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Is addiction the next frontier for GLP-1 receptor agonists?

Researchers are probing whether the blockbuster drugs that transformed obesity treatment could also quiet the brain's cravings for substances such as alcohol, nicotine and opioids. 

By [Natalie Healey](#)

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The clinical pipeline



Image credit: Denis Pobytov / DigitalVision Vectors / Getty

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have revolutionized the treatment of obesity and type 2 diabetes. Medicines such as semaglutide (Ozempic and Wegovy) and tirzepatide (Mounjaro/Zepbound) are remarkably effective at inducing substantial weight loss and improving markers of metabolic health. In addition to their metabolic effects, these medications act on other organs, including the kidney, liver and cardiovascular system.

Buoyed by these results researchers started looking at whether GLP-1RAs might also act on the brain. Retrospective studies suggested that semaglutide might have disease-modifying potential in early-stage Alzheimer's disease, but results from the first large-scale trials ([EVOKE/EVOKE+](#)) disappointed observers when 2-year trial data revealed no impact of semaglutide on disease progression. Now another possibility is capturing scientific attention: could these medicines reshape how addiction is treated?

From appetite to addiction

Hints emerged from the clinic and social media as soon as semaglutide and similar medicines became more widely used. Patients reported that their usual urge for alcohol and nicotine (as well as compulsive snacking) had dulled. [Animal research](#) suggests that GLP-1RAs seem to dampen drug-seeking behavior. “There’s close proximity between the GLP-1 receptors in the brain’s reward center and the fibers of the dopamine system. If you measure cocaine-induced dopamine increase in relevant areas, there’s a reduction when rodents are treated with GLP-1RAs,” says [Anders Fink-Jensen](#), a psychiatrist at the University of Copenhagen. But this mechanism seems to be more complicated in people, he cautions.

The human evidence thus far is most convincing for alcohol use disorder, he says, which kills an estimated [178,000 people](#) in the USA each year and is linked to liver disease, cardiovascular disease and cancer. Relatively few people who meet the criteria for alcohol use disorder seek or receive treatment (and [less than 2%](#) receive pharmacotherapy). In 2022, Fink’s team tested the older GLP-1RA compound exenatide on 127 participants with alcohol use disorder. Exenatide did not significantly reduce the number of heavy drinking days compared with placebo. Still, [medical imaging](#) showed it did reduce activity in crucial brain areas associated with drug reward and addiction, suggestive of a possible role for similar drugs in treating substance-use disorder.

“The preclinical data, the pharmacoepidemiology data and the anecdotal evidence are all very encouraging not just for alcohol, but for other substances, including cocaine, amphetamine, nicotine and also opioids,” agrees [W. Kyle Simmons](#), a pharmacologist and physiologist from Oklahoma State University. “But what we really need are the gold-standard, placebo-controlled trials.”

Simmons is a principal investigator on the [STAR-T trial](#) (Semaglutide Therapy for Alcohol Reduction – Tulsa), one of two harmonized randomized, double-blind, placebo-controlled phase 2 studies coordinated with Lorenzo Leggio at the US National Institute

on Alcohol Abuse and Alcoholism. The two teams designed nearly identical protocols. “We realized that if we could have two sites in very different parts of the country doing largely the same thing, that would be very valuable,” says Simmons. His group has completed data collection and will verify biomarkers of alcohol intake before unblinding results.

They hope to build on encouraging data published in early 2025 from a trial of 48 adults with alcohol use disorder who were not actively seeking treatment. Researchers at the University of North Carolina, led by Christian Hendershot, [reported](#) in *JAMA Psychiatry* that weekly injections of semaglutide (compared with placebo injections) reduced alcohol cravings, drinking quantity and the frequency of heavy drinking days.

Results also showed that after treatment, those in the semaglutide group consumed lower amounts of alcohol in the laboratory, and [these effects were larger](#) than those typically seen with approved medications for alcohol use disorder, such as naltrexone or acamprosate. [Klara Klein](#), an endocrinologist at the University of North Carolina who co-led the work, says the clinical observations match what doctors were already hearing from patients: “People who start on these agents will just say ‘My desire to drink is much less.’”

Searching for mechanisms

Disentangling the possible therapeutic effect on addiction from these drugs’ impact on satiety and metabolism remains challenging. “The question is how much of this is simply people not wanting to eat and so they just have less room for alcohol, and how much is really a central dopamine effect?” Klein asks.

[Joseph Schacht](#), a clinical psychologist and neuroscientist at the University of Colorado Anschutz Medical Campus, outlines three possibilities for the mechanism by which GLP-1RAs might result in a desire to drink less. “First, these drugs restrict gastric motility; they make you feel full or slightly nauseous, which could simply reduce the intake of a

caloric substance like alcohol,” he explains. “Second, they may be affecting the brain’s motivation circuitry, dampening down the urge to do anything that feels rewarding. And third, they clearly reduce inflammation in the body, and possibly in the brain.” It is possible, he says, that elevated inflammation, perhaps caused by chronic alcohol use, is being lowered in a way that also reduces the urge to drink or enhances a person’s control over their behavior.

