Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Semaglutide

Evidence Summary

Semaglutide is a recommended treatment for T2D and obesity. Early evidence suggests that semaglutide could have neuroprotective action in patients with metabolic syndrome, but more work is needed.

Neuroprotective Benefit: Early work indicates semaglutide is associated with lower dementia incidence in those with metabolic syndromes. Several studies are testing the efficacy of semaglutide for prevention and treatment of dementia.

Aging and related health concerns: Semaglutide is effective in treating diabetes, cardiovascular and renal complications relating to diabetes, and obesity. It is not clear whether it has beneficial effects in otherwise healthy individuals.

Safety: Semaglutide can cause a variety of gastrointestinal adverse events. These events can be common but are often mild and transient. Significant work is ongoing to clarify serious adverse events that are rarer or from long-term use.

Availability: By prescription	**Dose**: Subcutaneous formulations, once weekly dosing: Initial dose 0.25 mg, titrated up to a maximum of 2 mg for type 2 diabetes and 2.5 mg for weight loss. Oral formulation, once daily dosing: initial dose 3 mg, titrated up to a maximum of 14 mg.	**Chemical formula:** $C_{187}H_{291}N_{45}O_{59}$ **MW**: 4114 g/mol Semaglutide is a 31 amino acid long polypeptide Source: PubChem
Half-life: 7 days	**BBB**: Potentially not penetrant but does accumulate in brain in regions not protected by BBB.	
Clinical trials: The largest analysis of clinical trials included 17,645 patients.	**Observational studies**: The largest observational study identified had approximately 7,600 patients.	

What is it?

When lifestyle changes are not sufficient to control blood glucose levels in patients with diabetes, patients are often prescribed different drugs. Semaglutide belongs to one of these classes of drugs known as GLP-1 receptor agonists (GLP-1 RA). Glucagon-like-peptide-1 (GLP-1) is an incretin peptide hormone found in the gut that stimulates insulin release by binding to GLP-1 receptors (GLP-1R) on pancreatic β cells.GLP-1 levels increase after eating to help regulate blood glucose levels and induce satiety. GLP-1 is degraded within minutes by dipeptidyl peptidase-4 (DPP4). GLP-1 analogues, called GLP-1 receptor agonists, are polypeptides that are very similar to GLP-1 but are modified in order to resist degradation by DPP4; thus, they have a longer half-life. Semaglutide is a human GLP-1 analog and shares 94% homology with human GLP-1. Semaglutide contains three amino acid modifications to the native peptide; these modifications increase the half-life of semaglutide compared to both GLP-1 and to other GLP-1 analogs (Lau et al., 2015; Jensen et al., 2017). Semaglutide stimulates insulin production, slows gastric emptying, inhibits release of glucagon, and increases satiety. Through these actions, semaglutide helps to reduce blood glucose levels and reduce food intake (American Diabetes Association Professional Practice Committee, 2024; Kommu & Whitfield, 2024).

Semaglutide, under the brand names Ozempic® and Rybelsus®, is approved for type 2 diabetes, and Wegovy® is approved for chronic weight management in individuals with a Body Mass Index (BMI) ≥ 30 kg/m^2 or BMI ≥ 25 kg/m^2 with concomitant conditions such as hyperlipidemia, hypertension, or type 2 diabetes (American Heart Association, 2022). Pharmacological management of diabetes can be complex, and metformin remains the first-line pharmacotherapy. Semaglutide (or other GLP-1 RAs) is recommended for patients with type 2 diabetes who are at high risk of or have atherosclerotic cardiovascular disease, heart failure, and or chronic kidney disease; semaglutide can be prescribed with or without other medications. Semaglutide is considered to have very high glycemic efficiency (American Diabetes Association Professional Practice Committee).

Beyond their well-established benefit in type 2 diabetes and chronic weight management, semaglutide and other GLP-1 RAs are being explored for their potential in other areas, including polycystic ovarian syndrome, substance abuse, and neurodegenerative diseases. Type 2 diabetes and obesity are risk factors for dementia (Livingston et al., 2020). Insulin resistance, a feature of type 2 diabetes, is observed in dementia patients without other metabolic syndromes. GLP-1 receptors are also found in non-pancreatic cells such as neurons, and preclinical work has suggested that semaglutide and other GLP-1 RAs can be directly neuroprotective (Kopp et al., 2022).

