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.

GLP-1 Receptor Agonists

Evidence Summary

GLP-1 RAs are a recommended treatment for T2D and obesity. Preliminary evidence suggests that GLP-1 RAs may have neuroprotective action in patients with metabolic syndrome, but more work is needed.

Neuroprotective Benefit: Observational studies and early clinical work suggest that GLP-1 RAs could reduce incidence of dementia in those with metabolic syndrome. There is initial evidence that GLP-1 RAs could mitigate decline in patients with dementia.

Aging and related health concerns: GLP-1 agonists have significant benefits for treating diabetes, cardiovascular and renal complications relating to diabetes, and obesity. It is not clear whether they have beneficial effects in otherwise healthy individuals.

Safety: GLP-1 receptor agonists 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**: Varies. See dosing information in the 'What is it?' section
Half-life: Varies. See 'What is it' section	**BBB**: Varies by drug; some conflicting results. See information in the 'What is it?' and 'Neuroprotection' section
Clinical trials: The largest meta-analysis of RCTs identified included over 100,000 patients.	**Observational studies**: The largest observational studies identified included over 100,000 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. One class of drugs is 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. It is increased 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 modified in order to resist degradation by DPP4; thus, they have a longer half-life. GLP-1 RAs stimulate insulin production, slow gastric emptying, inhibit release of glucagon, and increase satiety. Through these actions, GLP-1 RAs help to reduce blood glucose levels and reduce food intake (American Diabetes Association Professional Practice Committee, 2024; Collins & Costello, 2024).

There are several GLP-1 receptor agonists that are approved for treatment of type 2 diabetes or weight management. Pharmacological management of diabetes can be complex, and metformin remains the first-line pharmacotherapy. GLP-1 RAs are 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; GLP-1 RAs can be prescribed with or without other medications (American Diabetes Association Professional Practice Committee). Particular doses of specific GLP-1 RAs are 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). The approved GLP-1RAs vary in their half-lives, blood-brain barrier penetrance, and dosing schedule:

Drug name	Half Life	BBB Penetrance[1]	Indication	Dosing
Dulaglutide (Trulacity®, subcutaneous injection, Eli Lilly)	5 days	Not known	Type 2 diabetes	Once weekly; initial dose 0.75 mg, titrated up to maximum of 4.5 mg weekly
Exenatide[2] (Byetta®, subcutaneous injection, AstraZeneca)	2.4 hours	Penetrant	Type 2 diabetes	Twice daily dosing 60 minutes before a meal; initial dose 5 mcg twice a day, titrated up to 10 mcg twice a day
Exenatide[2] (Bydureon®, subcutaneous injection, AstraZeneca)	2.4 hours	Penetrant	Type 2 diabetes	Once weekly; 2 mg per week
Liraglutide[3] (Saxenda®, subcutaneous injection, Novo Nordisk)	12 to 13 hours	Conflicting results in the literature	Chronic weight management	Once daily; initial dose 0.6 mg, titrated up to 3 mg
Liraglutide[3] (Victoza®, subcutaneous injection, Novo Nordisk)	12 to 13 hours	See above	Type 2 diabetes	Once daily; initial dose 0.6 mg, titrated up to a maximum of 1.8 mg
Semaglutide[4] (Ozempic®, subcutaneous injection, Novo Nordisk)	7 days	Not penetrant – or, low penetrance only in certain brain areas (animal data)	Type 2 diabetes	Once weekly; initial dose 0.25 mg, titrated up to a maximum of 2 mg
Semaglutide[4] (Wegovy®, subcutaneous injection, Novo Nordisk)	7 days	See above	Chronic weight management	Once weekly; initial dose 0.25 mg, titrated up to maximum of 2.5 mg

Semaglutide[4] (Rybelsus®, oral tablet, Novo Nordisk)	7 days	See above	Type 2 diabetes	Once daily; Initial dose 3 mg titrated up to a maximum of 14 mg daily.

[1] Brain penetrance data are largely from preclinical studies: Hunter & Hölscher, 2012; Salameh et al., 2020; Lee et al., 2023. See 'Mechanisms of action of neuroprotection' section for more information.

