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.

Dual GIP/GLP-1 Receptor Agonists

Evidence Summary

Dual GIP/GLP-1 RAs are a recommended treatment for T2D and obesity. There is theoretical basis for neuroprotective action, especially in patients with metabolic disease, but more work is needed.

Neuroprotective Benefit: While there is early evidence that single GLP-1 RAs may reduce incidence of dementia or mitigate decline and dual GIP/GLP-1 RAs may have similar effects, no observational or clinical trials have yet tested this for dual agonists.

Aging and related health concerns: Dual GIP/GLP-1 RAs have significant benefits for treating diabetes and obesity and have potential benefit for other metabolic syndromes. It is not clear whether there are benefits for otherwise healthy individuals.

Safety: Dual GIP/GLP-1 RAs can cause a variety of gastrointestinal adverse events. These events can be common but are often mild and transient. Significant work is required to clarify serious adverse events that are rarer or from long-term use.

Availability: By prescription	**Dose**: Varies by drug. For tirzepatide, the sole approved dual GIP/GLP-1 RA, the initial dose is 2.5 mg titrated up to a maximum of 15 mg, administered via once-weekly subcutaneous injection for both type 2 diabetes and obesity
Half-life: Approximately 5 days	**BBB**: Varies by drug, some conflicting results. See information in the 'Neuroprotection' section
Clinical trials: The largest meta-analyses of RCTs of tirzepatide include approximately 9800 participants.	**Observational studies**: The largest observational study identified included approximately 9100 patients who received tirzepatide.

What is it?

When lifestyle and diet changes are not sufficient to control blood glucose levels in patients with diabetes, patients are often prescribed one or more medications to establish glycemic control (ADA Standard of Care in Diabetes, 2024). Several of these drugs are known as incretin mimetics; that is, they mimic the activity of incretins, which are peptide hormones such as glucose-dependent insulinotropic polypeptide, originally known as gastric inhibitory polypeptide (GIP), and glucagon-like peptide 1 (GLP-1). These peptides are produced in the gastrointestinal tract and stimulate insulin secretion. The native peptides have short half-lives and are rapidly degraded by dipeptidyl peptidase-4 (DPP4), and so extensive research work has been performed to create modified peptides that resist degradation. Incretin mimetics include GLP-1 receptor agonists (GLP-1 RAs), and dual GIP/GLP-1 receptor agonists (dual GIP/GLP-1 RAs); as the name suggests, dual GIP/GLP-1 RAs stimulate both GIP and GLP-1 receptors. GLP-1 and its analogs stimulate insulin production, slow gastric emptying, and inhibits glucagon release in both normal and hyperglycemia states. GIP and its analogs also stimulate insulin production, increases the sensitivity of adipose tissue to insulin as well as increases the lipid-buffering capacity of adipose tissue, and modulates glucagon release depending on blood sugar levels (Samms et al., 2020; Mishra et al., 2023). It is thought that compared to single agonists, co-agonists may increase beneficial effects through complementary or potentially synergistic effects, and possibly achieve greater therapeutic efficacy with fewer dose-limiting adverse events by targeting multiple receptors and/or receptors instead of just one (Samms et al., 2020; Willard et al., 2020; Scheen, 2023).

Tirzepatide, marketed as Mounjaro® for type 2 diabetes (T2D) and Zepbound® for overweight and obesity by Eli Lilly, is the first dual GIP/GLP-1 RA to obtain FDA approval. Tirzepatide received its first FDA approval for T2D in 2022. Ongoing studies are assessing the efficacy of tirzepatide for other indications, including cardiovascular disease, metabolic dysfunction-associated steatohepatitis (MASH), and chronic kidney disease.

As of August 2024, there appear to be four other dual GIP/GLP-1 RAs in clinical development: VK2735 (Viking Therapeutics), NNC0090-2746 (Novo Nordisk), CT-388 (Roche), and Ray1255 (Raynovent Biotech). There are other dual GIP/GLP-1 RAs that are in earlier stages of development, such as DA-CH5 / KP405 (Kariya Pharmaceuticals), which is ready for Phase I trials. Dual GIP/GLP-1 RAs may have different pharmacological profiles for many different reasons, including their relative agonism of the GIP receptor versus the GLP-1 receptor. For instance, tirzepatide is an imbalanced dual agonist – that is, it agonizes the GLP-1 receptor less than the GIP receptor, whereas other dual agonists are balanced and have similar agonizing capability for both receptors. Tirzepatide also shows bias at the GLP-1 receptor and promotes cAMP production over β-arrestin recruitment (Willard et al., 2020). This report will focus on tirzepatide given that the bulk of the clinical data is from tirzepatide trials but will include data from other dual agonists where available.

