recently in *JAMA Psychiatry*, from academics at UCLA, positing the need for a way of thinking about psychiatric illness that goes beyond narrow disease-based reasoning, and they singled out our *Perspectives* approach as the forward-thinking path that will ultimately lead to better care for those with serious mental illness.

One of our areas of unique strength is our Women’s Mood Disorders Center, which has been featured on these pages in the past. Associate Center Director **Lauren Osborne** leads an effort to create a national curriculum in reproductive psychiatry, and Director **Jennifer Payne** has been chosen as president-elect of the International Marcé Society for Perinatal Mental Health, the world’s primary organization devoted to this area.

A year ago, we debuted a new center in the department, one focused on precision medicine for Alzheimer’s disease, led by **Kostas Lyketsos**. Recently, we were fortunate to be able to name it The Richman Family Center, in honor of the generosity and commitment of Arnie and Allison Richman, to help fulfill the promise of precision medicine for patients who suffer with Alzheimer’s, and their families. Hope remains at the heart of our mission.



Andy Angelino assists a nurse with donning personal protective equipment.

Creating an Inpatient Psychiatric Unit for Patients with Asymptomatic COVID-19

Last March, as the COVID-19 pandemic intensified in Maryland, several patients with psychiatric issues arrived at Howard County General Hospital’s emergency department and tested positive for the virus. Others in the same predicament had already been admitted to inpatient medical units.

The spike in psychiatric admissions was hardly surprising, says **Andrew “Andy” Angelino**, director of psychiatry at Howard County General — a member hospital of Johns Hopkins Medicine. “After all,” he says, “patients with mental illness may live in group homes, shelters and correctional facilities, where close contact and inadequate infection control are common.”

Yet the idea of closing or significantly changing inpatient psychiatry services, or treating such inpatients in medical units, “was unacceptable to us,” recalls Angelino. “Instead, we sought to preserve our established methods of teaching patients to practice new thoughts and skills, while finding a way to monitor symptoms and reduce the threat of contagion.”

“We were faced with a major challenge,” he said. “Our psychiatry leadership team was meeting daily and trying to find a place to care for these very vulnerable people.”

Fortuitously for Angelino and the department, a vacated former 20-bed psychiatric unit presented an opportunity. He and his staff fast-tracked a plan to renovate the area and make it available for up to six patients, following infection control regulations. Still, Angelino recognized the challenges these patients presented. He knew he needed to act swiftly to contain the spread of disease while supporting patients emotionally.

Unable to find a precedent for such a unit in U.S. hospitals, Angelino and his colleagues sought guidance from psychiatrist Mark Weiser, head of psychiatry of Sheba Medical Center, at Tel HaShomer, in Tel Aviv, Israel, who had recently set up a unit for SARS-CoV-2-infected patients with mental illness.

Drawing from Weiser’s experience, Angelino mobilized his team, which includes four psychiatrists, two nurses and a psychiatric nurse practitioner. By April 21, 2020, the

Howard County General inpatient psychiatric unit for asymptomatic COVID-19 patients was up and running. The unit also accepted patients from across the health system’s four other regional hospitals, and then began receiving referrals from hospitals across Maryland.

In a recent article published in *Psychosomatics*, Angelino and his colleagues describe what it took to set up and run the unit. The unit was made into a complete negative pressure space, allowing patients to freely roam the halls and spend time in common areas, behaviors that psychiatry recognizes as “normalizing,” says Angelino. “We emphasize rehabilitation toward normal daily behaviors, like eating in a common area, group activity and such.”

Typically, “We see one to five patients a day,” says Angelino. “Most have very mild COVID-19 symptoms. Zoom group sessions are incorporated into the day. And we have activities and snacks.” Some patients stay until their COVID quarantine is over — about two weeks. Others go home to quarantine, or are discharged to quarantine facilities, such as the Baltimore Convention Center, once psychiatrically stable.

Challenges remain. For many people with psychiatric illnesses, such as depression, group therapy is a given. But personal isolation forbids it. In addition, patients with severe psychosis and mania are vulnerable to inappropriate behaviors and disregard for rules, such as those related to wearing a mask or hand-washing.