Neuroprotective Benefit: Early work indicates semaglutide is associated with lower dementia incidence in those with metabolic syndromes. Several studies are testing the efficacy of semaglutide for prevention and treatment of dementia.

Types of evidence:

- 1 Cochrane systematic review and meta-analysis
- 11 RCTs, one of which was reported as a conference abstract
- 2 open label studies
- 1 pilot study
- 1 ex vivo study from patient samples
- 3 observational studies
- 6 reviews
- Multiple preclinical animal and in vitro studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function:

Whether or not semaglutide (or other GLP-1 RAs) can prevent dementia, decline, or positively affect cognitive function is an area of active research, both in patients with type 2 diabetes and/or obesity and in patients without those two particular risk factors. Several studies are ongoing; there are more details in the 'Research Underway' section.

Nørgaard et al., 2022 details an exploration of the effects of GLP-1 RA treatment in patients with type 2 diabetes on incidence of dementia diagnosis in two ways: first, through assessment of pooled data from three RCTs comprising 15,820 patients, and second, through 120,054 patients in a nationwide Danish prescription registry-based cohort. In the first analysis, the authors included data from LEADER (liraglutide), SUSTAIN-6 (subcutaneous semaglutide), and PIONEER (oral semaglutide). In the median 3.61 years of follow up in these studies, patients randomized to a GLP-1 RAs had a lower rate of dementia diagnosis compared to those randomized to placebo (HR: 0.47; 95% CI 0.25 to 0.86); 15 of 7907 total GLP-1 RA patients were diagnosed with dementia compared to 32 of 7913 placebo patients. The rate of dementia diagnosis started to diverge between the groups just past 1 year after randomization. One limitation of this part of the study is that these data come from adverse event reports from the studies; LEADER and PIONEER 6 only collected serious adverse events systematically, while all adverse events were collected in SUSTAIN-6. Therefore, underreporting cannot be discounted. In the second analysis, the authors identified a cohort of all of the dementia-free patients with a first prescription of a second-line diabetes treatment who then continued this medication for at least 5 years from 1995 to 2017. The authors collected dementia onset information from 2009 onward, as that was when GLP-1 RAs could be considered a well-known and available treatment in Denmark. They identified 4849 patients who were diagnosed with dementia in or after 2009. Using a nested case-control design, the authors age, sex, and calendar year matched each dementia case with 10 individuals in the cohort who did not develop dementia. The authors found that a GLP-1 RA prescription (95% of which were liraglutide) was associated with a lower incidence of dementia diagnosis (HR=0.89; 95% CI 0.86 to 0.93, for yearly increase in duration of exposure). The other second-line diabetes medications were not associated with lower incidence of dementia besides for sulfonylureas (HR=0.98; 95% CI 0.97-1.00, p=0.04). A limitation of the second part of the study is that while the authors were able to adjust for some medical conditions such as cardiovascular disease, hypertension, and education, they were not able to adjust for lifestyle factors such as smoking or physical activity. Moreover, there may be

confounding factors in why GLP-1 RAs were prescribed rather than another second-line treatment in these patients.

Other RCTs (Cuikerman-Yaffe et al., 2020, dulaglutide; Vadini et al., 2020, liraglutide) and observational studies of GLP-1 RAs as a class (Wium-Andersen et al., 2019) have also reported potential benefits of GLP-1 RAs over placebo or no GLP-1 RA treatment in terms of improving cognitive function and/or reduced incidence of dementia diagnosis in patients with type 2 diabetes and/or obesity.

Whether these data are applicable to semaglutide is not yet known; it is also not known whether any one GLP-1 RA has a more significant neuroprotective benefit than any other either for all patients or specific subgroups of patients. It is unclear whether treatment with any GLP-1 RA will have neuroprotective effects in patients without metabolic syndrome. Further work is needed to disentangle the indirect and direct effects of semaglutide and the GLP-1 RA drug class as a whole.

Human research to suggest benefits to patients with dementia:

As of June 2024, there are no completed studies that have published data on the use of semaglutide in patients with dementia. There are several ongoing studies exploring the use of semaglutide in this patient population; see 'Research Underway' for more information.

