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BENEFICIAL AND ADVERSE EFFECTS OF GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS

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ABSTRACT

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are a potent class of medications, which have become integral in the treatment for glycemic control and weight loss, indicated for use in type 2 diabetes and obesity. Variabilities exist in the efficacy of hemoglobin A1c reduction and weight loss, as well as the presence of beneficial cardiovascular outcomes amongst the available formulations. Subtle differences occur in the side effect profile of these medications, especially regarding the degree of gastrointestinal discomfort. Other less common side effects have been reported and warrant attention prior to prescribing. The purpose of this review is to describe the well-known beneficial effects, but also focus on the common and uncommon adverse effects described in the literature. Also included will be a strategy to help mitigate the most common gastrointestinal side effects seen clinically, as well as a plan on switching between equivalent formulations and dosages based on the available literature and our clinical experience.

KEYWORDS: Weight loss, Side effects, GLP-1RA, HbA1c, Type 2 diabetes.

INTRODUCTION

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have developed into one of the more powerful tools in the treatment of type 2 diabetes and obesity. GLP-1RAs improve glycemic control through a glucose-dependent mechanism that does not significantly increase the risk of hypoglycemia. Newer and higher dose formulations through the effects on satiety and gastric emptying have demonstrated significant outcomes on weight loss over time. The currently available formulations (Table 1) include oral and injectable options with varying

degrees of efficacy in hemoglobin A1c (HbA1c) reduction and weight loss. Long-term cardiovascular outcome studies have also shown significant benefit in major adverse cardiovascular events in some, but not all formulations of GLP-1RA.[1-3] Guideline recommendations for escalation of care in type 2 diabetes are primarily focused on individual patient specific characteristics and associated comorbidities such as cardiovascular disease, weight, risk of hypoglycemia and relative burden of cost to the patient.[4] The requirement of a subcutaneous injection form of administration for most GLP-1RAs, as well as the overall tolerability of these medications, can limit patient initiation and continuation. Newer and more potent formulations continue to be developed. Tirzepatide is the first combination GLP-1RA and glucose-dependent insulinotropic polypeptide receptor agonist (GIPRA) to gain FDA approval and carries an indication for the treatment of type 2 diabetes. This combination agonist appears to have even more potent effects on HbA1c and weight reduction than any of the currently available GLP-1RAs.[5-6]

The purpose of this review is to describe the well-known beneficial effects but also focus on the common and uncommon adverse effects of GLP-1RAs described in the literature. Also included will be mitigating strategies to overcome the most common gastrointestinal side effects seen clinically. Lastly, considerations regarding approximate equivalent dosages amongst formulations based upon the available literature and our clinical experience in a time where insurance formulary changes and drug shortages can limit everyday prescribing for patients are presented.

Beneficial Effects

Hemoglobin A1c and weight reduction

Multiple phase III and head-to-head clinical trials looking at the effectiveness of GLP-1RA on HbA1c lowering and weight reduction in patients with type 2 diabetes have been conducted. Reviews comparing the results of the available head-to-head trials have been nicely summarized and recently published,[7] and will not be repeated here in detail. Depending on the formulation, HbA1c reduction on average can be expected to range from 0.8% to over 2% with sustained use. Changes in body weight have ranged from +1.0kg to –11.2kg over time (Figures 1 and 2).[6, 8-18] Consistent with previous reports, SUSTAIN-FORTE, a randomized comparison of semaglutide 2.0mg weekly versus 1.0mg weekly, recently reported a mean HbA1c reduction of 2.1% with 2.0mg weekly compared to -1.9%

with 1mg weekly at 40 weeks of therapy. The mean reduction in bodyweight from baseline was 6.9kg with semaglutide 2.0mg versus 6.0kg with semaglutide 1.0mg.[18]

The effectiveness for weight loss has also been well documented in patients without diabetes. A 56-week double-blind trial involving obese patients without diabetes treated with once daily liraglutide 3.0 mg showed a mean weight loss of 8.4kg compared to 2.8kg with placebo used in addition to lifestyle modifications and counseling.[19] In a similar study, a 68-week double-blind trial of semaglutide 2.4mg weekly versus placebo, showed a weight reduction of 15.3kg in the semaglutide group versus 2.6kg in the placebo group.[20]