But perhaps the greatest hurdle in caring for these patients, says Angelino, is trying to help them understand why they were admitted to this unit in the first place. Most don’t have COVID-19 symptoms, or they’re mild. They simply tested positive for the virus. “Patients aren’t shy about complaining: ‘We don’t have anything wrong with us! Why are we here?’”

Despite the new unit’s success, Angelino expresses concern about scores of other people with mental health problems contracting COVID-19. “Psychiatric patients are vulnerable,” he says. “Unfortunately, many are in jail or shelters — the worst-case scenario is such crowded conditions. You just have to *breathe* to get COVID-19.” ■

A Text-Message Intervention for Patients with Schizophrenia

Sending daily text messages to patients with schizophrenia and related conditions could help identify early warning signs of relapse and promote medication adherence, a Johns Hopkins pilot study shows.

“Patients who are developing schizophrenia are now younger and growing up with technology, and may expect there would be some type of technology intervention available,” explains **Bernadette Cullen**, director of the Community Psychiatry Program. To that end, she and her colleagues developed the Texting for Relapse Prevention Program (T4RP) as a means of providing additional outreach to patients with schizophrenia and schizoaffective disorders who were already comfortable using their cell phones for text messages.

Providers participating in the program opted for text messaging over mobile applications because some patients with these disorders have cognitive difficulties, and the applications can be trickier to use. Then, during focus groups, patients asked for inspirational quotes to be part of the intervention, and providers wanted medication reminders included.



“Patients who are developing schizophrenia are now younger and growing up with technology, and may expect there would be some type of technology aid.”

— Bernadette Cullen

In a six-month study, about 40 patients were randomly assigned to receive text interventions or usual care. Those in the intervention group, working with their providers, identified their

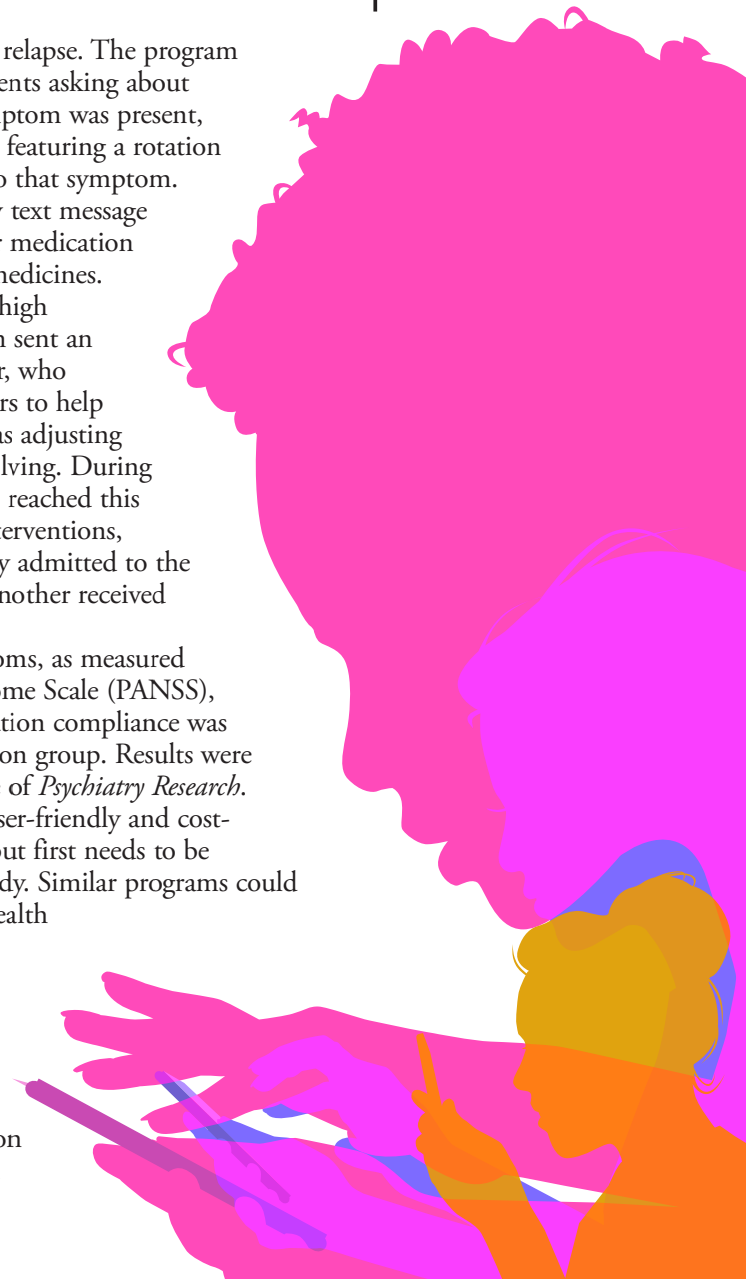
top-five early-warning symptoms of relapse. The program then sent daily text messages to patients asking about one of their five symptoms. If a symptom was present, the patient received a follow-up text featuring a rotation of coping skill suggestions specific to that symptom. In addition, patients received a daily text message with either an inspirational quote or medication reminders, and information about medicines.