Several studies have published on potential benefits of other GLP-1 RAs such as exenatide, liraglutide, and lixisenatide in patients with AD (Geji et al, 2016; Mullins et al., 2019; Femminella et al., 2019 and Edison et al., 2021) and in patients with PD, including a Cochrane meta-analysis (Mulvaney et al., 2020) and other studies (Malatt et al., 2022; Meissner et al., 2024). Some observational studies have reported potential associations between GLP-1 RA treatment and lower incidence of PD (Brauer et al., 2020). However, not all studies have found even suggestions of benefit of GLP-1 RAs (McGarry et al., 2024).

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

GLP-1 is perhaps best known for its interaction with GLP-1 receptors located on pancreatic β cells. This interaction leads to enhanced secretion of insulin, at least in part via activation of adenyl cyclase and subsequent cAMP production. The increased insulin secretion and concomitant blood glucose level reduction and reduced food intake from increased satiety and slowed gastric emptying can help normalize blood glucose levels and reduce weight (Nauck & Meier, 2018). As diabetes and obesity both

independently increase the risk of dementia (Livingston et al., 2020), medication that ameliorates these conditions may lead to a reduction in dementia as well.

This indirect mechanism of neuroprotection does not preclude other, more direct mechanisms of action. The localization of GLP-1 receptors on pancreatic β cells is particularly prominent in the literature, but these receptors are found on other cell types, including neurons, microglia, astrocytes, and pericytes (Kopp et al., 2022).

As reviewed in Kopp et al., 2022 and Kalinderi et al., 2024, among others, preclinical work indicates that stimulating GLP-1 receptors in the brain may be neuroprotective through a variety of mechanisms. Semaglutide, like other GLP-1 RAs, may protect against oxidative stress, excitotoxicity, and apoptosis, and promote neurogenesis, differentiation, neurite growth, autophagy, and synaptic plasticity. GLP-1 receptor germline knockout animals have synaptic plasticity and memory formation deficits that are rescued by GLP-1 receptor expression; wild-type animals overexpressing GLP-1 in the hippocampus have improvements in learning and memory. GLP-1 RAs have been reported to decrease plaque burden in animal models of AD as well as reduce aggregate load of α-synuclein in PD models. This drug class also has anti-inflammatory mechanisms of action, such as reducing levels of pro-inflammatory cytokines and microglial activation. GLP-1 RAs may also promote mitochondrial health (Luna-Marco et al., 2023). Preclinical work indicates that semaglutide displays these mechanisms of action in animal models (Meca et al., 2024).

One important question is whether GLP-1 RAs cross the blood-brain barrier (BBB) and accumulate in concentrations high enough to exert a physiologically relevant effect. It is thought that semaglutide is not BBB penetrant but does have access to and accumulate in parts of the brain that are not protected by the BBB. However, much of this work was completed in rodents; more work is needed to clarify whether, and the extent to which, semaglutide can access the brain (Mullins et al., 2019; Salameh et al., 2020; Kopp et al., 2022; Dong et al., 2022; Lee et al., 2023).

APOE4 interactions:

It is not yet known whether there are differential effects of semaglutide based on APOE4 status.

Aging and related health concerns: Semaglutide is effective in treating diabetes, cardiovascular and renal complications relating to diabetes, and obesity. It is not clear whether it has beneficial effects in otherwise healthy individuals.

Types of evidence:

- 12 systematic reviews and/or meta-analyses
- 2 professional practice committee documents or statements
- 5 clinical trials
- 1 combined posthoc analysis of clinical trials
- 1 observational study
- 3 professional resources
- 8 reviews
- Multiple laboratory studies

Diabetes: BENEFIT

As a GLP-1 RA, semaglutide is a recommended first- or second- line treatment for type 2 diabetes (T2D), depending on the specific patient and their co-morbidities. In patients who have or are at high risk for atherosclerotic cardiovascular disease or have chronic kidney disease, the American Diabetes Association (ADA) recommends either a GLP-1 RA or SGLT2s as first-line treatment. In patients without these risk factors, a GLP-1 RA is typically second-line recommendations unless additional glycemic control is called for, or when there is a contraindication to the first-line treatment, metformin. Clinicians may or should also incorporate other factors into prescription decision making, including weight loss goals, other underlying health conditions, and patient preference (ADA Standard of Care in Diabetes, 2024). GLP-1 RAs also are thought to be beneficial for patients with prediabetes, potentially increasing the incidence of reversion to normoglycemic states and preventing new-onset diabetes, as reviewed and meta-analyzed by Salamah et al., 2024.

