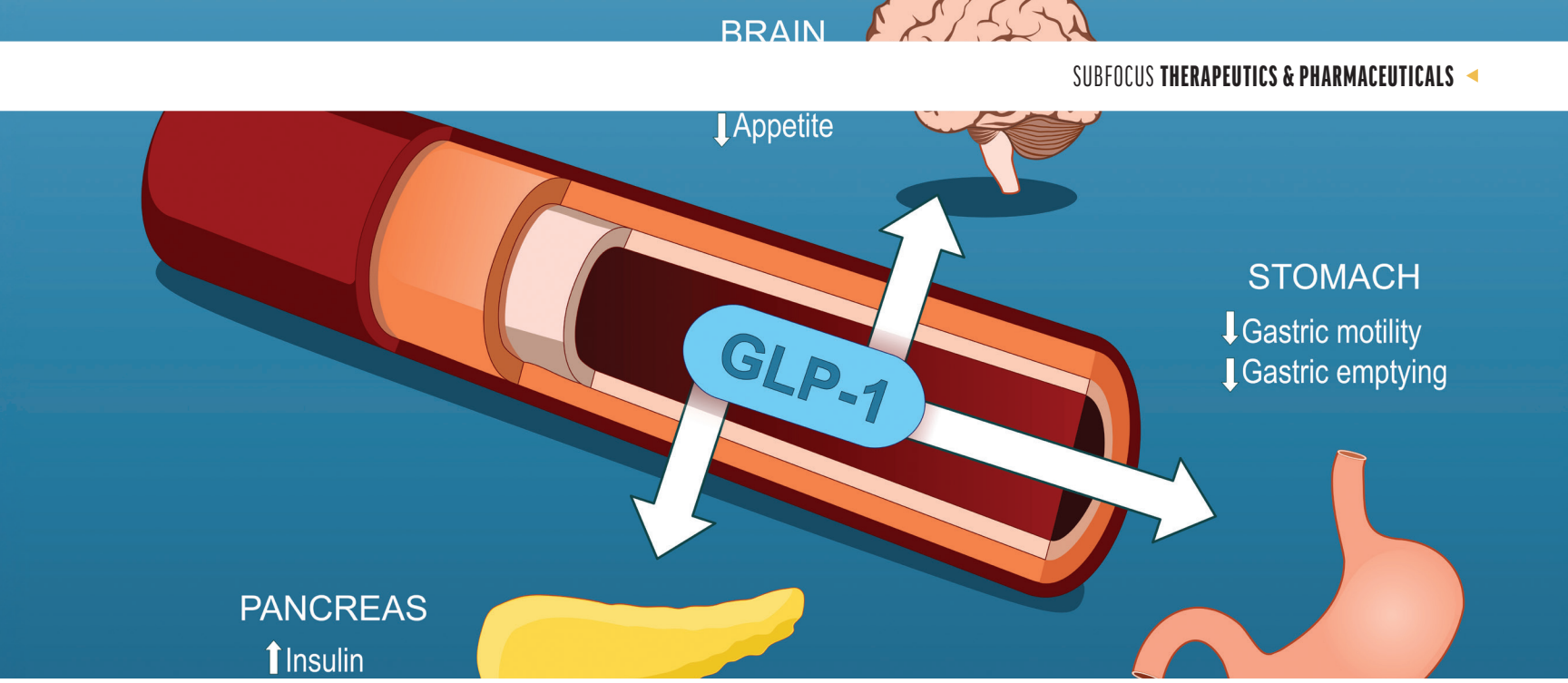

GLUCAGON-LIKE PEPTIDE 1 RECEPTOR AGONISTS AND THE EYE

These drugs offer a promising outlook as transformative therapies in glycemic control, weight management, and more, but what effect do they have on our patients' ocular health?

BY ALISSA COYNE, OD, MS, FAAO, FASOS

Forget *Barbie* and *Oppenheimer*; the true blockbuster of last summer was semaglutide. Raking in more than $16 billion, this drug, marketed as Ozempic (Novo Nordisk) and Wegovy (Novo Nordisk), became a household name and highly coveted commodity in the treatment of type 2 diabetes and for weight management, respectively. As optometrists, we must be mindful of any potential adverse effects our patients' medications might have on their overall health and/or on their existing health conditions. Glucagon-like peptide 1 receptor agonists (GLP-1RAs) such as semaglutide are no different, and I'll cover that a bit later. But first, here's a brief overview of this class of drugs.