[2] Byetta and Bydureon are different formulations of the same drug; one is for daily dosing, whereas the other is an extended-release formulation for once weekly dosing.

[3] Saxenda and Victoza are the same drug from the same company, but at different dosages and thus approved for different uses and populations.

[4] Ozempic, Wegovy, and Rybelsus are the same drug in different formulations and/or doses. Ozempic and Wegovy are the same formulation but different doses; Rybelsus is an oral tablet rather than a subcutaneous injection and has different dosing.

There are other GLP-1 RAs, such as lixisenatide, that have been discontinued in the US; the manufacturer cited business concerns (AlzForum), and lixisenatide continues to be prescribed as a combination therapy with insulin known as Soliqua®. When available as a monotherapy, lixisenatide (Adlyxin®) was given once daily via subcutaneous injection. The initial dose was 10 micrograms (mcg) and titrated up to a maximum of 20 mcg. The half-life of lixisenatide is 1.5 to 3 hours. There are also new GLP-1 RAs in development, such as orforglipron (Wharton et al., 2023) and efpeglenatide (Frias et al., 2022), or modifications of existing GLP-1 RAs like NLY101, which is a modified form of exenatide (McGarry et al., 2024).

Beyond their well-established benefit in type 2 diabetes and chronic weight management, 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 GLP-1 RAs can be directly neuroprotective (Kopp et al., 2022).

Neuroprotective Benefit: Observational studies and early clinical work suggest that GLP-1 RAs could reduce incidence of dementia in those with metabolic syndrome. There is initial evidence that GLP-1 RAs could mitigate decline in patients with 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 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.

Another nested case-control study examined dementia incidence in 170,417 patients with type 2 diabetes using the Danish National Diabetes Register and assessed whether incidence varied based on antidiabetic medication(s) the patient had been prescribed at any point. The authors identified 11,619 cases of dementia in this cohort and matched them to four dementia-free individuals with type 2 diabetes who were follow-up time and calendar year matched. As expected with an otherwise unmatched control group, there were significant differences in sex, age, education, and co-morbidities in the dementia group as compared to the control group. The authors controlled for many of these factors in their analyses. After multiple adjustments, people with type 2 diabetes who received GLP-1 RAs were less likely to receive a dementia diagnosis (OR=0.58; 95% CI 0.50 to 0.67) than people with type 2 diabetes who did not receive GLP-1 RAs; individuals who received other anti-diabetic medications including insulin (OR=0.93; 95% CI 0.87 to 0.99), metformin (OR=0.94; 95% CI 0.89 to 0.99), DPP4 inhibitors (OR=0.80; 95% CI 0.74 to 0.88), and sodium/glucose cotransporter-2 inhibitors (SGLT2i) (OR=0.58; 95% CI 0.42 to 0.81) also had a significantly lower incidence of dementia compared to those who did not receive these medications. The odds ratios were strongest for GLP-1 RAs and SGLT2 inhibitors, and the association was stronger with increasing dose and duration of medication exposure (Wium-Andersen et al., 2019).

REWIND was a multi-site international randomized controlled trial assessing the effects of dulaglutide in patients with type 2 diabetes and additional cardiovascular risk factors and a BMI of at least 23 kg/m^2. The study randomized 9901 patients to once weekly subcutaneous injections of either placebo or 1.5 mg dulaglutide; the median follow-up was 5.4 years. The trial met its primary outcome, which was a significant reduction of a composite of major cardiovascular events in patients receiving dulaglutide