The combination GLP-1RA/GIPRA medication tirzepatide has also been evaluated in the setting of diabetes and weight loss. In the latest head-to-head trial comparing tirzepatide weekly to semaglutide 1mg weekly, SURPASS-2, tirzepatide at all doses was noninferior and superior to semaglutide 1mg weekly in HbA1c reduction. Tirzepatide 15mg reduced HbA1c on average by 2.3% compared to 1.86% with semaglutide 1mg. At 40 weeks, tirzepatide 15mg produced an average weight loss of 11.2kg compared with a reduction of 5.7kg with semaglutide 1mg.[6]

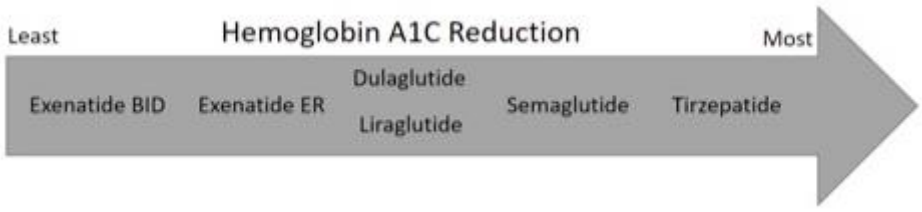

Figure 1: Comparative HbA1c reduction between GLP-1RA medications.

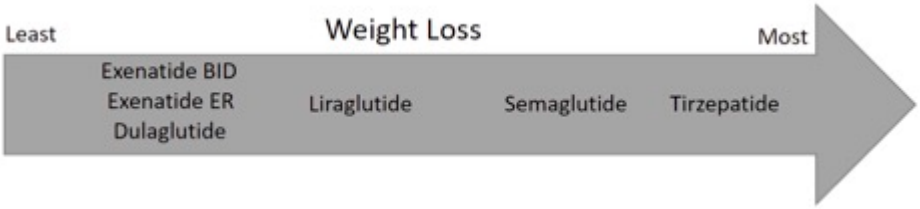

Figure 2: Comparative weight loss between GLP-1RA medications.

Major adverse cardiovascular events

Not only are these medications helpful for HbA1c and weight reduction, but they have also been found to be beneficial in regards to cardiovascular outcomes. Cardiovascular outcome trials (CVOT) have shown significant reduction in major adverse cardiovascular events (MACE) in patients with type 2 diabetes in some but not all formulations of GLP-1RA.

Reduction in ASCVD outcomes has been reported with liraglutide, dulaglutide and semaglutide.[1-3] CVOTs evaluating the more recently FDA approved tirzepatide are ongoing.[21]

Adverse effects

Gastrointestinal side effects

The most common adverse effects seen with GLP-1RA are gastrointestinal discomfort with nausea, vomiting, diarrhea and constipation. There is some subtle in-class variability seen between these medications, as well as overall prevalence in head-to-head clinical trials (Figure 1). Twice daily exenatide was compared to liraglutide 1.8mg daily in LEAD-6, where reports of overall gastrointestinal disorders were more common with exenatide, 78.9% versus 74.9%. It was noted that nausea was similar at treatment onset, but resolved more quickly with continued treatment in the liraglutide group.[8] DURATION-5 showed less nausea with exenatide weekly (14%), compared to exenatide dosed twice daily (35%).[22] DURATION-6 then compared exenatide weekly with liraglutide 1.8mg daily, with more nausea, vomiting and diarrhea seen in the liraglutide group. The frequency of events did correlate with starting treatment and decreased over several weeks with continued treatment.[10] AWARD-1 showed similarities in gastrointestinal adverse events with comparing dulaglutide 1.5mg to exenatide 10mcg twice daily.[11] AWARD-6 comparing dulaglutide 1.5mg weekly to liraglutide 1.8mg daily showed similar rates of nausea, vomiting and diarrhea.[12] Semaglutide 0.5mg weekly had more nausea, diarrhea and vomiting when compared to dulaglutide 0.75mg weekly in SUSTAIN-7, however similar frequency of events were seen with higher doses of semaglutide 1mg weekly compared to dulaglutide 1.5mg weekly.[14] SUPRASS 2 compared tirzepatide at varying doses to semaglutide 1mg weekly, with overall similar rates of gastrointestinal events. However, tirzepatide 15mg weekly had more nausea (22.1% versus 17.9%), diarrhea (13.8% versus 11.5%) and vomiting (9.8% versus 8.3%) when compared to semaglutide 1mg weekly.[6]