Neuroprotective Benefit: While there is early evidence that single GLP-1 RAs may reduce incidence of dementia or mitigate decline and dual GIP/GLP-1 RAs may have similar effects, no observational or clinical trials have yet tested this for dual agonists.

Types of evidence:

- 1 Cochrane meta-analysis of single GLP-1 RAs
- 4 clinical trials of single GLP-1 RAs
- 6 reviews
- 6 laboratory studies

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

There is not yet any human data to suggest that dual GIP/GLP-1 RAs can prevent dementia, decline, or improve cognition function.

Observational and early clinical trial results suggest that single GLP-1 RAs may have benefits for cognitive function and/or influence risk of dementia diagnosis in patients with type 2 diabetes and/or obesity (Cukierman-Yaffe et al., 2020; Vadini et al., 2020; Nørgaard et al.,2022). Whether these drugs are directly neuroprotective or indirectly neuroprotective by reducing risk factors such as poorly controlled blood sugar or obesity is not yet known, and the mechanisms of action are not mutually exclusive.

As dual GIP/GLP-1 RAs appear have a similar mechanism of action and equivalent if not superior performance in terms of peripheral effects such as glycemic control as compared to single GLP-1 RAs, it is possible that dual agonists will also have similar or potentially more significant indirect or direct neuroprotective effects compared to single GLP-1 RAs in cognitively intact individuals. It is also possible that single and dual agonists will have different neurological effects in at least some patient populations. Observational and clinical trial evidence is needed to assess whether dual agonists have cognitive or preventative benefit in cognitively intact individuals.

Human research to suggest benefits to patients with dementia:

There is not yet any human data to suggest that dual GIP/GLP-1 RAs can provide benefit to patients with dementia.

Several small trials have suggested that single GLP-1 RAs may have efficacy for AD or for Parkinson's disease (PD) (Geji et al., 2016; Mulvaney et al., 2020; Edison et al., 2021; Malatt et al., 2022; Meissner et al., 2024), though these results are not consistent and require confirmation in larger studies. Further confirmation will be required to assess whether dual GIP/GLP-1 RAs have similar effects in patients with dementia.

It is possible that the dual agonist nature of GIP/GLP-1 RA could have different effects than single agonists; see "Mechanisms of action for neuroprotection identified from laboratory and clinical research" for further details.

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

Dual GIP/GLP-1 RAs are best known as treatments for T2D and/or obesity and hold promise for treatment of other metabolic disorders, discussed in depth in the 'Aging and related health conditions' section. The role of dual agonists in stimulating insulin production and other metabolic effects via agonism of GLP-1 and GIP receptor can lead to improvements in glucose homeostasis and weight loss (Nauck & Meier, 2018). As diabetes and obesity both independently increase the risk of dementia (Livingston et al., 2024), medications that can reduce risk of or improve these conditions may lead to a reduction in dementia as well. Insulin resistance has also been observed in patients with dementia without metabolic syndrome(s); as dual GIP/GLP-1 RAs can improve insulin resistance, the drug class could exert a neuroprotective effect via improving insulin signaling (Girges et al., 2021).

An indirect neuroprotective effect via reducing risk factors for dementia does not preclude direct neuroprotective effects. Both GLP-1 and GIP receptors have been found in the brain in different brain areas and in neuronal and non-neuronal cells (Kopp et al., 2022; Nowell et al., 2023). Preclinical work suggests that stimulating GLP-1 receptors in the brain may protect against cell death, excitotoxicity, and oxidative stress, and promote neuronal growth, differentiation, autophagy, and synaptic plasticity. Animals that lack GLP-1 receptor have synaptic plasticity and memory formation deficits that are rescued by expression of GLP-1 receptor; wild-type animals that overexpress GLP-1 receptor in the hippocampus have improvements in learning and memory. Single GLP-1 RAs have been reported to decrease aggregate burden in animals models of AD and Parkinson's disease (PD) (reviewed by Kopp et al., 2022 and Kalinderi et al., 2024, among others), and have also been reported to have anti-inflammatory mechanisms of action (Luna-Marco et al., 2023).