compared to those receiving placebo. These details were published in Gerstein et al., 2019. Change in cognitive function was an exploratory aim. The patients underwent the Montreal Cognitive Assessment (MoCA) and the Digit Symbol Substitution Test (DSST) at baseline, 2 year, 5 years, and end of study visit, which was up to 8 years after study start. These cognitive data were collected from 8828 (89%) of the total participants. The authors then converted each individual score to country-standardized scores, and assessed the time until first instance of a test score that was 1.5 or more standard deviations below the baseline mean score in that participant's country, representing progression to country-standardized substantive cognitive impairment. They found that this cognitive outcome occurred in 4.05 per 100-patient years in the dulaglutide group, and 4.35 per 100 patient-years in the placebo group (hazard ratio (HR)=0.93; 95% CI 0.85 to1.02; p=0.11). The authors observed that there were greater effects in participants with lowest baseline scores. They therefore performed a post-hoc adjustment for baseline cognitive performance. When looking at adjusted scores, the patients receiving dulaglutide had a 14% lower risk of substantive cognitive impairment as compared to those in the placebo group (HR=0.86; 95% CI 0.79 to 0.95; p=0.0018). The primary outcome of the trial indicated that dulaglutide reduced risk of cardiovascular events, including stroke; adjusting the cognitive results for stroke did not affect the findings, indicating that this potential cognitive protection was not due entirely to protection against stroke. This large study hints at potential benefit, but the limitations, including the post-hoc analyses, mean that these exploratory findings require further validation (Cuikerman-Yaffe et al., 2020).

A small study looked directly at whether treatment with a GLP-1 RA could improve cognitive function in patients with obesity and prediabetes or early type 2 diabetes. The study recruited patients who were 49 to 60 years of age with a BMI over 30 kg/m^2 with prediabetes or a diabetes diagnosis in the past year. At enrollment, all patients were receiving metformin and diet therapy. The patients were randomized to either lifestyle counseling or liraglutide titrated up to 1.8 mg daily and stayed on the treatment until they lost 7% of their body weight or 15 months had passed, whichever came first. The median duration of the trial was 4 months in both groups. Cognitive assessments were performed at baseline and then after reaching the prespecified weight loss. The authors therefore compared the cognitive performance of only patients who lost the target amount of weight, with a final sample size of 32 evenly distributed between groups. When the researchers compared the two groups, they found that there was a significant increase in short term memory (p=0.041) and the composite memory score (p=0.033) in the liraglutide group as compared to the lifestyle counseling group. When adjusted for baseline performance, the difference in composite memory remained significant (p=0.031). The authors also found that the time-to-weight loss, which also represents time-on-drug, was correlated with the improvement of memory – that is, a longer exposure to liraglutide was positively correlated with greater improvement in memory, even though those patients also took longer to reach the weight loss target of the study. The authors could not rule out practice effects, but as the median time-to-weight-loss and thus end of study

assessments was the same between groups, practice effects would be predicted to affect both groups equally. As this study does not appear to be blinded, that is one source of potential bias (Vadini et al., 2020).

Taken together, GLP-1 RAs might positively impact cognitive function and/or influence progression to dementia in cognitively intact patients with type 2 diabetes and/or obesity. However, these data are still preliminary, and future work is needed to disentangle the indirect and direct effects of each particular GLP-1 RA. It is also not yet clear if treatment with GLP-1 RAs will have these potentially neuroprotective effects in adults without metabolic syndromes.

Human research to suggest benefits to patients with dementia:

One randomized controlled trial in 38 patients with Alzheimer's disease reported that 26 weeks of liraglutide (1.2mg daily) did not change cognition or brain amyloid accumulation. It did prevent a decrease in the uptake of glucose in the brain (between groups was only significant in cingulate cortex and cerebellum, likely due to low numbers). Blood pressure also decreased in the liraglutide group (Geji et al, 2016).

A pilot study assessed the effects of exenatide in patients with AD. The trial randomized 27 individuals to either exenatide or placebo. Participants received either placebo or 5 micrograms (mcg) exenatide twice daily for 1 week and then 10 mcg twice daily until the end of the 18-month study. Of the 27 enrolled patients, 21 had at least one follow up visit and 18 finished the study. The study was prematurely terminated due to AstraZeneca, the study sponsor, withdrew support. This decision was not due to safety concerns. The authors found that there were no trends towards or significant differences between the placebo group and exenatide group in terms of clinical or cognitive measurements, besides for one modest improvement on a test of attention and short-term memory at the 6-month timepoint only in the exenatide group. There were also no blood, CSF, or MRI biomarker changes besides for a decrease of $A\beta_{42}$ levels in extracellular vesicles. The authors cautioned that they did not want to overinterpret these results, especially due to the small size of the trial and early termination (Mullins et al., 2019).