If a patient reached a predefined high threshold of symptoms, the program sent an email or text to the person’s provider, who contacted the patient within 24 hours to help with additional management, such as adjusting medication or help with problem-solving. During the study, only a handful of patients reached this threshold and received successful interventions, Cullen says. One patient was quickly admitted to the intensive outpatient program, and another received help managing social stressors.

After six months, positive symptoms, as measured by the Positive and Negative Syndrome Scale (PANSS), were significantly lower, and medication compliance was significantly higher in the intervention group. Results were published in the July 29, 2020, issue of *Psychiatry Research*.

T4RP has the potential to be a user-friendly and cost-effective intervention, Cullen says, but first needs to be validated in a larger, multicenter study. Similar programs could be designed for additional mental health conditions such as depression and bipolar disorder, she says.

“The study demonstrates that patients are willing to engage in this type of program,” Cullen says. “It appeared to help with their recovery; it increased their medication adherence; and they felt empowered by it.” ■



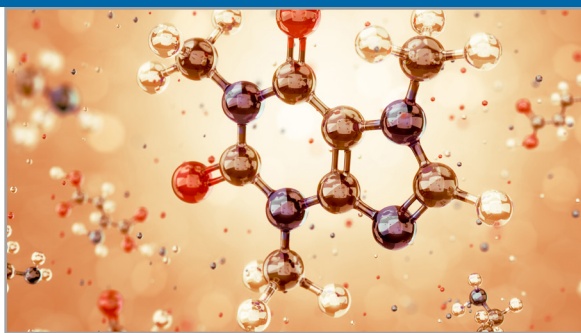
RESEARCH

New Insight into Caffeine Use Disorder

Mary “Maggie” Sweeney wants to make one thing clear: She has no intention of convincing people to give up their coffee or favorite caffeinated beverage. That said, the psychiatry researcher at Johns Hopkins Bayview Medical Center’s Behavioral Pharmacology Research Unit feels compelled to raise awareness about caffeine’s potential to cause distress.

Building on a long-running grant project in collaboration with **Roland Griffiths**, psychiatry researcher, a recent study on caffeine use disorder revealed responses to questions about caffeine use that Sweeney says were eye-opening and complementary to clinical trials conducted at Johns Hopkins — one in 2016 and one in 2019. The *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)* recognized caffeine use disorder as “a condition for further study.”

Caffeine use disorder is a problematic pattern of caffeine consumption characterized by a persistent desire to cut down or control use of the substance along with unsuccessful efforts to do so,



The molecular structure of caffeine.

despite problems caused or worsened by caffeine. Significant withdrawal symptoms or use of the drug to relieve or avoid withdrawal are also characteristics of the condition.

Sweeney, Griffiths and colleagues conducted the online research survey with 1,006 caffeine-consuming adults from across the U.S. Data were collected by an online survey panel aggregator used in other peer-reviewed research studies. The goal was to better understand caffeine use disorder’s prevalence and clinical significance in the general population.

Milligrams of caffeine per serving were calculated using typical milligrams per ounce for brewed/drip coffee (200 mg/12 oz.); brewed tea (40 mg/6 oz.); and soft drinks (40 mg/12 oz.). Total caffeine intake in a typical week from all sources was summed

and divided by seven to estimate daily caffeine consumption. To qualify for the study, participants needed to report consuming some caffeine-containing beverage or supplement in a typical week.

