In the Know

Gain Changers: New Generation of Weight Loss Medications

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Hosting the 95th Academy Awards, Jimmy Kimmel opened his monologue by saying, "Everybody looks so great! When I look around this room, I can't help but wonder, 'Is Ozempic right for me?'"

Semaglutide (Ozempic, Wegovy, and Rybelsus) is blowing up social media because it works (*Diabetes Obes Metab* 2017; 19:1242-51; *Lancet* 2018;392:637-64; *N Engl J Med* 2021;384:989-1002; *N Engl J Med* 2021;384:1066-7; *N Engl J Med* 2022; 387:2245-57; *Nat Med* 2022;28:2083-91; *Obesity* 2023;31:703-15; *JAMA* 2021; 325:1414-25). Patients on semaglutide typically lose 15% of their weight after a year of weekly injections. The weight loss is accompanied by reduced blood glucose and reduced HbA1c (uniformly demonstrated in all trials), improved cardiac function (*N Engl J Med* 2016;375:1834-44), improved renal function (*N Engl J Med* 2016;375:1834-44), improved liver function (*N Engl J Med* 2021;384:1113-24), reduced indicators of metabolic syndrome (*N Engl J Med* 2021;384:1113-24), and reduced all-cause mortality (*Lancet Diabetes Endocrinol* 2021;9:653-62). Secondary analyses of the published clinical trial data even suggest therapeutic efficacy in Parkinson's disease and Alzheimer's disease (*Pharm Res* 2022;39:1233-48; *Alzheimers Dement*. 2022;8:e12268)!

It seems to be too good to be true! However, the impressive list of references in leading medical and scientific journals documenting efficacy speaks to the sustained and highly reproducible benefits of semaglutide in treating obesity. The possibility of benefit in neurodegenerative diseases has not been demonstrated in a prospective randomized controlled trial with a primary endpoint of cognitive decline, but such studies are ongoing (asamonitor.pub/3Dmbas2).

Incretins are gastrointestinal peptide hormones induced by eating (asamonitor.pub/44wOOQA). Incretins promote insulin secretion and inhibit the secretion of glucagon. Scientists have long studied

incretins for the treatment of diabetes. The incretin of greatest interest has been the glucagon-like peptide-1 (GLP-1), a peptide comprising 30 or 31 amino acids secreted when food is consumed (asamonitor.pub/3pOx8AX). Not surprisingly, GLP-1 binds to the glucagon-like peptide-1 receptor, appropriately located on beta cells in the pancreas (regulating insulin) and the brain regions that control appetite. Drugs that target this receptor, mimicking the action of GLP-1, are called GLP-1 receptor agonists. GLP-1 receptor agonists increase insulin production, decrease glucagon production, and reduce appetite.

Semaglutide is one of several approved GLP-1 receptor agonists, a list that includes exenatide, liraglutide, albiglutide, dulaglutide, lixisenatide, and tirzepatide (Mounjaro®). The latter is also an agonist of the glucose-dependent insulinotropic polypeptide (mercifully abbreviated as "GIP") that lowers blood sugar after eating. In prospective randomized clinical trials, tirzepatide has been more effective than semaglutide in the treatment of diabetes and obesity (*N Engl J Med* 2021;385:503-15; *Diabetes Obes Metab* 2023; 1-8; *Int J Obes* 2023; 47:677–85; *Diabetes Ther* 2023;14:925-36). Tirzepatide may be cost-effective compared to semaglutide (*Diabetes Obes Metab* 2023;25:1292-1300). Currently, tirzepatide is only indicated for diabetes (asamonitor.pub/3OnEQvj). However, Lilly has received FDA fast track designation for approval of tirzepatide for obesity (asamonitor.pub/3pOEy7g), so we can anticipate Mounjaro blowing up social media in the very near future.