Dual agonists, theoretically, could have at least similar effects through their agonism of GLP-1 receptors. Less is known about the effects of GIP agonism in the brain, though it is thought to promote neurogenesis and neuronal survival and reduce neuroinflammation and aggregate load (Ji et al., 2016; Nowell et al., 2023). As reviewed by Nowell et al., 2023, multiple studies have reported that different dual GIP/GLP-1 RAs reduce plaque load and mitigate memory deficits or cognitive impairment in different animal models of AD; some of these studies also report improvements in synaptic plasticity and/or numbers. In animal models of PD, dual GIP/GLP-1 RAs have been reported to be neuroprotective and mitigate both neuroinflammation and motor impairments. Some of these studies have reported that the dual GIP/GLP-1 RA enhanced release of neurotrophic factors, improved mitochondrial health indices, or inhibited apoptosis. Some of these studies compared a dual GIP/GLP-1 RA to a single GLP-1 RA and found that while both single and dual agonists had beneficial neurological action, the dual agonist was superior to the single agonist. For instance, one study in an animal model of AD reported

that treatment with a preclinical dual GIP/GLP-1 RA, DA4-JC, was more effective at enhancing synaptic plasticity, reducing memory impairment, amyloid plaque burden, and pro-inflammatory cytokine levels in the brain compared to a single GLP-1 RA liraglutide; both single and dual agonists improved these measures compared to control (Maskery et al., 2020). A study in an animal model of PD reported that another preclinical dual GIP/GLP-1 RA, DA5-JC / KP405, more significantly improved motor performance and reduced levels of inflammation and α-synuclein than liraglutide, though again, both single and dual agonists significantly improved these outcomes compared to control treatment (Zhang et al., 2023). More work is needed to further explore these initial findings.

Tirzepatide is the only approved dual GIP/GLP-1 RA. Preclinical experiments have reported that tirzepatide reduces amyloid plaque load in some brain regions, overall inflammatory burden, and neuronal apoptosis, and enhanced brain glucose metabolism in cellular and animal AD models, though it did not improve memory deficits (Yang et al., 2024). Tirzepatide was reported to improve memory in animal models of diabetes, in addition to mitigating plaque accumulation and reducing neuroinflammation and insulin resistance (Guo et al., 2023). Whether the differences in effects on cognitive function were due to the disease model or specific cognitive domain studied remains to be further explored. Cellular models of high glucose environments suggest that tirzepatide can mitigate the effects of hyperglycemia and insulin resistance in neurons, in part via promoting neuronal growth and differentiation pathways (Fontanella et al., 2024).

An important question is whether dual GIP/GLP-1 RAs cross the blood-brain barrier (BBB) and accumulate in high enough concentrations to exert a physiologically relevant effect. Preclinical work shows that some dual agonists like DA5-CH appear to rapidly cross the BBB and accumulate; others like tirzepatide appear to have limited BBB penetrance (Rhea et al., 2023). Further work in humans is necessary to determine whether dual GIP/GLP-1 RAs can cross the BBB at appreciable levels or otherwise have direct effects on cell types in the brain.

APOE4 interactions:

It is not yet known whether there are differential effects of dual GIP/GLP-1 RAs based on APOE4 status.

Aging and related health concerns: Dual GIP/GLP-1 RAs have significant benefits for treating diabetes and obesity and have potential benefit for other metabolic syndromes. It is not clear whether there are benefits for otherwise healthy individuals.

Types of evidence:

- 8 meta-analyses and/or systematic reviews
- 1 professional practice committee document
- 8 clinical trials
- 1 observational study
- 6 reviews
- 1 laboratory study

Diabetes: BENEFIT

Tirzepatide is approved for treatment of T2D and is typically used as a second-line treatment unless a very high glycemic efficacy medication is called for, or when there is a contraindication to the first-line pharmacological 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; Farzam & Patel, 2024). Tirzepatide is considered to have a very high glycemic efficacy and lowers $HbAI_c$ and fasting blood glucose.