Gastrointestinal side effect mitigation

There is limited information in the literature regarding ways to help mitigate side effects due to GLP-1RAs, and most recommendations are based on clinical experience/expert opinion.[23-24] We agree with previous published recommendations[23-24] that extensive patient counseling regarding dietary modifications is essential to reduce gastrointestinal side effects and help facilitate patient continuation of GLP-1RA therapy.[23-24] Modifications of quantity, content

and timing of food should all be considered (Table 2).[23-24] It is also important to note that side effects often improve or resolve over time with continuation of GLP-1RA therapy.[23-25]

The Ozempic®, Wegovy®, and Rybelsus® patient websites do include general suggestions for managing nausea that include eating more slowly and avoiding lying down after eating.[26-28] The recommendation to avoid fried, greasy or sweet foods is included only on the Ozempic® and Rybelsus® websites.[26,28] Our own institutional protocols for nausea/dyspepsia related to GLP-1RA use include using ginger gum/candies, bismuth subsalicylate tablets prior to largest meal, or if persistent and unresponsive to other interventions, use of prescription anti-emetics. For constipation, after optimization of hydration and fiber intake, use of stool softeners[23-24] or laxatives can be considered (limited duration of any stimulant laxatives). Of note, constipation can last longer than other side effects.[24-25] It can also be useful to ensure awareness of any patient baseline gastrointestinal symptoms and consider treatment prior to initiation of GLP-1RA.[23]

Pancreatitis

Since approval of GLP-1RA in 2005, several case reports of acute pancreatitis were published[29] resulting in an FDA warning,[30] but this has remained a significant area of controversy.[31-32] Subsequently, trials showed that GLP-1RA can increase pancreatic enzymes such as amylase or lipase,[10,13,22] however increasing pancreatic enzyme levels alone have been shown to be poor predictors of pancreatitis. A study looking at the impact of liraglutide on pancreatic enzymes or incidence of acute pancreatitis over 56 weeks showed a dose-independent and reversible increase in amylase and lipase that was not predictive of acute pancreatitis. Secondary analysis on the combined data of four trials totaling over 5000 patients resulted in acute pancreatitis in 12 patients receiving liraglutide and 1 patient receiving placebo. Half of the cases of pancreatitis were possibly attributed to gallstone disease evident at the time of onset.[33]

A review of the US FDA database showed an increased odds ratio for reported pancreatitis events in those administered exenatide for type 2 diabetes (OR = 10.68; 95% confidence interval {CI}: 7.75–15.1; P < 10−16).[34] However, systemic reviews published in 2014 suggested no increase in the risk of acute pancreatitis with the use of GLP-1RA.[35-36] A systematic review in 2017 of ELIXA, LEADER and SUSTAIN-6 trials looking at the incidence of acute pancreatitis demonstrated that when compared to placebo, treatment with GLP-1RA was not associated with increased risk of acute pancreatitis (Peto OR 0.745 [95%

CI, 0.47-1.17]).[37] Another review of 43 trials published in 2020 comparing GLP-1RA to placebo or non GLP-1RA in patients with type 2 diabetes with duration of ≥ 52 weeks again showed no association with pancreatitis (MH-OR 1.24 [0.94, 1.64]; p=0.13).[38]

Early symptoms of acute pancreatitis can be difficult to isolate from other well-known GI adverse events during GLP-1RA treatment. Appropriately distinguishing acute pancreatitis from other gastrointestinal side effects can also be challenging within clinical trials. Acute pancreatitis amongst those receiving GLP-1RA within large clinical trials occurred in less than 1% of participants.[39-46] Although it appears uncommon, patients should be warned of the symptoms of acute pancreatitis to monitor after initiation of therapy. Caution should be taken prior to initiating GLP-1RA in patients with a history of pancreatitis.