GLP-1 receptor agonists share common side effects. The most common are gastrointestinal symptoms, including nausea, diarrhea, vomiting, constipation, abdominal pain, dyspepsia, distention, burping, GERD, and flatulence. These are experienced by nearly half of the subjects in some trials. In several of the semaglutide trials, approximately 5% of the study subjects in the active arm discontinued therapy because the GI effects could not be tolerated. Fortunately (for everyone involved), these adverse events attenuated or completely disappeared within a month or two. It should be mentioned that recent news stories have uncovered cases of severe gastroparesis that may have resulted from or been exacerbated by Ozempic, but no scientific conclusions have been reached as of this publication date (asamonitor.pub/3rBFdJx). On June 29, the ASA Task Force on Preoperative Fasting released consensus-based guidance on the preoperative management of patients taking GLP-1 receptor agonists, which included recommendations to hold dosing up to a week before surgery (asamonitor.pub/3O9to4O)

GLP-1 receptor agonists share a black box warning about thyroid C-cell tumors because they cause thyroid tumors in rats. A case control study of 2,562 patients with thyroid cancer and 45,184 matched controls found a hazard ratio of 1.6 for thyroid cancer in patients treated with GLP-1 receptor agonists (*Diabetes Care* 2023;46:84-390).

Because GLP-1 receptor agonists delay gastric emptying, there is the possibility of aspiration risk in patients taking semaglutides (*Anaesthesia* July 2023). Regurgitation of large gastric volumes following anesthesia induction in a fasted patient on semaglutide has been recently documented (*Can J Anaesth* March 2023). Because these drugs are often given as weekly injections, reducing the risk of aspiration may require withholding them for a week or more prior to elective surgery (asamonitor.pub/3O9to4O).

The indirect mechanism of action for GLP-1 inhibitors would theoretically make hypoglycemia less likely than for drugs that directly decrease blood glucose levels. The risk of hypoglycemia in patients on GLP-1 receptor agonists – including semaglutide – is very low in clinical trials, approaching zero in randomized controlled trials for obesity where both active and control groups are not taking additional medications to reduce blood glucose (*Advances in Therapy* 2021;38:1470-82). As of this writing, hypoglycemia has not been documented during anesthesia in patients on GLP-1 receptor agonists.

The success of GLP-1 receptor agonists in treating obesity has led to additional research. As recently documented in Nature News, another generation of obesity medications is in development (*Nature* 2023;619:19). A problem with the existing GLP-1 receptor agonists is that they are peptides that must be given by injection. Orforglipron is a nonpeptide GLP-1 receptor agonist that can be given as a daily oral tablet. Randomized controlled trials demonstrate efficacy similar to semaglutide (*N Engl J Med* June 2023; *Lancet* 2023:S0140-6736).

The peptide retatrutide is a "triple agonist," binding the GLP-1, GIP, and glucagon receptors. A phase 2 study recently published in the *New England Journal of Medicine* demonstrated 24% weight loss at one year – an astonishing result (*N Engl J Med* June 2023).

Obesity is a global health concern, estimated to affect more than 40% of the U.S. population including more than 17% of children and adolescents (*J Obes* 2022;2022:7652408; *Mol Diagn Ther* 2020;24:653-63). Obesity is a cause of major health care disparities, disproportionately affecting minorities and lower socioeconomic groups (*Curr Diab Rep* 2015;15:95). Obesity increases the risk of diabetes, cardiovascular diseases, certain cancers, sleep apnea, osteoarthritis, and mental health conditions (*Sensors (Basel)* 2020;20:2734; *Comput Biol Med* 2021;136:104754). It is also a risk factor for surgical complications and increased hospital stays (*BMJ Open Diabetes Res Care* 2016;4:e000200). In the United States, obesity has been estimated to account for $147 billion in additional health care expenses and lost productivity (*Diabetes Metab Syndr Obes* 2010;3:285-95).

The high cost of GLP-1 receptor agonists must be weighed against the health care and economic costs of obesity. GLP-1 receptor agonists are currently primarily used in patients whose diabetes cannot be managed with generic medications. However, from what we know now, the efficacy of these drugs, documented in both the peer-reviewed literature and publicized on social media, will increasingly draw attention to their benefits. Given the personal and societal costs of obesity, we will increasingly see these drugs in our patients.

So, yes, Jimmy Kimmel, Ozempic might be right for you. ■

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