Tirzepatide has been shown to significantly reduce $HbA1_c$ compared to placebo and active controls, including dulaglutide and semaglutide, two single GLP-1 RAs with very high glycemic efficacies. A meta-analysis including 28 trials of a total of 23,622 patients with T2D assessed RCTs that compared 5, 10, and 15 mg doses of tirzepatide to placebo, 0.5, 1, or 2 mg of semaglutide, or other glucose-lowering drugs. The authors found that compared to placebo, 15 mg tirzepatide was the most effective at lowering $HbA1_c$ (-1.96%), followed by 10 mg tirzepatide (-1.84%), then 2.0 mg semaglutide (-1.59%). When they compared tirzepatide directly to semaglutide, all doses of tirzepatide were had comparable glycemic efficiency to 2 mg semaglutide, but significantly better than 1 mg or 0.5 mg semaglutide (Karagiannis et al., 2024). A systematic review of meta-analyses reports that other meta-analyses similarly find significant benefits in terms of glycemic control of tirzepatide over placebo and active controls, including single GLP-1 RAs like semaglutide (reviewed in Kaore et al., 2024).

NNC0090-2746 is a dual GIP/GLP-1 RA still under clinical development. It was tested in a 12-week Phase 2a trial in 108 patients with type 2 diabetes who had not reached adequate glycemic control on metformin. The trial had a placebo arm, a NNC0090-2746 arm (1.8 mg once daily), and an open-label liraglutide arm (titrated up to 1.8 mg once daily). There were significant improvements in $HbA1_c$ compared to placebo (estimated treatment difference: -0.96%; 95% CI -1.36 to -0.56, p <0.0001). There was no significant difference in change in $HbA1_c$ between patients treated with NNC0090-2746 as compared to liraglutide (Frias et al., 2017).

There is also some evidence that dual GIP/GLP-1 RAs can be beneficial in prediabetes. Trials in patients with obesity have reported that more prediabetic patients treated with a dual GIP/GLP-1 RA such as tirzepatide or CT-388 became normoglycemic by the end of the trial compared to the placebo treated group (Jastreboff et al., 2022; Roche news release) and a post-hoc analysis of the 72-week primary analysis of SURMOUNT-1, a large RCT comparing tirzepatide to placebo suggests that in patients with overweight or obesity, tirzepatide treatment reduces the predicted risk of developing T2D (Hankosky et al., 2023). SURMOUNT-1 ran for a further 104 weeks and announced their topline data in August 2024: when the researchers pooled the doses of tirzepatide and compared to placebo, they found a 94% reduction in the risk of progression to T2D in the tirzepatide group compared to placebo (Eli Lilly news release).

Overweight or Obesity: BENEFIT

Tirzepatide is approved for weight management in patients with or without diabetes (FDA).

The meta-analysis by Karagiannis et al., 2024 assessed the efficacy of tirzepatide compared to placebo, semaglutide, and other antidiabetics in patients with T2D. The meta-analysis included 28 trials that lasted between 24 and 104 weeks. The authors found that compared to placebo, tirzepatide was the most effective medication for reducing body weight, with weight loss ranging from 5.27 kg (95% CI 3.98 to 6.56) with 5 mg tirzepatide to 9.57 kg (95% CI 8.36 to 10.78) with 15 mg tirzepatide; in comparison, 2 mg semaglutide was associated with loss of 4.97 kg (95% CI 1.68 to 8.26). When comparing tirzepatide to semaglutide, all studied doses of tirzepatide led to significantly more weight loss than all doses of semaglutide, though the confidence in estimates was low for the comparisons to the highest dose of semaglutide.

Other meta-analyses of RCTs also find significant benefit of tirzepatide in terms of weight loss compared to both placebo and to active controls like semaglutide (reviewed in Kaore et al., 2024). Observational studies also report similar overall conclusions. A cohort study using electronic health records of 18,386 adults with overweight or obesity assessed the on-treatment weight change of people receiving semaglutide as compared to tirzepatide. The study reported that compared to patients receiving semaglutide, patients receiving tirzepatide were more significantly likely to lose weight, with higher hazard ratios for more significant weight loss (≥5% body weight, HR=1.76; 95% CI 1.68 to 1.84; ≥10% body weight HR=2.54; 95% CI 2.37 to 2.73; and ≥15% body weight HR=3.24; 95% CI 2.91 to 3.61). The weight changes in those receiving tirzepatide were more significant as compared to those receiving semaglutide at 3 months (difference -2.4%; 95% CI -2.5% to -2.25), 6 months (-4.3%; 95% CI, -4.7% to -4.0%), and 12 months (-6.9%; 95% CI -7.9% to -5.8%) (Rodriguez et al., 2024).

