Q&A: Can weight loss drugs help in addiction treatment?

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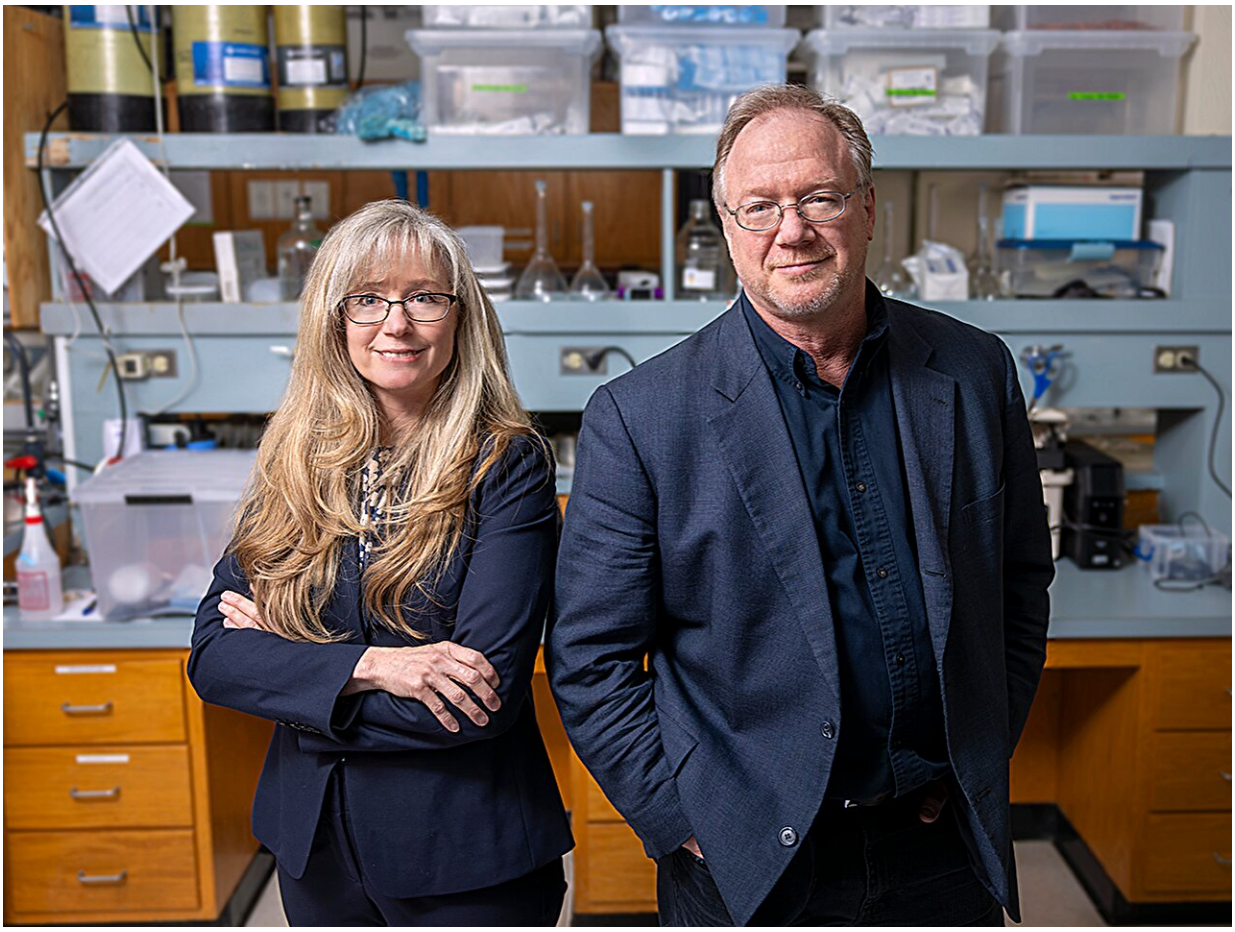

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In recent years, the popularity of drugs like Ozempic and Wegovy has skyrocketed. While this new class of drugs, called GLP-1 receptor agonist drugs, are approved for use in diabetes and for weight loss, researchers have found that they might help with other conditions too, like cardiovascular disease and addiction. They've made such a splash that the journal *Science* named GLP-1 drugs the 2023 Breakthrough of the Year.

Among those investigating the potential of GLP-1 drugs for the treatment of addiction are Patricia "Sue" Grigson, professor and chair of the department of neural and behavioral sciences at Penn State College of Medicine, and Scott Bunce, associate professor in the department of psychiatry and behavioral health at Penn State College of Medicine.

In the United States, one person dies from an overdose every five minutes, according to the White House Office of National Drug Control Policy. Grigson and Bunce are among the first to investigate whether GLP-1 drugs could play a role in the treatment of opioid use disorder. In February, Grigson presented early results from a small clinical trial at the American Association for the Advancement of Science conference in Denver.

And the results, she says, look promising. Later this year, Grigson and Bunce plan to begin a larger clinical trial of a GLP-1 drug to treat opioid addiction in the outpatient setting.

Penn State News caught up with Grigson and Bunce to discuss their work.

There's a lot of buzz about drugs like Ozempic and

how they may be helpful for more than just weight loss. When did you start to think that they might have a role in addiction medicine?