Cholecystitis and Biliary obstruction

Type 2 diabetes and obesity are known risk factors for the development of gallstone disease. Significant weight reduction is also a known risk factor for stone formation, although the mechanism is poorly understood.[47-48] Studies have reported a potential association between GLP-1RAs and biliary-related diseases in patients with type 2 diabetes. A meta-analysis showed an increased risk of cholelithiasis when compared to alternative therapy with a hazard ratio of 1.3 [95% confidence interval: 1.01-1.68, p =0.041).[49] Post-hoc analysis of the cardiovascular outcome trial LEADER looked at events that included uncomplicated and complicated gallbladder stones as well as biliary obstruction and rates of cholecystitis. There was an increased risk of gallbladder or biliary events with liraglutide versus placebo (n = 141 vs. n = 88 patients, respectively; hazard ratio [HR] 1.60; 95% CI 1.23, 2.09; P < 0.001).[50] A systematic review and meta-analysis of RCTs including over 100,000 patients found that use of GLP-1RAs was associated with increased risk of gallbladder or biliary disease with a relative risk of 1.37, (95% CI, 1.23-1.52). They also report an increased risk in those treated with higher doses for a longer duration, which is important with the increased prescribing seen for medical weight loss management.[51]

A history of gallbladder or biliary disease is an important consideration when considering GLP-1RA therapy and may limit use in those with significant disease. Patients should be educated on the symptoms of biliary colic and cholecystitis as they initiate therapy.

Gastroparesis

The gastrointestinal side effects that have been reported with both short and longer-acting GLP-1RA are felt to be in part related to delayed gastric emptying, and feelings of satiety and diminished appetite.[52] There are GLP-1 receptors present in multiple tissues throughout the body, together with the pancreas and multiple areas of the brain including the hypothalamus and the hindbrain. Effects of GLP-1 receptor agonism on the brain are thought to primarily mediate reduction in food intake, with a subset of those effects on the area postrema being linked to induction of nausea. Differential ability to cross the blood brain barrier may account for some of the differences between GLP-1RAs regarding propensity to cause gastrointestinal side effects and degree of weight reduction.[53] Overtime, the gastrointestinal symptoms can diminish with the longer-acting versions. The improved side effect profile is likely due to a tolerance or tachyphylaxis that develops with time.[54]

A prospective study investigated liraglutide on gastric emptying measured by acetaminophen absorption in obese patients without diabetes. At five hours there was no significant difference in gastric emptying studies between those receiving liraglutide versus placebo. However, the study did find significantly delayed gastric emptying at one hour in the liraglutide group when compared to placebo.[55] This brings the safety concerns of whether patients with diagnosed or suspected gastroparesis should be treated with GLP-1RA. A randomized, cross-over study, reported that patients with normal gastric emptying had a more exaggerated delay in gastric emptying compared to those with baseline slower gastric emptying time when treated with exenatide.[56] Another small study looked at the effects of exenatide in patients with type 2 diabetes with and without gastroparesis. In those with normal gastric emptying time prior to GLP-1RA, 75% of participants treated with exenatide fulfilled criteria for gastroparesis. In contrast, 30% of those with pre-existing gastroparesis had worsening gastric emptying, with the other 70% showing no difference or even improved gastric emptying.[57] A retrospective review of gastric emptying studies performed at an academic medical center could not find statistical significance between GLP-1RA use and gastroparesis. They observed that the duration of diabetes was a stronger predictor of delayed gastric emptying study compared to HbA1c levels.[58]

Based on current literature, it may be inappropriate to withhold GLP-1RA in patients with gastroparesis, as it is possible they would aid from the known therapeutic benefits without significantly worse adverse events than patients without gastroparesis.

Package inserts for GLP-1RA include information regarding delayed gastric emptying and effects on other oral medications.[59-67] The newest available drug in this class, tirzepatide, comes with the combination effect of both GLP-1 and GIP action. The package insert for tirzepatide brings the warning of possible decreased effectiveness of oral contraceptives on initiation and escalation of therapy which has not present in prior GLP-1RA formulations.[66] Gastric emptying appears to be impacted most after the initial dose, with diminished effects with subsequent doses. Following administration of an oral contraceptive in the presence of tirzepatide 5mg, the max concentration and mean AUC were both decreased.

Female patients using oral contraceptives should be advised to switch to an alternative non-oral contraceptive method for 4 weeks after initiation of tirzepatide and for 4 weeks after each dose increase to prevent pregnancy.