GLP-1 RAs are considered to have high or very high glycemic efficacy and lower $HbA1_c$ and fasting blood glucose. Semaglutide is considered to have very high glycemic efficiency (ADA Standard of Care in Diabetes, 2024). While comparative effectiveness research continues, the results thus far indicate that semaglutide is the most effective of the currently approved GLP-1 RAs at lowering $HbA1_c$ and fasting glucose. For instance, one meta-analysis found that patients taking semaglutide had significantly better odds at achieving target and optimal $HbA1_c$ with a 0.44% greater reduction in $HbA1_c$ and 0.48 mmol/L

decrease in fasting glucose compared to other GLP-1 RAs (Patoulias et al., 2023). Other meta-analyses also report greater efficacy of semaglutide at glycemic control compared to the other GLP-1 RAs (reviewed and/or meta-analyzed by Latif et al., 2024; Nauck et al., 2024; Yao et al., 2024).

Beyond their demonstrated ability to lower blood sugar and $HbA1_c$ levels in T2D populations, semaglutide has been found to have other benefits. As reviewed in Drucker, 2024, among others, treating patients with T2D with semaglutide or other GLP-1 RAs can help improve numerous health indices, such as weight management and lipid profiles and reduce major cardiovascular events, stroke, kidney disease, blood pressure, and mortality. The details are described in sections below.

Cardiovascular outcomes: BENEFIT IN CERTAIN POPULATIONS

Treating T2D with semaglutide reduces major adverse cardiovascular events (MACE). A Cochrane network meta-analysis of different anti-diabetic drugs for individuals with cardiovascular disease examined seven trials of GLP-1 RAs, including some with semaglutide, and found high-certainty evidence that compared to placebo, GLP-1 RAs reduce risk of mortality from cardiovascular events (OR=0.87; 95% CI 0.79 to 0.95) (Kanie et al., 2021).

A 2022 review by the American Heart Association of management of cardiovascular risk factors for adults with type 2 diabetes reviewed RCTs involving GLP-1 RAs and stated that lixisenatide, exenatide, and oral semaglutide were 'non-inferior to standard care', and that liraglutide, subcutaneous semaglutide, dulaglutide, and efpeglenatide all showed statistically significant 12% to 27% reductions in MACE (Joseph et al., 2022). A combined posthoc analysis from RCTs of semaglutide, comprising a total of 17,645 patients, suggested that semaglutide reduced risk of MACE in comparison to placebo and also to active comparators, including other GLP-1 RAs (Husain et al., 2020). It should be noted, though, that this is specific to the subcutaneous injection formulations of semaglutide; oral semaglutide is not inferior to placebo in reducing MACE, but neither does it significantly reduce risk (Husain et al., 2019; Kommu & Whitfield, 2024). There is still uncertainty as to the specific effects of GLP-1 RAs in certain populations, such as in patients with heart failure (Sattar et al., 2021; Kanie et al., 2021; Merza et al., 2023).

It is thought that GLP-1 RAs can reduce blood pressure and improve measures of cardiac health such as cardiac output and endothelial function (Collins & Costello, 2024). GLP-1 RAs are also thought to increase heart rate; this may be most relevant for specific patient populations, such as those with advanced heart failure (Khan et al., 2020).

There are several mechanisms by which GLP-1 RAs may be cardioprotective, such as by reducing inflammation, body weight, and blood glucose (reviewed by Ussher & Drucker, 2023). Systematic reviews and meta-analyses have reported that GLP-1 RAs improve lipid profiles in patients with T2D, such as lowering low density lipoprotein cholesterol (LDL-C), total cholesterol, and triglycerides (Chae et al., 2024; Yao et al., 2024, among others). Some studies have found that GLP-1 RAs decrease carotid intima-media thickness (cIMT) back to "healthy" measurements (Rizzo et al, 2016; Rizzo et al, 2014). In patients undergoing carotid endarterectomy, plaques removed from individuals taking a drug that affects the incretin system (either GLP-1 agonists or DPP4 antagonists) had decreased macrophage-rich areas, decreased number of T-cells, increased collagen content, decreased TNF-α levels, and increased SIRT6 expression compared to those not taking an incretin-based therapy (Balestrieri et al, 2015).