ALL ABOUT GLP-1

GLP-1 orchestrates activation of insulin release and inhibition of glucagon release. This endogenous hormone is discharged from the small intestine into the bloodstream post-food consumption. GLP-1 binds GLP-1Rs in the pancreas, triggering insulin release from beta cells.[1-3] GLP-1 also binds pancreatic alpha receptors, impeding glucagon synthesis. Glucagon stimulates glucose release into the bloodstream during fasting periods; reducing its levels aids in reducing blood glucose levels. Endogenous GLP-1 has a half-life of 2 minutes, as dipeptidyl peptidase enzymes rapidly inactivate incretin hormones. Consequently, GLP-1RAs extend the half-life of GLP-1 by mimicking its actions.[1,2] Given that GLP-1 is a large protein, analogs are primarily administered via subcutaneous injection, with the exception of oral semaglutide 7 mg or 14 mg (Rybelsus, Novo Nordisk).

Four GLP-1RAs are available on the market (Table). These incretin-based therapies are synthetic mimetics of GLP-1. These analogs emulate endogenous GLP-1 by activating GLP-1R, stimulating release of insulin. Elevated levels of GLP-1 with GLP-1RA prompt increased insulin secretion and decreased glucagon production. GLP-1RAs contribute to improved glycemic control by lowering glycated hemoglobin (HbA1c) and promoting weight loss without causing hypoglycemia, a notable advantage

TABLE. Breakdown of Available GLP-1RAs

DRUG	TRADE NAME (MNFR)	INDICATION	DOSAGE	FORM
Semaglutide injection 0.5 mg, 1 mg, 2 mg	Ozempic (Novo Nordisk)	Type 2 diabetes	Once a week	Injection
Semaglutide tablets 7 mg, 14 mg	Rybelsus (Novo Nordisk)	Type 2 diabetes	Once a day	Oral
Semaglutide injection 2.4 mg	Wegovy (Novo Nordisk)	Weight loss	Once a week	Injection
Dulaglutide injection 0.75 mg, 1.5 mg, 3.0 mg, 4.5 mg	Trulicity (Eli Lilly)	Type 2 diabetes	Once a week	Injection
Liraglutide injection 1.2 mg, 1.8 mg	Victoza (Novo Nordisk)	Type 2 diabetes	Once a day	Injection
Liraglutide injection 3 mg	Saxenda (Novo Nordisk)	Weight loss	Once a day	Injection
Tirzepatide injection 0.5 mL, 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, 15 mg	Mounjaro (Eli Lilly)	Type 2 diabetes	Once a week	Injection
Tirzepatide injection 0.5 mL, 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, 15 mg	Zepbound (Eli Lilly)	Weight loss	Once a week	Injection

over sulfonylureas and meglitinides. GLP-1RAs vary in their efficacy in reducing HbA1c, magnitude of weight loss, duration of action, dosing frequency, and side effects.[4]

GLP-1RAs are FDA-approved for treating type 2 diabetes, which may be linked to potential GLP-1 impairment and slowed GLP-1 activation post-prandial.[5,6] Without the appropriate GLP-1 activation, insulin is not released promptly, and glucagon production releases glucose into the bloodstream, contributing to elevated blood glucose levels.

GLP-1RAs such as semaglutide and liraglutide (Saxenda, Novo Nordisk) are employed in weight loss regimens. Although the weight loss mechanism is not well-understood, GLP-1RAs curb hunger, leading to a reduction in food intake. Additionally, they slow gastric emptying from the stomach to the small intestine, promoting satiety more quickly and for longer.[7] As practitioners, the slowed gastric emptying effect raises concern for co-administered drug absorption. However, one study found that drug exposure was not clinically significant, and no dosing adjustments were necessary for most oral medications.[7] Special consideration should be given to medications that have a narrow therapeutic index and in individuals with kidney dysfunction. It's worth noting that GLP-1RAs do not result in cytochrome-dependent or transporter-mediated drug-drug interactions.[8]

Gastrointestinal side effects are most common, particularly during medication initiation and with dose escalation. Nausea is most often reported by patients, and vomiting, diarrhea, abdominal pain, and/or constipation have also been documented.[9] GLP-1RAs should not be prescribed in patients with a history of pancreatitis, a personal or family history of medullary thyroid cancer, or multiple endocrine neoplasia due to the observed development of thyroid tumors in animal studies.[9] Reactions at the injection site have also been reported. A consideration in the optometric setting is transient, elevated IOP associated with vomiting, particularly in the pre- and postoperative period of ophthalmic surgery.