Whether GLP-1RAs could still be effective in people with a low body mass index (BMI) is becoming a focal point for the field, says Schacht. He is leading a [phase 2 trial](#) of oral semaglutide for alcohol use disorder, for which participants must be overweight, with a BMI of at least 25. “That’s a large part of the US population,” he notes, “but it is an interesting question in alcohol use disorder, because some folks are underweight.”

In Fink’s exenatide trial, Schacht adds, “the drug was not effective except in those with the highest BMI. To me, that suggests that there’s something about the weight-loss effect that is related to the propensity of the drug to reduce alcohol use.” Klein’s group is planning follow-up studies in leaner people and in treatment-seeking patients to determine whether reduced drinking persists when weight loss is not the desired effect.

Addiction-specific GLP-1RAs

Developing compounds that act mainly in the brain while minimizing metabolic effects could be a solution. Pharmaceutical companies are already exploring GLP-1 analogues that cross the blood–brain barrier more efficiently or combine GLP-1 signaling with other incretin pathways to better target dopamine circuits, says [Riccardo De Giorgi](#), a psychiatrist at the University of Oxford. “We kind of assume that they will have the same effects,” he says, “but I would not be surprised if we found out that they differ quite a bit.”

The biotech firm Altimune, headquartered in Gaithersburg, Maryland, is evaluating the dual agonist pemvidutide, which works by mimicking the effects of glucagon, as well as of GLP-1, in a dedicated [phase 2 trial](#) for alcohol use disorder. The study includes

about 100 participants with alcohol use disorder who are also overweight or obese. The US Food and Drug Administration has granted [Fast Track designation](#) to pemvidutide for this indication. If initial trials are positive, says Simmons, “I think there will be a lot of interest, and probably a lot more companies turning in that direction.”

Another question is what the eventual treatment model might look like. Would it be like diabetes, for which patients take the drug chronically, or would it be a short-term adjuvant used during early recovery to blunt cravings? “Nobody’s answered that yet, but it will have big implications for cost and access,” says Simmons. Also, addiction is a complex condition, which makes it unlikely that GLP-1RA drugs would replace behavioral therapy. “You want to give people all the resources you can. But as with obesity, some people will respond dramatically, and others won’t.”

Safety concerns are equally pressing. Off-label use has already outpaced the evidence for GLP-1RA use in addiction, says Klein, and many health experts are concerned about unregulated access. “We got so many emails from people asking, ‘Can you prescribe this for my loved one who’s drinking?’” she says. “We need to make sure people are safe. These are revolutionary therapies, but they have side effects, and we don’t yet know how to use them responsibly in this population.” For instance, alcohol is a leading cause of pancreatitis, and GLP-1RA medications can increase the risk for this too.

Beyond alcohol

Although the strongest evidence for GLP-1RA drugs in substance use so far relates to alcohol, researchers are also exploring their role in treating nicotine, opioid and stimulant addiction (Table 1). A [National Institute of Drug Abuse-funded phase 2 trial](#) will test tirzepatide for smoking cessation. [Early studies](#) suggest that GLP-1RAs might help people smoke fewer cigarettes per day while preventing the weight gain that often follows quitting. [Studies are also underway](#) testing semaglutide as an adjunct to buprenorphine or methadone treatment for opioid use disorder, as [research](#) using

electronic health records has found that people prescribed GLP-1RA drugs were less likely to experience an opioid overdose.

Clinical research on the potential link between GLP-1RAs and stimulants remains limited. [Marc Potenza](#), a psychiatrist and neuroscientist at Yale University, [tested exenatide](#) in people with cocaine-use disorder but did not see strong results. “But that does not preclude the possibility that different ligands or doses could modify such behavior,” he says. He also believes GLP-1RAs might have a role in treating non-substance addiction, including gambling disorder, for which there is currently no pharmacological treatment.

Despite the uncertainties surrounding the use of GLP-1RAs for addiction, the field is gaining clear momentum. Several phase 2 trials are expected to report soon, potentially clarifying whether GLP-1RA drugs can meaningfully reduce cravings or relapse in alcohol use disorder, and if they are successful, they could provide the first new pharmacological treatment for the condition in decades. But researchers remain careful not to oversell. “It’s fine to be optimistic,” De Giorgi says, “but we don’t want to get overexcited. The best thing we can do now is focus on understanding these medications mechanistically and clinically.”

Table 1 | Trials with GLP-1 receptor agonists for addiction disorders

Trial	Stage	Compound	Indication
NCT06015893 and NCT05891587	Phase 2	Semaglutide	Alcohol use disorder
NCT05892432	Phase 2	Semaglutide (oral)	Alcohol use disorder

Trial	Stage	Compound	Indication
NCT05895643	Phase 2 completed	Semaglutide	Alcohol use disorder
NCT06987513	Phase 2 recruiting	Pemvidutide	Alcohol use disorder
NCT06548490	Phase 2 recruiting	Semaglutide	Opioid use disorder

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