Renal Outcomes: BENEFIT IN CERTAIN POPULATIONS

Semaglutide, as a GLP-1 RA, is a recommended treatment for patients with T2D and kidney disease (ADA Standard of Care in Diabetes, 2024). A 2021 systematic review and meta-analysis included eight trials testing either semaglutide, albiglutide, dulaglutide, efpeglenatide, exenatide, liraglutide, or lixisenatide, , in a total of 60,080 patients with T2D. When the authors analyzed the studies that included kidney events such as worsening kidney function, kidney replacement, or kidney death, they found a 21% reduction in kidney events in patients receiving GLP-1 RAs compared to placebo (HR=0.79; 95% CI 0.73 to 0.87; p<0.0001) (Sattar et al., 2021).

Longevity: BENEFIT IN CERTAIN POPULATIONS

Meta-analyses have also found that treatment with GLP-1 RAs, including semaglutide, is associated with reduced mortality in patients with T2D. A Cochrane meta-analysis found high-certainty evidence that compared to placebo, GLP-1 RAs reduce the risk of cardiovascular mortality (OR=0.87; 95% CI 0.79 to 0.95) and all-cause mortality (OR=0.88, 95% CI 0.82 to 0.95) (Kanie et al., 2021).

Stroke: BENEFIT IN CERTAIN POPULATIONS

A Cochrane meta-analysis that included seven studies of GLP-1 RAs, including semaglutide, found high certainty evidence that compared to use of placebo, use of GLP-1 RAs reduce the risk of stroke (OR=0.87; 95% CI 0.77 to 0.98) (Kanie et al., 2021). Other, more recent meta-analyses have also reported

a reduction of stroke risk in patients receiving semaglutide or other GLP-1 RAs (Adamou et al., 2024; Stefanou et al., 2024, among others).

Obesity: BENEFIT

High-dose semaglutide is approved for weight management in patients with or without diabetes (Michos et al., 2023; Latif et al., 2024). Meta-analyses have found that use of semaglutide leads to significantly more weight loss when compared with placebo, which was often lifestyle modification (Ma et al., 2023; Shi et al., 2024, among others). Both Ma and colleagues and Shi and colleagues, along with other meta-analyses like Patoulias et al., 2023, found that semaglutide was more effective as a weight loss agent compared to the other individual drugs in their studies, including other GLP-1 RAs

Semaglutide or GLP-1 RAs more broadly may also benefit patients with a variety of other diseases, including PCOS, NAFLD, substance abuse, and depression, among others (Bandyopadhyay et al., 2023; Chen et al., 2024; Drucker, 2024).

Safety: Semaglutide can cause a variety of gastrointestinal adverse events. These events can be common but are often mild and transient. Significant work is ongoing to clarify serious adverse events that are rarer or from long-term use

Types of evidence:

- 5 systematic reviews and/or meta-analyses
- 4 observational studies
- 1 case report
- 2 professional resources
- 1 review
- 1 commentary

The most common side effects of semaglutide are gastrointestinal in nature (e.g. nausea and diarrhea). These adverse events are common, with approximately 40 to 65% of participants reporting a gastrointestinal adverse event in trials. Typically these effects are transient and mild, but can lead to dose reductions or discontinuations from trials. Other adverse events include dizziness, infections, headaches, and injection site reactions. While there have not been any reports of major hypoglycemia events, care should be taken when prescribing semaglutide with other drugs that can affect blood sugar

levels (Kommu & Whitfield, 2024; Drucker, 2024). Comparative research is still ongoing, but at least some meta-analyses do find an increase in frequency of gastrointestinal adverse events with semaglutide compared to other GLP-1 RAs (Patoulias et al., 2023; Xie et al., 2023).