The ELAD study investigated the effects of liraglutide in patients with AD. The study protocol was detailed in Femminella et al., 2019. The authors randomized 204 patients with mild AD to either placebo or liraglutide treatment. Patients would receive weekly subcutaneous injections of up to 1.8 mg liraglutide or matching placebo; the liraglutide would be titrated up as per typical dosing instructions,

and the study would last for a total of 12 months. The final results have been presented at conferences, and a brief synopsis has been published as a conference abstract. The trial failed to meet its primary endpoint; no significant difference was observed in glucose uptake into the brain between patients treated with liraglutide as compared to placebo. The authors did see some positive signals in three of five secondary outcomes. Compared to the placebo group, the liraglutide group had: better cognitive scores as measured by ADAS-Exec, a cognitive outcome that was a combination of the ADAS-Cog and the executive domain portions of the Neuropsychological Test Battery, mitigated loss of temporal lobe volume; and attenuated loss in total brain gray matter volume, the latter two measured by MRI. Other secondary outcomes, including measures of functioning and other measures of cognition such as CDR-SB did not identify any differences between groups (Edison et al., 2021, Conference Abstract; AlzForum).

A 2020 Cochrane review by Mulvaney et al., 2020 assessed the utility of GLP-1 RAs for Parkinson's disease (PD). The review included two studies, summarized below. The conclusion of the Cochrane review was that there was low-certainty evidence that exenatide improves motor symptoms. The motor improvement persisted after cessation of exenatide, raising the possibility that exenatide was disease modifying.

- In a 60-week clinical study (the drug was given for 48 weeks) in patients with PD, 2 mg exenatide once per week improved motor symptoms on the MDS-UPDRS (a PD scale) when patients were off-medication (i.e. having not taken a dopaminergic drug for 8-36 hours). The MDS-UPDRS is a scale to measure symptoms of PD and consists of four parts: 1) Cognition, behavior, mood; 2) Activities of daily living; 3) Motor evaluation; 4) Complications of medication. There were no effects on parts 1, 2, or 4. Additionally, there were no changes on the MDS-UPDRS when patients were on-medication (i.e. taking dopaminergic drugs). Exenatide patients did have more severe PD at baseline (Athauda et al., 2017). Athauda et al., 2019 found that the patients treated with exenatide had improved insulin signaling in the brain measured by IRS-1 tyrosine phosphorylation and phosphorylation of downstream effectors such as mTOR and AKT in neuronally-derived extracellular vesicles.
- Another trial randomized 45 patients with moderate PD to either no treatment or exenatide; this design meant blinding patients was not possible, though the assessments were performed by blinded study researchers. Patients in the exenatide group received up to 10 micrograms twice a day for 12 months; all participants were evaluated during dosing as well as 2 months after end of dosing. Over the course of the 12-month dosing period and 2-month washout period, patients with no treatment declined, as expected, whereas patients treated with exenatide had improvements in motor symptoms as measured by MDS-UPDRS and global

cognition as measured by the Mattis dementia rating scale-2. The difference between the groups was statistically significant for both motor and cognitive symptoms. The authors caution that this should be viewed as proof-of-concept data, given the limitations in the study design, though also state that the differences detected were clinically relevant (Aviles-Olmos et al., 2013). The researchers followed up with the patients again 12 months after cessation of dosing. They found that the motor (p=0.002) and cognitive improvements (p=0.006) in the patients treated with exenatide compared to placebo persisted, with a mean score improvement from baseline for those treated with exenatide and a mean score decline from baseline for those who did not receive treatment (Aviles-Olmos et al., 2014).

