



Ozempic & Brain Health

A Breakthrough or Just Another Trend?

Unless you've been living under a rock lately, you've heard of Ozempic®.

You may think of it as a weight loss medication, but Ozempic is technically only approved for lowering blood sugar and reducing the risk of heart attack and stroke in people with Type 2 diabetes.

It's not your fault for thinking Ozempic is for weight loss. Off-label demand for it soared in 2022 when there were supply shortages of Wegovy®, an approved medication for treating obesity. Wegovy contains semaglutide, the same active ingredient found in Ozempic.

Semaglutide belongs to a class of medications called glucagon-like peptide-1 (GLP-1) agonists. Many celebrities, including Oprah Winfrey, Sharon Osbourne, Whoopi Goldberg, and Kathy Bates, have reported that GLP-1 drugs helped them achieve their weight loss goals.

Part of the success of these blockbuster drugs is that they don't just act on the gut; they also act on the brain.

Researchers are now investigating whether they may provide additional brain health benefits, such as helping people quit cigarette smoking and as a potential treatment for early Alzheimer's disease (AD).

GLP-1 & GLP-1 DRUGS

GLP-1 is an endocrine hormone produced in the small intestine in response to eating. It triggers the pancreas to release insulin, the hormone that allows your body to convert food to energy and lowers blood glucose levels.

GLP-1 produced in the gut communicates with receptors in the brain through the central nervous system. When GLP-1 binds to receptors in the hypothalamus, it activates neurons that promote feelings of fullness and inhibits neurons that produce hunger signals. Scientists have discovered the brain also makes GLP-1.

GLP-1 drugs mimic the GLP-1 hormone, binding to GLP-1 receptors and causing the same effects as natural GLP-1, including enhancing the release of insulin to lower blood sugar, inhibiting the release of glucagon, a hormone that raises blood sugar, delaying gastric emptying, and promoting satiety.

The U.S. Food and Drug Administration approved exenatide (Byetta®), the first GLP-1 drug for treating diabetes, in 2005. More recently, the drug class has expanded significantly

to include several others, such as liraglutide (Saxenda® or Victoza®) and tirzepatide (Mounjaro® for diabetes and Zepbound® for weight loss).

OBESITY IS A BRAIN DISORDER

Experts are increasingly regarding obesity as a brain disorder, not a failure of willpower or just a reflection of personal diet and exercise choices.

“Obesity is now considered a disease not of the intestines or your stomach, but of the brain. It’s a huge shift in the way that we think, with huge implications for treatment,” said Dr. Sanjay Gupta, CNN Chief Medical Correspondent, in his special report *Is Ozempic Right for You?* that aired on CNN in November 2024. “But these are still early days, and remember, at one time, even depression and addiction were seen as failures of willpower instead of a brain disease. Changing the perception of obesity – that’s going to take time.”

According to Obesity Canada, obesity is a chronic disease of the brain involving an imbalance in the regulation of energy intake and expenditure to maintain weight.

Complex and powerful interactions between genetic, environmental, behavioural, and social factors cause disruptions in the hypothalamus, the “control centre” deep in the brain that manages hunger, body temperature, heart rate, mood, sleep, and sex drive. The imbalance results in excess body fat that has a negative impact on physical and mental health, as well as quality of life.

GLP-1 DRUGS FOR PEOPLE WHO ARE OVERWEIGHT OR OBESE

The Oscar-winning actress Kathy Bates, 76, told *People* magazine she lost 80 pounds over seven years through diet and lifestyle changes and then used Ozempic to lose another 20 pounds. She was diagnosed with Type 2 diabetes in about 2017.

Like Ozempic, Wegovy is taken once weekly by injection. In the clinical trial that led to its approval for treating overweight and obesity in people without diabetes, Wegovy led to a 15% decrease in body weight (an average loss of 15.3 kg) compared to a drop of only 2.4% (or 2.6 kg) in people who took a placebo over 68 weeks.

The results of the international Phase 3 study, the STEP trial, were published in March 2021 in *The New England Journal of Medicine*.

Interestingly, 74% of the study participants were women.

Wegovy comes with some unwanted side effects. In the STEP trial, 74% of people taking the drug experienced gastrointestinal problems like nausea, diarrhea, vomiting, and constipation, compared with 48% in the placebo group. Most of these issues were mild-to-moderate in severity, with nausea being the most common, and mainly emerging during the dose-escalation period.