The Phase 2a study of NNC0090-2746 published by Frias et al., 2017 found a significant decrease in body weight at 8 weeks of treatment with 1.8 mg daily NNC0090-2746 as compared to placebo (estimated treatment difference: -1.80%; 95% -3.24 to -0.37, p=0.0141) but this change was no longer significant at the end of the trial at 12 weeks. A news release reported that a Phase 1b RCT of CT-388 compared to placebo reported a placebo-adjusted weight loss of 18.8% in the CT-388 group at 24 weeks of treatment. At 24 weeks, 100% of the CT-388 treated patients had lost at least 5% of their body weight (Roche news release).

While it is clear that dual GIP/GLP-1 RAs can have real benefits in terms of weight management, there are still unanswered questions regarding its long-term efficacy. For instance, studies suggest that weight loss is at minimum not completely maintained after cessation of medication for many individuals (Aronne et al., 2024). Some, such as Dr. Peter Attia, have also brought up the question of how much total weight loss is fat as compared to muscle as measured by DEXA scans (AMA #45), or have looked at changes in the proportion of lean mass in the body. Initial results from a trial of tirzepatide compared to placebo found that the mean reduction in total body fat mass was 33.9% and the mean reduction in lean mass was 10.9% (Jastreboff et al., 2022) and overall studies have reported that most of the weight loss of single GLP-1 RAs and dual agonist GIP/GLP-1 RAs are driven by loss of fat (Drucker, 2024). Further work will be required to validate these findings and to compare between tirzepatide and other single GLP-1 RAs or dual GIP/GLP-1 RAs.

Cardiovascular Indices and Mortality: LIKELY BENEFIT

Single GLP-1 RAs such as dulaglutide are known to reduce major cardiovascular events (MACE). It is not yet known whether dual GIP/GLP-1 RAs like tirzepatide also reduce MACE; an ongoing study known as SURPASS-CVOT is currently assessing whether tirzepatide is noninferior or superior to dulaglutide in reducing MACE as measured by a time-to-event analysis in 13,229 individuals with T2D and atherosclerotic cardiovascular disease. The study is fully enrolled (Nicholls et al., 2024).

Evidence thus far indicates that tirzepatide at least does not increase cardiovascular risks compared to control treatment. A pre-planned meta-analysis of seven RCTs of tirzepatide (n=4,887) compared to controls (n=2,328), including placebo and active comparators such as insulin or single GLP-1 RAs, found no significant difference between tirzepatide and pooled comparators in terms of MACE (HR=0.80; 95% CI 0.57 to 1.11), cardiovascular death (HR=0.90; 95% CI 0.50 to 1.61), or all-cause death (HR=0.80; 95% CI 0.51 to 1.25) (Sattar et al., 2022). A systematic review and meta-analysis that assessed only placebo-controlled studies of tirzepatide or placebo-controlled studies of GLP-1 RAs found that compared to placebo, single GLP-1 RAs and tirzepatide reduced MACE (OR=0.87; 95% CI 0.81 to 0.94), cardiovascular mortality (OR=0.88; 95% CI 0.80 to 0.96), and all-cause mortality (OR=0.88; 95% CI: 0.82 to 0.96), without differences between single GLP-1 RAs and tirzepatide (Stefanou et al., 2024). These data suggest that tirzepatide may at minimum have cardioprotective benefits compared to placebo treatment.

Meta-analyses have reported benefits of tirzepatide on cardiovascular indices such as blood pressure and lipid profiles. One meta-analysis of participants in phase 3 RCTs in patients with T2D included approximately 7,000 individuals in trials of tirzepatide. They reported that tirzepatide treatment was associated with significant decreases in LDL-c (range of mean differences: -11.61 to -6.77%), total cholesterol (range of mean differences -7.94% to -5.09%), and triglycerides (range of mean differences -19.94% to -13.31%) compared to placebo, insulin, and sodium-glucose co-transporter 2 (SGLT2) inhibitors (Chae et al., 2024). A systematic analysis of meta-analyses of outcomes of tirzepatide treatment in patients with T2D also reported improvements in lipid profiles for those taking tirzepatide compared to placebo. This systematic review also reported improvements in blood pressure compared to control (Kaore et al., 2024). A meta-analysis with 3,901 participants with overweight or obesity without diabetes in RCTs testing tirzepatide compared to placebo reported reductions in systolic (-7.37 mmHg; 95% CI -9.12 to -5.62) and diastolic (-4.38 mmHg; 95% CI -5.39 to -3.36) blood pressure in the tirzepatide treated groups compared to placebo in this patient population as well (Liu et al., 2024).