Semaglutide is available in both an oral and a subcutaneous injection formulation. Researchers analyzed the FDA adverse event reporting system and found a total of 16,346 adverse events from subcutaneous administration and 2,496 from oral administration. Subcutaneous administration of semaglutide is more likely to lead to endocrine system adverse events than oral administration. In contrast, oral administration is more likely to lead to gastrointestinal adverse events. Oral administration is also associated with a more rapid onset of the adverse event compared to subcutaneous injection. The data also indicated that a higher proportion of all semaglutide adverse event reports were in women compared to men (Niu et al., 2024).

There are theoretical concerns for, or reports of, rarer adverse events with GLP-1 usage, many of which are still being explored as more and more people use these medications and/or use them long-term. These concerns include:

- Thyroid C-cell tumors: in rodent models, semaglutide treatment resulted in thyroid C-cell tumors at clinically relevant exposures in a dose- and duration- dependent manner. There is a black box warning on all GLP-1 RAs with this concern, and GLP-1 RAs are contraindicated for individuals with a personal or family history of medullary thyroid carcinoma or patients with multiple endocrine neoplasia syndrome type 2. Groups have reported conflicting results in humans, with some studies finding an increased incidence of thyroid cancer in individuals receiving GLP-1 RAs (Bezin et al., 2023), and some studies finding no association (Pasternak et al., 2024). This topic is also reviewed in Drucker, 2024, among others.
- Pancreatitis / pancreatic cancer: Preclinical studies and postmarketing pharmacovigilance studies suggest some concerns over chronic use and pancreatitis (due to overstimulation of GLP-1 receptors on the pancreas) or pancreatic cancer. Clinical trials and meta-analyses of clinical trials have largely not found an increase in the incidence of these events with GLP-1 RA usage, including meta-analyses specifically looking at semaglutide, but research in this area continues (Gallo, 2013; Monami et al, 2017; Zhang et al., 2022; Hidayat et al., 2023; Nagendra et al., 2023). However, semaglutide and other GLP-1 RAs are still not recommended for use in patients with history of pancreatitis, and patients who develop pancreatitis while on semaglutide or other GLP-1 RAs should discontinue use of the drug (Kommu & Whitfield, 2024; Collins & Costello, 2024).

- Gallstones: A meta-analysis of RCTs reported an increased risk of gallstones with GLP1 agonists (OR 1.30; 95%CI 1.01-1.68; incidence 141/14,872 for GLP-1 agonists, 99/17,232 for comparators) (Monami et al, 2017). Other meta-analyses have replicated these results (He et al., 2022).
- Bowel obstruction: some observational studies have found increased incidence of intestinal blockages in patients receiving GLP-RAs, though others have not replicated these results. More work is required to assess the incidence and causality of this and other serious gastrointestinal adverse events (reviewed by Drucker, 2024).
- Retinopathy: There have been some concerns of diabetic retinopathy in patients receiving semaglutide (Sharma et al., 2022), though not all studies replicate this concern or find that it might be a risk based on age and/or duration of semaglutide use (Wang et al., 2022). An ongoing trial called FOCUS (NCT03811561) is assessing the risk of this adverse event.
- Suicidal ideations: postmarketing surveillance of GLP-1 RAs such as semaglutide included reports of suicidal thoughts or actions. The preliminary review by the FDA has not found evidence that GLP-1 RAs cause these thoughts or actions, but due to the small number of events, they cannot yet definitively rule out the possibility that GLP-1 RAs are involved. The FDA is continuing to investigate and will report on their findings (FDA). Wang et al., 2024 similarly did not find an association between GLP-1 RA usage and suicidal ideations in populations with either obesity or T2D.

As semaglutide is known to slow gastric emptying, there are potential concerns for individuals on semaglutide who require anesthesia. The American Society of Anesthesiologists has released a consensus-based guidance for providers, including holding GLP-1 RAs on the day of the procedure/surgery (or for a week if on weekly dosing) (American Society of Anesthesiologists, 2023).