Thyroid cancer

When GLP-1RAs were initially introduced, there was concern for increased risk of medullary thyroid carcinoma (MTC) given that rodent studies showed increased rates of c-cell hyperplasia.[68-69] Hence, GLP-1RA therapy is contraindicated in persons with a history of Multiple Endocrine Neoplasia, Type 2 (MEN2), and in those with a family history of medullary thyroid carcinoma. Since it is unknown whether this translates to increased rates of medullary thyroid carcinoma in humans, in the United States, there is a MTC surveillance registry tracking the rates of MTC in those who have received GLP-1RA therapy.[70] Liang et al. performed a retrospective review combined with nested case control studies and reported no increased risk of thyroid cancer with liraglutide.[71] Alves et al. also performed meta-analysis of 25 studies and reported no association between thyroid cancer and liraglutide.[72] In 2019, Cao et al. performed a meta-analysis of 37 studies and reported no significantly increased risk of thyroid or pancreatic cancers with GLP-1RA usage.[73] However, Mali et al. recently reported data from the Eudra Vigilance database, which includes the time since GLP-1RA inception until 2020. In this analysis, 11,243 cases of thyroid cancer out of 6,665,794 total were reported and 236 were in patients who were on GLP-1RA therapy. Exenatide, liraglutide, and dulaglutide all generated a safety signal indicating thyroid cancer was reported more often with these drugs than other drugs. The proportional reporting ratio (PRR) was higher for all “thyroid cancers” at a ratio of 14.4, PRR was 221.5 for “medullary thyroid carcinoma” and 31.5 for “thyroid neoplasm”.[74] This will need to be continually monitored, but in general, those at high risk should not receive GLP-1RA therapy.

GLP-1 receptors have also been noted in papillary thyroid carcinomas, hence heightening awareness of the potential risk of GLP-1RA users developing non-medullary thyroid carcinoma. In this arena, there have been conflicting reports. Previous studies, as noted above, have not reported any increase in thyroid cancer with GLP-1RA usage.[71-73] However, Funch et al. reported the relative risk of thyroid cancer with liraglutide use was 1.7%, with 85% of those having papillary or follicular variant of papillary thyroid carcinoma, and 45% were microscopic (< 1 cm).[75] They evaluated GLP-1RA users from 2010-2014 through a US health plan and followed them for a median of 17 months. Incidence rates using relative risk estimated within propensity score matched cohorts were reported.[75] Bezin et al. also recently reported an increased risk of all thyroid cancer and medullary thyroid cancer with the use of GLP-1RA, especially after 1-3 years of treatment.[76] The hazard ratio for all thyroid cancers was 1.58 and for medullary thyroid carcinoma 1.78.[76] Commentary from Thompson and Sturmer caution about the potential for detection bias of small clinically insignificant thyroid cancers and overinterpretation of these findings. They recommend weighing the overall risk/benefit ratio when considering treatment with a GLP-1RA.[77] An editorial by Pappa et al. also questions the significance of these findings given the inability to account for classic risk factors of non-medullary thyroid cancer including family history of thyroid cancer, radiation exposure and obesity.[78] Hu et al. performed a meta-analysis evaluating the association between GLP-1RA and all thyroid disorders. Forty-five trials were included and overall GLP-1RA were associated with increased risk of overall thyroid disorders, with a RR of 1.28. However, on subgroup analyses and meta-regression analyses, there was no increased or decreased risk of thyroid cancer, hyperthyroidism, hypothyroidism, thyroiditis or thyroid mass/goiter.[79]

In summary, there may be an increased risk of both medullary and non-medullary thyroid carcinoma in those using GLP-1RA therapy. These agents should not be used in those with a genetic predisposition to medullary thyroid carcinoma, such as those with MEN2, family history of medullary thyroid carcinoma and those with germline RET mutations. However, it is unclear what to recommend in patients with a personal or family history of non-medullary thyroid carcinoma. Non-medullary thyroid carcinoma is frequently not hereditary, and in those who have had non-medullary thyroid carcinoma, they have usually undergone total thyroidectomy. If considering GLP-1RA therapy in persons with thyroid nodules, or those with a personal or family history of non-medullary thyroid carcinoma, it is important to have a discussion with them regarding the risks and benefits of therapy and plan for surveillance.