Tirzepatide or other dual GIP/GLP-1 RAs may have other benefits for age-related diseases or conditions that contribute to age-related diseases. For instance, two phase 3 trials have shown benefit of

tirzepatide for adults with sleep apnea and obesity compared to placebo treatment (Malhotra et al., 2024). A phase 2 RCT of patients with metabolic dysfunction–associated steatohepatitis (MASH) compared three doses tirzepatide treatment to placebo and found that of the 190 randomized participants, all doses of tirzepatide treatment resulted in statistically significantly higher percentages of patients who met criteria for resolution of MASH without worsening of fibrosis compared to placebo (44%, 56%, 62% in the 5 mg, 10 mg, and 15 mg tirzepatide groups, respectively, compared to 10% in placebo) (Loomba et al., 2024). Initial data also suggests that in patients with T2D and high cardiovascular risk, tirzepatide treatment may lead to improvements in indices of renal health and/or reduced occurrence of composite kidney endpoint compared to at least certain anti-diabetic treatments like insulin (HR=0.58; 95% CI 0.43 to 0.80). Further, targeted studies into renal function are needed (Heerspink et al., 2022; reviewed in Caruso & Giorgino, 2024).

Safety: Dual GIP/GLP-1 RAs can cause a variety of gastrointestinal adverse events. These events can be common but are often mild and transient. Significant work is required to clarify serious adverse events that are rarer or from long-term use.

Types of evidence:

- 10 meta-analyses or systematic reviews
- 1 pooled analysis of RCTs
- 1 disproportionality analysis from FAERs
- 1 open label clinical trial
- 2 professional resources
- 2 reviews
- 1 news release

The most common side effect of dual GIP/GLP-1 RAs like tirzepatide are gastrointestinal complaints such as nausea and diarrhea. A meta-analysis of ten trials comprising 6,830 patients reported that 40 to 50% of participants receiving tirzepatide reported gastrointestinal adverse events (Mishra et al., 2023). These gastrointestinal symptoms can lead to other adverse events, such as acute kidney injury secondary to dehydration from the gastrointestinal complaints. Injection site reactions and hypersensitivity have also been reported, as has dizziness, headache, and sinus tachycardia with increased heart rate (Gallwitz 2022; Farzam & Patel, 2024; Liu et al., 2024). Alopecia has also been reported to be more frequent with tirzepatide use as compared to placebo in clinical trials and has been reported to adverse event

reporting systems. This side effect has also been linked to single GLP-1 RAs such as semaglutide. It is thought that this effect may be due to rapid weight loss, but further work is needed to clarify whether this is an effect from stimulating GLP-1 receptors (Godfrey et al., 2024; Liu et al., 2024; Drugs.com).

Overall, it is thought that dual GIP/GLP-1 RAs have similar safety profiles to single GLP-1 RAs, though this is still being studied and there may be some key differences depending on dose and comparator single GLP-1 RA. One systematic review of RCTs reported that while there was overall no difference between tirzepatide and single GLP-1 RAs in terms of incidence of adverse events or severe adverse events, the highest dose of tirzepatide of 15 mg was significantly associated with risk of hypoglycemia compared to GLP-1 RAs (pooled RR=3.83; 95% CI 1.19 to 12.30, p=0.02), and higher doses of tirzepatide were more associated with discontinuations (10 mg pooled RR=1.75; 95%CI 1.16 to 2.63, p=0.007; 15 mg pooled RR=2.03; 95%CI 1.37 to 3.01, p=0.0004). It is thought that the increased incidence of hypoglycemia might be related to concomitant antihyperglycemic medications, but more work is needed in this area (Meng et al., 2023). A meta-analysis of RCTs comparing tirzepatide to comparators including GLP-1 RAs reported that odds of GI adverse events were similar between tirzepatide and single GLP-1 RAs except for diarrhea with 10 mg tirzepatide, and that 15 mg tirzepatide was associated with higher discontinuation rate compared to all comparators, including GLP-1 RAs (Karagiannis et al., 2022). This may be influenced by whether the comparison is between all GLP-1 RAs or individual drugs. For instance, another meta-analysis compared tirzepatide to semaglutide and similarly reported no statistical difference in serious adverse events and similar risks of GI adverse events, and only found a difference in discontinuation rates due to GI adverse events when comparing 15 mg tirzepatide to 0.5 mg semaglutide (Karagiannis et al., 2024). A cohort study did not find a significant difference in rates of moderate or severe GI adverse events between tirzepatide and semaglutide (Rodriguez 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).