Other studies of GLP-1 RAs in patients with PD have been completed since the publication of the Cochrane review. One tested the effects of once-daily lixisenatide or placebo treatment in 156 patients with PD. Participants received study drug for 12 months, and an additional follow-up visit was completed at 14 months after a 2-month washout. The authors found that motor symptoms stabilized or slightly improved in those treated with lixisenatide, whereas motor function declined in the placebo group. The difference was statistically significant (p=0.007). Motor function scores were still numerically better in the lixisenatide treated group than placebo after a 2-month washout period, but the authors state that this result was not adjusted for multiplicity and that no conclusions could be drawn from that data. A post hoc analysis suggested the treatment effect may have been greater in patients younger than 60. There were no other differences between groups in other outcomes (Meissner et al., 2024). Another study randomized 63 patients with PD to either placebo (n=21) or liraglutide (n=42). Dosing lasted for 52 weeks after titrating to final dose. The authors report a significant improvement in the liraglutide treated group as compared to placebo treated group in non-motor symptoms; a secondary outcome analysis also indicated a significant improvement in activities of daily living in the liraglutide group compared to placebo group (Malatt et al., 2022).

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 describes a randomized controlled double-blinded study comparing the safety, tolerability, and efficacy of placebo vs. NLY01 in patients with early untreated PD. NYL01 is a brain-penetrant, modified form of exenatide administered via subcutaneous injection. The trial randomized 255 individuals to either placebo or one of two doses of NLY01. The authors found no differences between groups in terms of

motor or non-motor symptoms. A prespecified subgroup analysis found that NLY01 might have been beneficial in patients younger than 60, but these findings are preliminary.

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. 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).

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. Some GLP-1 RAs such as exenatide and lixisenatide appear to be or are BBB penetrant, though it is not fully clear whether brain concentrations are high enough for clinically meaningful effects. There are some conflicting results for liraglutide, with some studies reporting no penetrance and some studies reporting penetrance at some

doses and time points. 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. Much of this work was completed in rodents; future work will hopefully confirm or otherwise clarify the extent of brain access of each GLP-1 RA (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 GLP-1 RAs based on APOE4 status.

Aging and related health concerns: GLP-1 agonists have significant benefits for treating diabetes, cardiovascular and renal complications relating to diabetes, and obesity. It is not clear whether they have beneficial effects in otherwise healthy individuals.

Types of evidence:

- 9 systematic reviews and/or meta-analyses
- 2 professional practice committee documents or statements
- 4 clinical trials
- 1 professional resource
- 8 reviews
- Multiple laboratory studies

Diabetes: BENEFIT

GLP-1 RAs are 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 GLP-1 RAs or SGLT2s as first-line treatment. In patients without these risk factors GLP-1 RAs are 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 and dulaglutide are considered to have very high glycemic efficiency, while other GLP-1 RAs are considered to have 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, closely followed by dulaglutide and liraglutide – some studies report dulaglutide to be more effective, some find no difference – with exenatide typically significantly less effective at lowering $HbA1_c$ compared to its GLP-1 RA counterparts (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, GLP-1 RAs have been found to have other benefits. As reviewed in Drucker, 2024, among others, treating patients with T2D with 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 GLP-1 RAs reduces major adverse cardiovascular events (MACE). A Cochrane network meta-analysis of different anti-diabetic drugs for individuals with cardiovascular disease included seven trials of GLP-1 RAs 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). 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).

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).

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).

A small RCT in patients with T2DM reported that exenatide (2x bid) over 3 months had no effect on exercise capacity or endothelial function (measured with flow-mediated dilation) but did slightly improve arterial stiffness compared to placebo (Scalzo et al, 2017).

Renal Outcomes: BENEFIT IN CERTAIN POPULATIONS

GLP-1 RAs are 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 albiglutide, dulaglutide, efpeglenatide, exenatide, liraglutide, lixisenatide, or semaglutide, 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 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 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 GLP-1 RAs (Adamou et al., 2024; Stefanou et al., 2024, among others).

Obesity: BENEFIT

High-dose semaglutide and liraglutide are both 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 GLP-1 RAs 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 found that semaglutide was particularly effective as a weight loss agent compared to the other individual drugs in their study, though in the latter study, it was a posthoc analysis.

GLP-1 RAs may also benefit patients with a variety of other diseases, including PCOS, MASLD/MASH, substance abuse, and depression, among others (Chen et al., 2024; Drucker, 2024).