Acute kidney injury

There are reports of acute kidney injury (AKI) in the post market research in the package inserts of the GLP-1RAs.[59-61,63,65,67] It has also been noted that worsening of renal function is more common with those who have nausea, vomiting, diarrhea and gastrointestinal side effects, indicating this may be due to dehydration and intravascular volume loss.[59-61,63,65,67] AKI was also noted in persons that were taking other medications known to potentially affect renal status. Additionally, Leehey et al. reported acute renal worsening after semaglutide therapy where the patients developed advanced diffuse and nodular glomerulosclerosis accompanied by interstitial lymphoplasmacytic and eosinophilic infiltrate with evidence of acute tubular injury on kidney biopsy.[80] In the cases of allergic or immune mediated side effects the GLP-1RA should be discontinued.

Overall, however, GLP-1RA are considered to be beneficial for the kidneys. Yin et al. performed a systematic review and reports that GLP-1RA are considered safe and effective in patients with declining renal function and their impact on glomerular filtration rate (GFR) is not significant. They are also helpful in reducing progression to proteinuria.[81] Kristensen et al. performed a meta-analysis of 27 studies and found GLP-1RA therapy reduced development of new onset macroalbuminuria, decline in estimated GFR and progression to end stage renal disease, or death attributable to kidney disease by 17% ($p< 0.0001$). This was felt to be due to a reduction in microscopic urinary albumin excretion.[82] This was further substantiated by Sattar et al. in 2021 with meta-analysis of eight trials with 60,080 participants who found that GLP-1RA reduced overall composite kidney outcomes by 21%. These included development of macroalbuminuria, doubling time of serum creatinine or at least 40% decline in estimated GFR, kidney replacement therapy and death due to kidney disease.[83]

Thrombocytopenia

The only significant reports of thrombocytopenia with GLP-1RA are with Bydureon®.[67] The Bydureon® package insert cautions about drug induced immune mediated thrombocytopenia with exenatide use. The effect is felt to be an immune mediated reaction with anti-platelet antibodies that are exenatide dependent. However, in the absence of an immune mediated reaction, GLP-1 receptor activation in platelets have been shown to improve endotoxemia associated microvascular thrombosis in mice and result in improvements in circulating platelets, reduction in microvascular thrombosis, improvement

in endothelial dysfunction and decreased markers of inflammation.[84] GLP-1 is an inhibitor of thrombus formation. GLP-1RA and dipeptidylpeptidase-4 (DPP4) inhibitors can reduce platelet aggregation, reducing thrombotic events.[85] It is also well known that GLP-1RA therapy is associated with reduced MACE, including cardiovascular death, myocardial infarction and stroke. Recent systematic review and meta -analysis showed a 14% reduction in MACE with GLP-1RA therapy.[83] Hence, in general, the effect of GLP-1RA on platelets is favorable and is associated with reduced MACE. If thrombocytopenia occurs, it is likely due to an immune mediated reaction and the drug should be discontinued and not resumed.

Nasopharyngitis

Nasopharyngitis and upper respiratory infections have been noted with liraglutide, but none of the other GLP-1RA, indicating they are occurring < 5% of the time with all GLP-1RA, except for liraglutide.[59-67] Upper respiratory infections (URI) were noted in 9.5% of those taking liraglutide vs 5.6% in those on glimepiride. Both the glimepiride and liraglutide groups were reported to have nasopharyngitis in 5.2% of patients.[62] For liraglutide, this may be due to the development of anti-liraglutide antibodies, since the rates of mild upper respiratory tract infections are higher in those who developed antibodies (11%) than those that did not (5%).[62] Immunogenicity and antibody production against the drug is reported with all GLP-1RAs, however, they do not all develop the same adverse effects, and URIs and nasopharyngitis do not appear to be a class effect. Li et al. performed a systematic review and meta-analysis evaluating this issue. Fifty randomized controlled trials were included, evaluating seven GLP-1RA therapies versus placebo or other diabetes agents. The GLP-1RAs included were liraglutide, lixisenatide, taspoglutide, albiglutide and dulaglutide. Overall, taspoglutide reduced the incidence of nasopharyngitis with an OR of 0.67.[86] In summary, liraglutide has been associated with a slight increase in non-serious URI and nasopharyngitis, but the remainder of the GLP-1RAs and GLP-1RA/GIPRA are not associated with >5% incidence.