The researchers found that 8% of the sample fulfilled *DSM*-proposed criteria for caffeine use disorder when the structured caffeine use disorder interview questions were adapted to the online survey format.

“What I find fascinating,” says Sweeney, “is how little people think about coffee or other caffeinated drinks as stimulants. Although for many people consumption of caffeine is benign, we learned from our study that there is a small but important subset of caffeine consumers who report that caffeine has interfered with their lives in clinically meaningful ways.”

People who met criteria for caffeine use disorder reported problems such as insomnia, gastrointestinal troubles and anxiety, which were caused by or exacerbated by caffeine. The study also found that participants who met criteria for caffeine use disorder tended to consume more caffeine, and were younger and more likely to be cigarette smokers. A larger sample or sample with

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New Insight into Caffeine Use Disorder

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greater substance use history may be necessary to detect the association between caffeine use disorder and other substance use.

About 90% of adults in the United States use caffeine regularly, says Griffiths, and their average consumption exceeds 200 milligrams of caffeine per day — more caffeine than is contained in two 6-ounce cups of coffee, or five 12-ounce cans of soft drinks.

This latest research study, notes Sweeney, is the most thorough evaluation to date of the prevalence and clinical significance of caffeine use disorder. These data complement results from their recent clinical trial, which showed that people seeking treatment for caffeine reduction were able to reduce their caffeine consumption and decrease their

symptoms following the study intervention.

“In our clinical trial, our hypothesis was that people who have had trouble cutting back on caffeine on their own may be able to reduce their caffeine consumption with our guidelines to cut back over several weeks,” says Sweeney. “We also thought this could help people reduce their caffeine-related distress, such as withdrawal symptoms or consuming more caffeine than they intended.”

In both the online survey study and clinical trial, it was common for participants who met criteria for caffeine use disorder to report withdrawal symptoms from caffeine that reduced their function. Caffeine withdrawal symptoms can include headache, fatigue and irritability, which tend to peak at 24 to 48 hours after stopping caffeine, but can last for as long as 10 days in some individuals.

Prior research has also revealed that caffeine can result in withdrawal symptoms following cessation of much lower doses than previously thought. A

6-ounce cup of regular coffee delivers 100 milligrams of caffeine. Even this small amount of caffeine can cause withdrawal symptoms in some people when they stop using it regularly. Other studies have shown that caffeine doses as low as 10–20 milligrams are psychoactive.

The researchers acknowledge that caffeine can have positive health effects, such as reducing the risk of type 2 diabetes and boosting some aspects of cognition. “I want to be clear that caffeine isn’t all good or bad,” says Sweeney. “We’re not arguing that everyone needs to cut back on their consumption. A moderate amount of caffeine — up to 400 milligrams/day (about two 12-ounce cups of coffee) — is not generally associated with negative health effects. But, caffeine reduction is a good goal if caffeine causes significant impairment through withdrawal symptoms or by worsening an underlying problem, such as insomnia or anxiety.” ■

Hopkins **BrainWise**

This newsletter is published for the Department of Psychiatry and Behavioral Sciences by Johns Hopkins Medicine Marketing and Communications. 901 S. Bond St., Suite 550 Baltimore, MD 21231

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Department of Psychiatry and Behavioral Sciences

James “Jimmy” Potash, M.D., M.P.H.
Director

Marketing and Communications

Suzanne Sawyer, Senior Vice President,
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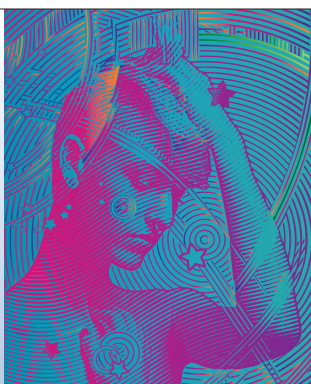
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Hopkins **BrainWise** WINTER 2021

THE NEWSLETTER OF THE JOHNS HOPKINS DEPARTMENT OF PSYCHIATRY AND BEHAVIORAL SCIENCES



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