There are theoretical concerns for or reports of rarer adverse events with single GLP-1 RAs or dual-agonist GIP/GLP-1 RAs. Many of these adverse events are still being explored as more and more people use these medications and/or use them long-term; as the first dual GIP/GLP-1 RA was approved in 2022 whereas single GLP-1 RAs have been on the market for almost two decades, some data from single GLP-1 RAs will be discussed. These potential serious adverse events 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, and significant signals have been detected in the FDA Adverse Event Reporting System between single GLP-1 RAs and specific types of thyroid and pancreatic cancer (Yang et al., 2022). There is a black box warning with this concern on all single GLP-1 RAs and dual GIP/GLP-1 RAs, and both drug classes are contraindicated for individuals with a personal or family history of medullary thyroid carcinoma or patients with multiple endocrine neoplasia syndrome type 2. A meta-analysis of RCTs of tirzepatide in patients with T2D reported that there was no difference in incidence for any cancer or any specific cancer type between tirzepatide and control, which included placebo and active controls like insulin or single GLP-1 RAs. However, the authors strongly caveat their findings, given that these trials were at most 72 weeks long and did not specify cancer as an outcome of interest. The authors state that their findings should be considered as preliminary (Popovic et al., 2024).
  Single GLP-1 RAs have been in use for more time than dual agonists. Groups have reported conflicting results regarding use of single GLP-1 RAs 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. As obesity and T2D can be associated with increased incidence of cancer, more work is needed to disentangle the theoretically competing risk/benefits of these drugs in different patient populations.
- 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 single GLP-1 RA usage (Gallo, 2013; Monami et al, 2017; Zhang et al., 2022; Hidayat et al., 2023), and a meta-analysis of RCTs of tirzepatide in patients with T2D or obesity (n=9871) similarly found no increased risk of pancreatitis in tirzepatide treated patients compared to control, which included placebo, insulin, or single GLP-1 RA (Zeng et al., 2023). The meta-analysis of cancer incidence by Popovic et al., 2024 similarly did not find an increase in incidence of pancreatic cancer in patients receiving tirzepatide compared to control treatment. Research into this area continues, as this event is rare and may require more time and larger sample sizes to fully explore. Tirzepatide and single GLP-1 RAs are not recommended for use in patients with history of pancreatitis, and patients who develop pancreatitis while on either type of drug should discontinue use of the drug (Farzam & Patel, 2024; Collins & Costello, 2024).

- Gallbladder and biliary disease: a meta-analysis of RCTs comprising 9,871 patients with T2D or obesity reported an increased risk of composite of gallbladder or biliary disease in patients receiving tirzepatide compared to those receiving placebo or insulin (RR=1.97; 95% CI 1.14 to 3.42) (Zeng et al., 2023). Increased risk of gallstones have also been reported with use of single GLP-1 RAs (Monami et al, 2017; 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 (reviewed by Drucker, 2024). Whether there is a causal relationship between single and/or dual agonists and bowel obstruction is not yet known.
- Retinopathy: There have been some conflicting data on whether single GLP-1 RAs such as semaglutide are associated with retinopathy. There have been reported cases of retinopathy in RCTs of tirzepatide (Frías et al., 2021). It has been thought that rapid changes in blood sugar might result in transient worsening of diabetic retinopathy. A pooled analysis of RCTs of tirzepatide in 10,164 patients with T2D found that there was no increase in risk of diabetic retinopathy with tirzepatide treatment compared to placebo, single GLP-1 RA, or insulin (Popovic et al., 2024). However, robust clinical trials are required to fully explore this potential adverse event.
- Suicidal ideations: postmarketing surveillance of single GLP-1 RAs and dual GIP/GLP-1 RAs included reports of suicidal thoughts or actions. The preliminary review by the FDA has not found evidence that single or dual agonists cause these thoughts or actions, but due to the small number of events, cannot yet definitively rule out the possibility that the drug class(es) are involved. The FDA is continuing to investigate and will report on their findings (FDA). While no study has yet looked at tirzepatide and suicidal ideations, Wang et al., 2024 did not find an association between semaglutide and suicidal ideations in populations with either obesity or T2D, compared to non-GLP-1 RA anti-obesity or anti-diabetic drugs.