Grigson: For decades people have thought about addiction as hijacking the brain's reward pathway. We started thinking about people's behavior and the lengths they will go to satisfy their need for their substance of choice. If it's a physiological need, we wondered if a drug that elicits satiety or fullness could be helpful. That led us to GLP-1 receptor agonists.

In our lab, we mostly look at opioid use disorder. We completed our first preclinical study in 2017. Since then, we've found that GLP-1 agonists work very nicely in preclinical models. We've found that they reduce relapse to heroin and fentanyl seeking whether elicited by cues, stress, or the drug itself and reduce heroin and fentanyl-induced seeking behavior in both male and female rats.

But we wanted to translate our data and study this in human participants. Scott and I joined forces and were awarded a grant from the NIH Heal Initiative. We started a small clinical trial in 2019.

You recently presented early findings from a study with participants in a residential treatment facility for opioid use disorder. Can you tell me about the study?

Grigson: This was a fully randomized, double blind, placebo-controlled trial with 20 participants. It was conducted at the Caron Treatment Centers, a residential treatment facility in Wernersville [Pennsylvania]. Half of the participants were given the GLP-1 drug liraglutide, and the

other half received placebo. All participants were given their choice of taking an approved medication for opioid use disorder, in this case, buprenorphine.

Bunce: Safety was an important consideration when we designed the study. It was important that we design it around a clinical setting with a medical center on-site.

What did you measure?

Bunce: Our hypothesis is that these drugs can reduce craving in individuals with an opioid use disorder, which will help them refrain from misusing opioids. Other investigators, like Lorenzo Leggio at the National Institute on Alcohol Abuse and Alcoholism (NIAAA), have been looking at the potential to use a GLP-1 drugs to reduce the misuse of other addictive substances, such as alcohol, for a number of years. But this is the first study to address this issue in opioids.

Measuring craving, however, can be a bit of a moving target, and difficult to capture. Using a methodology known as ecological momentary assessment, or EMA, we asked participants to use a smartphone app to gather in-the-moment data four times a day. In those real-time surveys, participants reported not only on craving, but also on their moods, stress, nausea, sleep, fatigue and pain in that specific moment in time.

What did you find?

Grigson: We saw a 40% reduction in opioid craving among participants who were taking the GLP-1 drugs compared to those who received the placebo. It was a significant reduction, equivalent to the percent reduction in craving that Scott and his team have previously seen

following two weeks of intensive residential treatment at Caron.

The GLP-1 drugs reduced craving beginning with the lowest dose of liraglutide, even when patients were reporting high levels of stress. Those on placebo usually experienced an increase in craving in the afternoon or evening. Our data showed that craving among those who were on liraglutide stayed flat.

Bunce: Patients have told me that it slows down their need for immediate gratification of their craving, allowing them to make better—and healthier—decisions. It's like craving food. Most of us have had days when we craved pizza or chocolate. One way this medication appears to work is to minimize that drive, allowing you to slow down and make a healthy choice.

But there is still a lot that we do not know. In no way are we saying, "take this medicine and you will not need a medication for opioid use disorder, such as buprenorphine or methadone." It is possible, but there is not enough evidence to support that approach at this time.

What's next for your work?

Grigson: We're really encouraged. The data is promising but we have to see it in a larger clinical trial.

We're starting a larger outpatient study this summer or fall where we will recruit 200 people across three sites—Penn State's Pennsylvania Psychiatric Institute, New York University and the University of Maryland. Timothy Brick, associate professor in Penn State's College of Health and Human Development, and Jennifer Nyland, assistant professor in the department of neural and behavioral sciences at Penn State College of Medicine, will join the team as principal investigators.

This will be a randomized, placebo-controlled clinical trial, so we will evaluate participants taking the GLP-1 receptor agonist semaglutide, the medication that is in Ozempic and Wegovy, compared to those who will be on placebo. Because our preliminary data suggested that patients did better in the study if they were on both the GLP-1 drug and medication for opioid use disorder, in this study, half of the participants will be on methadone and half will be on buprenorphine for opioid use disorder treatment.

Each participant will be evaluated for three months. It will take approximately two years to collect data on 200 participants across the three sites.

There are some pluses with using semaglutide. First, it is a once-a-week injection, whereas liraglutide is once daily, so this may be more tolerable and less time-consuming for participants. Previous studies also have found that semaglutide has fewer gastrointestinal side effects.

Is the hope that the U.S. Food and Drug Administration (FDA) might approve these drugs for the treatment of opioid use disorder? If GLP-1 agonist drugs are already approved for human use, does that fast-track things?

Bunce: Yes. If we demonstrate that these medications are efficacious in reducing craving and the return to opioid use, it is a high priority for the National Institute on Drug Abuse (NIDA) to have the FDA approve these medications as a treatment for opioid use disorder. And certainly, a medication that has already been approved for use in humans is a huge time saver and one of the reasons we looked at these existing medications. Further, inclusion of the safety measures in the first study, even though they were burdensome, helped validate the safety of these

medications in individuals with an opioid use disorder.

Grigson: If our data show that it is safe and is saving lives, it might be possible to move it quickly through the FDA, but we will have to wait to see what will happen. We are hopeful.

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