The above data are generally in populations with T2D or obesity. There is some preliminary data on the safety of GLP-1 RAs in patients with dementia. None of these trials involved semaglutide, but the adverse event information may be informative for semaglutide trials. As with other patient populations, nausea and weight loss are generally the most commonly reported adverse events, affecting approximately 40% to 50% of patients on active treatment; the incidence of these adverse events are in line with the incidence in trials in other populations. Other common non-nausea adverse events included weight loss, loss of appetite, upper GI infection symptoms, reflux, fatigue, and GI disorders. (Mullins et al., 2019; Aviles-Olmos et al., 2013; Malatt et al., 2022; Meissner et al., 2024). One study of lixisenatide reported one serious adverse event: a case of pancreatitis in the lixisenatide group. Another

study reported a potential trend towards increased dyskinesias in PD patients treated with exenatide compared to no treatment (Aviles-Olmos et al., 2013).

As of June 2024, semaglutide and other GLP-1 RAs are in high demand that supply cannot always match, particularly weight loss formulations like Wegovy®. There are concerns about counterfeiting. There have also been reports of adverse events after incorrect administration of GLP-1 RAs acquired from compounding pharmacies and aesthetic spas (Lambson et al., 2023). Individuals are encouraged to obtain these medications from a state-licensed pharmacy, using a valid prescription (FDA).

Drug interactions:

Semaglutide is known to interact with 251 drugs; 2 are major, 248 are moderate, and 1 is minor. The major interactions are with gatifloxacin, as it can affect blood sugar levels, and the other is with bexarotene, due to increased risk of pancreatitis. The full list of drug interactions can be seen on Drugs.com.

Individuals who are taking semaglutide or any GLP-1 RA as well as other drugs that can affect blood sugar or cause hypoglycemia, like insulin, must carefully monitor their blood sugar. As all GLP-1 RAs can affect stomach emptying, there may be concerns about how this class of drugs affects other medications taken by mouth. It is always important to discuss your full medication and supplement list with your doctor and pharmacist, and this is particularly true for semaglutide and other GLP-1 RAs.

Semaglutide, like other GLP-1 RAs, should be taken with caution with alcohol, as alcohol can affect blood sugar. Some semaglutide formulations should be timed around food intake, such as Rybelsus. The prescribing information contains detailed instructions on when to take the GLP-1 receptor agonist.

There are currently 6 disease interactions for semaglutide. Semaglutide should be avoided in patients with personal or family history of medullary thyroid carcinoma, or with personal history of multiple endocrine neoplasia syndrome type 2, or patients with suicidal behavior and ideation. Both of these disease interactions are either based on preclinical work or preliminary adverse event reporting information and are not confirmed causation, but should nonetheless be taken seriously. Semaglutide should be used with caution in patients with history of diabetic retinopathy; these patients may require additional monitoring, as do patients who experience significant gastrointestinal side effects, who may

require monitoring for renal function. All patients should also be monitored for pancreatitis, and should discontinue semaglutide if pancreatitis is suspected (Drugs.com)

Research underway:

There are just under 200 ongoing trials of semaglutide that are registered on clinicaltrials.gov.

Studies on Cognitively Intact / MCI Populations:

NCT06363487 is a study of the effects of semaglutide on particular domains of cognition in healthy volunteers. The study aims to enroll 60 healthy adults aged 21 to 55. The volunteers will be randomized to receive a single dose of either placebo or 0.5 mg semaglutide. The primary outcomes focus on performance on reward sensitivity tasks. Secondary outcomes include other cognitive domains, such as memory, emotional processing, and energy levels.

NCT05786521 is a study exploring the effect of semaglutide on physical function, body composition, and markers of aging in older adults. The study enrolled 20 adults aged 65 to 90 years who were overweight or obese and had prediabetes or diabetes and randomized patients to either lifestyle intervention or the lifestyle intervention plus once weekly semaglutide injections. Those receiving semaglutide were titrated up to a final dose of 1 mg. The treatment period was for a total of 20 weeks. Given the study design, it was not possible to blind the participants. The primary and only outcome measure is lean body mass change, though the title of the study indicates other assessments are performed.

A trial in the UK is assessing the impact of semaglutide on tau levels in the brain. The study aims to enroll 88 amyloid-positive individuals without dementia; these participants will be randomized to either once a day oral placebo or semaglutide. Dosing will last for one year, with a follow-up visit after the end of treatment. The primary outcome is change in levels of tau in the brain as measured by tau PET. Secondary outcome measures include levels of other AD-related biomarkers, measures of cognition, and safety (ISRCTN).