There have been concerns of counterfeit or compounded tirzepatide. Individuals are encouraged to obtain tirzepatide from a state-licensed pharmacy using a valid prescription (Eli Lilly news release).

Drug interactions:

The only approved dual GIP/GLP-1 RA is tirzepatide. Tirzepatide is known to interact with 410 drugs; 15 are major, 394 are moderate, and 1 is minor. The major drug interactors include bexarotene, as there is

an increased risk of pancreatitis, and gatifloxacin, as there is an increased risk of hypo- or hyperglycemia. Individuals who are taking dual GIP/GLP-1 RAs and other drugs that can affect blood sugar levels or cause hypoglycemia, like insulin, must carefully monitor their blood sugar.

The other major interactors are all drugs used during anesthesia. As described in the 'Safety' section, as use of dual GIP/GLP-1 RAs or GLP-1 RAs is known to slow gastric emptying, there are concerns that use of these drugs before surgery may increase risk of regurgitation and subsequent pulmonary aspiration of gastric contents during anesthesia (American Society of Anesthesiologists, 2023). The effect on stomach emptying may also have implications for medications taken by mouth; it is always important to discuss your full medication and supplement list with your doctor and pharmacist (FDA).

There are 5 disease interactions for dual GIP/GLP-1 RAs (Drugs.com).

- 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.
- Acute pancreatitis has also been reported in patients using tirzepatide; therefore, patients should be aware of signs of pancreatitis and discontinue tirzepatide if pancreatitis is suspected.
- Tirzepatide has been associated with gastrointestinal adverse events; it is therefore not recommended for patients with severe gastrointestinal disease such as gastroparesis.
- Acute kidney injury and worsening of chronic renal failure has also been reported in postmarketing surveillance of tirzepatide; it is hypothesized that at least some of these events may be due to dehydration from gastrointestinal events. It is recommended that renal function be monitored in patients with renal dysfunction reporting severe gastrointestinal events. Dose does not need to be adjusted for renal insufficiency.
- Patients with history of diabetic retinopathy should be monitored for progression of retinopathy, as sudden improvements in glycemic control have been associated with temporary worsening of diabetic retinopathy. While this has not been studied in tirzepatide, it has been studied in GLP-1 RAs.

Research underway:

There are approximately 50 clinical trials of dual GIP/GLP-1 RAs that are registered on clinicaltrials.gov. All of these are in patient populations with metabolic disease, such as T2D, overweight or obesity, or

metabolic dysfunction-associated steatotic liver disease. No ongoing trial is exploring the effects of dual GIP/GLP-1 RAs in dementia.

There are 43 ongoing trials assessing the effects of tirzepatide registered on clinicaltrials.gov; these studies are for a variety of metabolic indications or in different patient populations. Of these, NCT05556512 is a study of the effects of tirzepatide on morbidity and mortality in adults with obesity. This study has enrolled 15,374 individuals who have been randomized to receive either placebo or tirzepatide and will follow participants for up to 5 years to assess the time to first occurrence of a composite of all-cause death or specific major cardiovascular events. NCT05553093 is a study assessing the effects of tirzepatide on brain function in patients with T2D. The study plans to enroll 150 individuals and randomize them to either tirzepatide treatment or treatment with insulin glargine. The primary outcomes include brain function as assessed by fMRI and voxel-based morphometry. Other outcomes include assessment of inflammatory cytokine levels.

There are 2 ongoing studies of VK2735 registered on clinicaltrials.gov; one is a Phase 1 safety and tolerability study, and one is for weight management.

There is 1 ongoing study of CT-388 registered on clinicaltrials.gov.

Search terms:

Pubmed, Google: dual GIP/GLP-1 receptor agonists, tirzepatide

- Diabetes, obesity, cardiovascular disease, MASH, cancer, dementia, Alzheimer's disease, Parkinson's disease, alopecia

Websites visited for dual GIP/GLP-1 receptor agonists:

- Clinicaltrials.gov: GIP; Tirzepatide; VK2735; CT-388
- Drugs.com: Tirzepatide
- WebMD.com: Mounjaro, Zepbound (both tirzepatide)
- PubChem: Tirzepatide
- DrugBank.ca: Tirzepatide
- Cafepharma: GIP; Tirzepatide

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