AT A GLANCE

- Glucagon-like peptide 1 receptor agonists (GLP-1RA) are FDA-approved for treating type 2 diabetes and are commonly used in weight loss regimens.
- Two large, randomized control trials investigating liraglutide and semaglutide have suggested worsening retinopathy as an adverse effect of GLP-1RA use.
- The association between GLP-1RA use and a decreased risk of glaucoma, along with its potential implication for other neurodegenerative diseases, offers a promising avenue for targeted treatment as further research findings emerge.

GLP-1RAS AND DIABETIC RETINOPATHY

The phenomenon of worsening diabetic retinopathy (DR), often termed rebound retinopathy, is a

well-established, paradoxical retinal finding linked to improved blood glucose levels, typically observed 3 months to 3 years after intense glucose lowering.[10-14] The Diabetes Control and Complications Trial demonstrated a relationship between improved blood glucose control and increased risk of early worsening of DR, as well as between long-term risk reduction of DR with sustained blood glucose improvement.[15]

Two large, randomized control trials (RCTs) investigating liraglutide and semaglutide also suggested worsening retinopathy as an adverse effect of GLP-1RA use. In the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results study, a numerically higher incidence of complications associated with DR, such as panretinal photocoagulation, anti-VEGF injection, vitreous hemorrhage, and blindness, was observed, although results did not reach clinical significance.[16] The RCT associated with semaglutide use displayed a statistically significant increased risk of DR complications.[17] Conversely, findings from another population-based study suggested there was no overall increased risk of DR associated with GLP-1RA use, while a meta-analysis indicated albiglutide, a GLP-1RA no longer commercially available due to limited prescribing, was associated with an increased risk of early worsening (the four GLP-1RAs available did not exhibit a statistically significant association with DR).[18,19]

Given the confounding information, there is no established DR screening protocol upon GLP-1RA initiation. Communication with primary care providers and endocrinologists regarding retinal health and the severity of any existing DR is imperative before initiating GLP-1RA use.[20] If DR is observed with GLP-1RA use, accelerated follow-up compared with typical monitoring should help rule out treatable retinopathy. The presence of severe nonproliferative DR or proliferative DR requires comanagement with retinology and further intervention, including intravitreal injection and/or laser photocoagulation consistent with the clinical standard of care.[21]

Although the long-term retinal effects of GLP-1RA in DR aren't fully understood at this time, an ongoing trial is investigating the extended effect of semaglutide on DR after 5 years of treatment. The trial is set to conclude in the first quarter of 2027.[22]

GLP-1RAS AND GLAUCOMA

GLP-1Rs are found in neurons and glial cells located throughout the central nervous system, as well as in ganglion cells of the retina and optic nerve.[23] Animal studies have demonstrated neuroprotective effects associated with GLP-1RA use in Alzheimer and Parkinson disease, stroke, and ocular hypertension.[11,24-26] A retrospective study of 1,961 individuals with newly initiated GLP-1RA therapy found a reduced risk of developing open-angle glaucoma.[26] Another study also found a statistically significant decrease in the development of glaucoma, with a duration-response pattern: Individuals using GLP-1RAs for 3 or more years had a higher risk reduction of 29%.[27] Contemporary glaucoma management targets only IOP. The association between GLP-1RA use and a decreased risk of glaucoma, along with its potential implication for other neurodegenerative diseases, offers a promising avenue for targeted treatment.

PROMISING POTENTIAL

GLP-1RAs offer a promising outlook as transformative therapies in glycemic control, weight management, neuroprotection, and cardiovascular and renal protection. With innovative drug delivery systems on the horizon, the potential of GLP-1RAs in optometry is only expected to rise. ■

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