The study authors wrote, “Weight loss with semaglutide stems from a reduction in energy intake, which is thought to result from direct and indirect effects on the brain.” People who have taken semaglutide for weight loss have also reported the drug quiets persistent thoughts about what to eat, called “food noises.”

GLP-1 DRUGS FOR SMOKING CESSATION?

About a decade ago, while working as a nurse practitioner in a family practice, Dr. Luba Yamine prescribed GLP-1 medications to patients with Type 2 diabetes. She was surprised when some reported they were no longer craving cigarettes or quit smoking altogether.

GLP-1 DRUGS MAY INDEED HELP PEOPLE STOP SMOKING, ACCORDING TO A GROWING BODY OF EVIDENCE.

For example, semaglutide was associated with a lower risk of nicotine dependence compared to other medications for Type 2 diabetes in an analysis of patient records of 20,000 Americans. Conducted by researchers at the University of Oxford, the study was published in the journal *eClinicalMedicine* in July 2024.

Another study published a month later in *Annals of Internal Medicine* by researchers at Case Western Reserve University School of Medicine in Cleveland, Ohio, found that compared with some other medications for diabetes, semaglutide use was associated with a lower risk of healthcare visits related to tobacco use and fewer prescriptions for smoking cessation therapies and counselling appointments in patients with Type 2 diabetes who smoked at baseline.

These findings were similar for people with and without obesity, and most differences occurred within 30 days of starting the medication. ➔

In the U.S., 77.1% of men are overweight or obese compared to 69.4% of women. In Canada, the rates are somewhat lower at 70% for men and 61.5% for women in 2023.

A study by researchers at the University of Pennsylvania and Cedars-Sinai Medical Center in Los Angeles found that the number of people with overweight or obesity but not diabetes who started taking GLP-1 drugs in the U.S. grew by 700% from 2019 to 2023. Between 2011 and 2023, 60% of new users were women.

“These observational studies provided promising, albeit unproven, signals,” said Dr. Yammine, an associate professor in the Department of Psychiatry and Behavioral Sciences at McGovern Medical School at UTHealth Houston.

“We believe that GLP-1 drugs may help with smoking cessation in two primary ways: (1) by modulating the release of dopamine in the reward pathways of the brain and thereby reducing the motivation to smoke; and (2) by causing aversion via acting on the brain area called the habenula, resulting in unpleasant effects. For example, some patients have told me that after starting to take GLP-1 drugs, cigarettes became stale-tasting and smoking made them feel nauseated,” Dr. Yammine explained.

These effects are similar to quieting food noises and causing nausea in people taking GLP-1 drugs for overweight and obesity.

“ WE THINK THAT THE EFFECTS OF THESE DRUGS ON CONSUMING FOOD AND SUBSTANCES OF ABUSE ARE SIMILAR BECAUSE THE CENTRES IN THE BRAIN THAT ARE RESPONSIBLE FOR FOOD AND DRUG REINFORCEMENT OVERLAP.

Dr. Yammine conducted a pilot study of the GLP-1 drug exenatide in combination with a nicotine patch in 84 people who smoked and had prediabetes and/or were overweight.

Results showed that the treatment combination improved smoking abstinence, reduced withdrawal symptoms and cravings, and decreased post-cessation weight gain compared with the nicotine patch alone. The study results were published in *Nicotine & Tobacco Research* in April 2021.

“Studies show that 80% to 90% of individuals who quit smoking gain an average of five to 15 pounds of body weight by the end of the first year,” said Dr. Yammine. “About 14% gain more than 20 pounds, which may have negative health

consequences, such as new-onset Type 2 diabetes and other metabolic problems.”

“ WEIGHT GAIN ASSOCIATED WITH QUITTING SMOKING IS ALSO PROBLEMATIC BECAUSE IT MOTIVATES SOME PEOPLE TO RETURN TO SMOKING JUST TO MAINTAIN A LOWER BODY WEIGHT.

“While the fear of post-cessation weight gain is endemic among women who smoke, it is also a concern among men,” she added.

The pilot study results formed the basis for two Phase 2 trials led by Dr. Yammine: a study of exenatide opened in December 2022 at two sites in Houston and a study of semaglutide began April 2024 in Houston and Austin. The trials are evaluating these GLP-1 drugs in the context of smoking cessation in patients who are overweight or obese and/or have elevated blood glucose levels indicative of prediabetes.

In addition to examining whether GLP-1 agonists improve smoking and weight outcomes, the researchers are trying to understand *how* these medications work in the context of smoking cessation.