Safety: GLP-1 receptor agonists 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:

- 4 systematic reviews and/or meta-analyses
- 3 observational studies
- 1 case report
- 1 professional resource
- 1 review
- 1 commentary

The most common side effects of GLP-1 RAs 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 GLP-1 RAs with other drugs that can affect blood sugar levels (Collins & Costello, 2024; Drucker, 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, but research in this area continues (Gallo, 2013; Monami et al, 2017; Zhang et al., 2022; Hidayat et al., 2023). However, GLP-1 RAs are still not recommended for use in patients with history of pancreatitis, and patients who develop pancreatitis while on GLP-1 RAs should discontinue use of the drug (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 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, 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 (Wang et al., 2024).

As GLP-1 RAs are known to slow gastric emptying, there are potential concerns for individuals on GLP-1 RAs 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. 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 (Mullins et al., 2019; Aviles-Olmos et al., 2013; Malatt et al., 2022; Meissner et al., 2024). The below table includes the reported incidence of common adverse events in trials in patients with dementia. The studies reported that the adverse events were all mild or moderate unless otherwise noted.

Study + Drug	Nausea	Common Non-Nausea Adverse Events
Mullins et al., 2019, exenatide vs. placebo, respectively	38% vs. 0%	Weight loss / loss of appetite (31% vs. 0%), upper GI infection symptoms (31% vs. 0%)
Meissner et al., 2024, lixisenatide vs. placebo, respectively	46% vs. 12%	Vomiting (13% vs. 3%), reflux (8% vs. 1%), weight loss (8% vs. 0%), fatigue (8% vs. 1%)

McGarry et al., 2024, 2.5 or 5 mg NLY01 (modified exenatide) vs placebo, respectively	39% vs. 58% vs. 19%	GI disorders (61% vs. 75% vs. 36%)

In Meissner et al., 2024 there was one serious adverse event attributed to lixisenatide: a case of pancreatitis in the lixisenatide group. Overall, 36% of the participants in the lixisenatide group had unacceptable side effects at the maximum target dose of 20 micrograms per day and required a dose reduction to 10 micrograms per day; the one withdrawal for an adverse event was in the placebo group. Aviles-Olmos et al., 2013, a trial of exenatide in PD patients, reported a potential trend towards increased dyskinesias in the patients treated with exenatide compared to no treatment.

The ELAD study was a larger trial testing liraglutide in 204 patients with AD over the course of 12 months. Patients were randomized to once weekly subcutaneous injections of either placebo or liraglutide, with a maximum dose of 1.8 mg of liraglutide. The study has not been published in full, but details from conference presentations indicate that no safety concerns were raised during the trial; there were no deaths, and fewer adverse events in the liraglutide group than the placebo group (Edison et al., 2021, Conference Abstract; AlzForum).

As of June 2024, 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:

Drug interactions vary based on the specific GLP-1 RA, but all have 2 major interactions: one with gatifloxacin (as it can affect blood sugar levels), and one with bexarotene (due to increased risk of pancreatitis). Drug interactions lists for each GLP-1 RA can be seen on drugs.com (dulaglutide; exenatide; liraglutide; lixisenatide; semaglutide).

Individuals who are taking GLP-1 RAs and other drugs that can affect blood sugar or cause hypoglycemia, like insulin, must carefully monitor their blood sugar. As 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 GLP-1 RAs.

GLP-1 RAs should be taken with caution with alcohol, as alcohol can affect blood sugar. Some GLP-1 RAs 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 disease interactions for GLP-1 receptor agonists. All drugs in this class should be avoided or used with caution in patients with personal or family history of medullary thyroid carcinoma, or with personal history of multiple endocrine neoplasia syndrome type 2.

Research underway:

There are at least 200 ongoing studies of GLP-1 receptor agonists that are registered on clinicaltrials.gov. Most of these involve patients with type 2 diabetes and/or obesity. Several of these studies involve either neurodegenerative disease, neurological disease, cognition, or aging.

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.