NCT06072963 is a proof-of-concept study that may shed light on the potential of GLP-1 receptor agonists as prevention tools. The study aims to enroll 80 patients with metabolic syndrome and MCI, a population that is enriched for risk of cerebrovascular disease and dementia. Participants will be

randomized to one of four groups: one will receive intranasal insulin and oral semaglutide, one will receive intranasal insulin and oral semaglutide placebo, one will receive intranasal insulin placebo and oral semaglutide; and one will receive placebo for both. The insulin dosage will be 20 IU, and semaglutide will be titrated up to a maximum of 14 mg daily, assuming no adverse events, and treatment will last for 1 year. The primary outcome measures are change in cognitive function and the effects of treatment(s) on cerebral blood flow and brain glucose intake as measured by Arterial Spin Labeling MRI scans and FDG-PET, respectively. The secondary outcomes include a variety of blood biomarkers such as Aβ, tau, and GFAP, daily functioning, brain structure information from MRI, and cognitive function on specific domains. The study rationale and design is published in Davidy et al., 2024.

Studies in Patients with Alzheimer's Disease:

NCT04777396 and NCT04777409 are two ongoing studies of semaglutide in patients with early onset AD. The two studies are called EVOKE and EVOKE+ and are essentially identical, except that EVOKE did not include patients with cerebral vascular changes, whereas EVOKE+ did include those patients (NHS). The studies each aim to enroll 1,840 patients and randomize them to either oral semaglutide once daily or matching placebo for 173 weeks. The dose of semaglutide will be titrated up to 14 mg daily. The primary outcome for both studies is change in cognitive function as assessed by the Clinical Dementia Rating – Sum of Boxes (CDR-SB). Secondary outcomes include time to progression of disease severity, measures of cognition and daily functioning, and safety information. As of mid-2023, both of these trials are reported to be fully enrolled. The study is estimated to reach primary completion in Fall 2025, with study completion estimated in Fall 2026.

NCT05891496 is a study seeking to characterize the immunological and other biological effects of semaglutide treatment in patients with AD. The researchers plan to enroll 24 individuals with MCI or mild dementia; the patients will be randomized to receive either semaglutide or placebo for 12 weeks. After this first randomized, blinded period, all participants will receive semaglutide for 52 weeks. The primary outcome measures are changes in gene expression in CSF and blood; other outcome measures include pharmacokinetic measures and safety.

Studies in Patients with Parkinson's Disease:

NCT0365968 is a randomized trial of weekly doses of subcutaneous semaglutide or placebo in patients with newly diagnosed PD. The study plans to enroll 100 to 300 patients. Patients will receive blinded

treatment for 24 months, and then move to a 2-year open label extension wherein both groups will receive semaglutide. The primary outcome measure is motor function as assessed by UPDRS.

Other Studies:

NCT04466345 is investigating whether semaglutide improves cognitive function in patients with major depressive disorder.

Some studies are also assessing the utility of GLP-1 receptor agonists in cerebral blood flow and/or stroke. These studies include NCT05780905, which is assessing the effects of semaglutide on intracranial blood flood and blood-brain barrier permeability in patients with type 2 diabetes; and NCT05920889, which is testing semaglutide for use in patients with a specific type of stroke known as acute large vessel occlusion stroke who were treated with endovascular thrombectomy.

Search terms:

Pubmed, Google: semaglutide

- Alzheimer's, Parkinson's, dementia, cardiovascular, renal, pancreatitis, thyroid cancer, blood pressure, lipid profile, stroke, APOE

Websites visited for semaglutide:

- Clinicaltrials.gov
- Examine.com
- Drugs.com
- WebMD.com
- PubChem
- DrugBank.ca
- Cafepharma

***Disclaimer**: Cognitive Vitality Reports® do not provide, and should not be used for, medical advice, diagnosis, or treatment. You should consult with your healthcare providers when making decisions regarding your health. Your use of these reports constitutes your agreement to the **Terms & Conditions**.*

If you have suggestions for drugs, drugs-in-development, supplements, nutraceuticals, or food/drink with neuroprotective properties that warrant in-depth reviews by ADDF's Aging and Alzheimer's Prevention Program, please contact INFO@alzdiscovery.org. To view our official ratings, visit Cognitive Vitality's Rating page.