For example, participants in the exenatide study will undergo electroencephalography testing at the beginning of the study and after several weeks of taking the medication to assess for any changes in how the brain responds to smoking- and food-related images as a result of taking the medication.

“ If the research confirms that GLP-1 drugs are beneficial for smoking cessation and prevention of weight gain in those who quit smoking, that would be a game-changer for a whole lot of people.

SEMAGLUTIDE FOR EARLY ALZHEIMER'S?

Researchers are also studying semaglutide as a potential treatment for early AD and mild cognitive impairment (MCI).

“While the field has made much progress with new treatment options for people with Alzheimer's disease, the recently approved drugs for removing amyloid are not a home run. We need to cast a wide net and keep exploring other

treatment avenues,” said Dr. Carmela Tartaglia, Site Clinical Research Unit Medical Lead and Director of the Memory Clinical Trials Unit at Toronto Western Hospital, University Health Network, and associate professor in the Temerty Faculty of Medicine at the University of Toronto.

Researchers at Case Western Reserve University School of Medicine studied the association between GLP-1 drugs and a first-time diagnosis of AD in health records.

They found that semaglutide use was associated with a 40% to 70% lower risk of a first-time AD diagnosis compared to seven other diabetes medications, including insulin and other GLP-1 drugs. The findings held regardless of obesity status, gender, and age, suggesting semaglutide may have potential for preventing AD.

In their paper published in *Alzheimer's & Dementia: The Journal of the Alzheimer's Association* in October 2024, these authors noted that semaglutide has demonstrated it can reduce neurotoxicity caused by amyloid buildup, enhance the clearance of dead cells, improve brain glucose uptake, and reduce amyloid-beta plaques and tau tangles in preclinical studies.

“GLP-1 drugs work on receptors all over our bodies, including in the brain,” Dr. Tartaglia explained.

EMERGING EVIDENCE ALSO INDICATES SEMAGLUTIDE CAN REDUCE INFLAMMATION AND MAYBE IMPROVE DNA REPAIR, ADDING TO THE COMPELLING RATIONALE FOR STUDYING THEM IN THE CONTEXT OF EARLY ALZHEIMER'S.

At Toronto Western Hospital, Dr. Tartaglia is the principal investigator of two clinical trials testing whether semaglutide may improve cognition in people with early AD or MCI compared to taking a placebo. The hospital is one of 340 international locations participating in the Phase 3 studies, called EVOKE and EVOKE Plus.

Both trials compare oral semaglutide taken once daily to a placebo over a period of 173 weeks (about three years and four months) in adults aged 55 to 85. Eligible participants have a confirmed diagnosis of early AD or MCI, are amyloid positive, and scored 22 or higher on a Mini-Mental State Examination.

Dr. Tartaglia and her team are assessing study participants' cognitive function and their ability to function in daily life activities according to self-reports or reports from their study partner such as a spouse or care partner. They are also looking at the time to progression in AD or MCI disease stage, and inflammation as measured by C-reactive protein in the blood.

A new treatment to help people stop smoking would be a welcome advancement. Despite the fact the percentage of American adults who smoke declined from 42% in 1965 to about 12% in 2022 smoking remained the leading cause of preventable disease and death.

Canadian statistics show similar trends, decreasing from about 50% of adults smoking in 1965 to about 10% in 2020. Tobacco use is the leading modifiable risk factor for disease and death in Canada, according to the Canadian Cancer Society.

“One of the nice things about the EVOKE Plus study is that it includes people with cerebrovascular disease. These individuals are often excluded from Alzheimer's trials, but the two diseases frequently occur together,” said Dr. Tartaglia.

“*Semaglutide may attack the Alzheimer's pathology and also have a positive effect on the cerebrovascular pathology.*”

Dr. Tartaglia is cautiously optimistic about the potential of semaglutide for treating early AD and MCI. “The current pipeline of drugs that are being tested for Alzheimer's is very vast, targeting many different pathways,” she said. “GLP-1 drugs may show a benefit but we won't know until we see study results in 2025 or 2026. Until then, we're keeping an open mind.”

TIME WILL TELL

While obesity, tobacco use disorder, and AD continue to affect the lives of so many people, there is still much to learn about how GLP-1 drugs affect the brain and whether they will prove to be beneficial for these brain health issues. Mind Over Matter® is cautiously optimistic that the clinical research underway may lead to new approved treatments in the future. 🧠

FURTHER READING

Magic Pill: The Extraordinary Benefits and Disturbing Risks of the New Weight-Loss Drugs
by Johann Hari