NCT06171152 is assessing the effects of liraglutide on BDNF levels in patients who are obese, have multiple sclerosis, acute leukemia (in remission), or long-COVID, and have subjective cognitive issues such as trouble with memory, concentration, or decision making. The study plans to enroll 30 individuals, all of whom will be randomized to one of two dosing regimens of liraglutide. Dosing will last for 12 weeks. The primary outcome of the study is change in serum BDNF 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.

NCT05313529 plans to enroll 324 patients with mild cognitive impairment and type 2 diabetes that is inadequately controlled by metformin monotherapy. Patients will continue their metformin monotherapy and will be randomized to one of three additional treatment groups: liraglutide, empagliflozin (an SGLT-2 inhibitor), or linagliptin (a DPP-4 inhibitor). The study has an open-label design and will last for 76 weeks. The primary outcome is change in cognitive function from baseline to the end of dosing. Other outcome measures include change in $HbA1_c$ levels and olfactory function.

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.

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:

NCT04232969 is a Phase 3 trial of exenatide in PD patients. The study enrolled 194 patients and randomized them to either placebo or 2 mg weekly exenatide via subcutaneous injection. Dosing is set to continue for 96 weeks. The primary outcome measure is motor function as measured by UPDRS Part III. Secondary outcome measures include other measures of PD disease progression, cognitive function, and safety.

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.

NCT04154072 is an ongoing Phae II study assessing the safety, tolerability, and efficacy of NLY01 in 255 patients with early-stage, untreated Parkinson's disease (PD). NLY01 is a chemically modified version of exenatide. The patients were assigned to either placebo or NLY01 for 36 weeks. The primary outcome is

change in PD symptoms in terms of motor function and activities of daily living, as assessed by the Unified Parkinson's Disease Rating Scale (UPDRS) Part II and Part III.

NCT04305002 is an ongoing study of the use of exenatide in PD patients. The study enrolled 60 patients with early PD and randomized them to either placebo or 2 mg weekly exenatide via subcutaneous injection. The patients will be treated for 18 months. The primary outcome measure is FDG-PET to assess glucose-related changes in the brain. Secondary outcome measures include measures of PD disease progression, cognition, and safety.

NCT05768945 is an observational retrospective comparative risk study assessing the incidence of dementia / AD onset in 65+ year old patients with type 2 diabetes treated with DPP4 inhibitors as compared to those treated with semaglutide using Medicare claims data.

Other Studies:

Two studies are assessing the effects of GLP-1 receptor agonists on cognitive function in patients with psychiatric disorders. NCT06331286 is testing the utility of dulaglutide adjuvant therapy in patients with bipolar disorder with obesity, and 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; NCT02829502, which is examining the effect of an acute dose of exenatide on blood flow and brain oxygenation in patients in the subacute phase of stroke; 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, and NCT03948347, which is investigating the use of liraglutide in the treatment of acute minor stroke or high-risk transient ischemic attack in patients with type 2 diabetes.

Search terms:

Pubmed, Google: GLP-1 receptor agonist, dulaglutide, exenatide, liraglutide, lixisenatide, semaglutide

- Alzheimer's, cognition, dementia, aging, longevity, lifespan, cardiovascular [MA/SR], mortality [MA/SR], peripheral neuropathy, orthostatic hypotension, atherosclerosis, cancer, apoe,

apolipoprotein, blood brain barrier, insulin resistance, thyroid cancer, pancreatitis, blood pressure, retinopathy

Websites visited for GLP-1 receptor agonists:

- Clinicaltrials.gov: GLP-1 receptor agonist; dulagatine; exenatide; liraglutide; lixisenatide; semaglutide
- Examine.com
- Drugs.com: GLP-1 receptor agonists; dulaglutide; exenatide; liraglutide; lixisenatide; semaglutide
- WebMD.com: dulaglutide; exenatide; liraglutide; semaglutide
- PubChem: dulaglutide; exenatide; liraglutide; lixisenatide; semaglutide
- DrugBank.ca: dulaglutide; exenatide; liraglutide; lixisenatide; semaglutide
- Cafepharma: GLP-1 receptor agonist; dulaglutide; exenatide; liraglutide; lixisenatide; semaglutide