Hypoglycemia

GLP-1RA monotherapy is not associated with hypoglycemia. Hypoglycemia has been noted in the package inserts of all GLP-1RA.[59-67] but these occurrences are when a GLP-1RA is used in conjunction with insulin or an insulin secretagogue or sulfonylurea. Rates of hypoglycemia are as high as 12.6%,[63] but that is compared with placebo that had a 6.6% rate

of hypoglycemia. In general, when starting a GLP-1RA, it is recommended to reduce the doses of insulin or insulin secretagogue in order to avoid hypoglycemia.

Diabetic retinopathy

Several currently available GLP-1RAs (semaglutide, dulaglutide) carry a package insert warning regarding increased risk of diabetic retinopathy complications with use as compared to placebo.[59,65] The Mounjaro® label does not report increased risk of diabetic retinopathy complications, but notes that Mounjaro® has not been studied in patients with non-proliferative diabetic retinopathy requiring acute therapy, proliferative diabetic retinopathy, or diabetic macular edema.[66] The Mounjaro®, Ozempic®, Wegovy®, Rybelsus® and Trulicity® package inserts all note that rapid improvement in glucose control has been associated with temporary worsening of diabetic retinopathy and carry the recommendation to monitor those with a history of diabetic retinopathy for progression.[59-61, 65-66]

Wang et al. evaluated U.S. Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) data and did not find any signal of increased risk of diabetic retinopathy events in those exposed to GLP-1RAs. Though only data on exenatide, liraglutide, albiglutide and dulaglutide was available, semaglutide was given later FDA approval.[87] Of note, albiglutide is no longer on the market. A study by Zheng et al., published in 2023 utilizing data from nationwide Swedish patient registries, compared patients diagnosed with incident diabetes and subsequent diabetic retinopathy who were prescribed a GLP-1RA to those that did not use a GLP-1RA. Found a hazard ratio for DR in patients treated with GLP-1RA of 0.42 (95% CI, 0.29-0.61) as compared with non GLP-1RA users.[88] Douros et al. evaluated a cohort population from the UK Clinical Practice Research Datalink with newly treated type 2 diabetes. When compared to a group with current use of two or more oral antidiabetic medications, overall current use of an injectable GLP-1RA (exenatide, liraglutide, lixisenatide) was not associated with increased risk of diabetic retinopathy as compared to use of two or more oral medications. When patients newly initiated on GLP-1RAs were compared to patients newly initiated on insulin in a post hoc ancillary analysis, overall use of GLP-1RAs was associated with a decreased risk of DR (HR 0.67: 95% CI 0.51-0.90) though it was noted that residual confounding was possible.[89]

In a meta-analysis and meta-regression of GLP-1RA cardiovascular outcome trials by Bethel et al. published in 2021, the meta-analysis did not demonstrate an association between GLP-1RA use and retinopathy, while meta-regression demonstrated that HbA1c decrease was

significantly associated with increased retinopathy risk.[90] Yoshida et al. published a systematic review and meta-analysis in 2023 that included 13 randomized controlled trial data with semaglutide (oral and injectable), liraglutide and dulaglutide. When restricted to 4 studies that demonstrated CV benefit or lack of inferiority to placebo, authors identified a small, elevated risk of DR progression (OR 1.23, 95% CI 1.05-1.44). When restricted to randomized controlled trials of longer length (greater than 52 weeks) or using only placebo as comparator, GLP-1RA use was associated with small statistically significant increased risk of diabetic retinopathy, OR 1.2 (95% CI 1.00-1.43) and OR 1.22 (95% CI 1.05-1.42) respectively. No statistically significant increased risk of DR was identified in patients with a history of diabetes for over 10 years, subjects were enrolled in multiple countries, randomized controlled studies with baseline diabetic retinopathy, or baseline HbA1c greater than 8%.[91]

Completed studies to date are limited by lack of diabetic retinopathy as a prespecified prospective primary outcome and relatively short median/mean follow up times. Of note, there is basic science animal study evidence indicating that topical ocular application of liraglutide decreases retinal neurodegeneration (which is thought to occur early in the time course of development of diabetic retinopathy), in mice models of diabetes.[92-93] Further information should be provided by the ongoing FOCUS trial, in which T2DM patients with diabetic retinopathy are randomized to addition of semaglutide injection or placebo to their pre-existing diabetes regimen for up to 5 years and monitored for evidence of retinopathy progression.[94] In the interim, the data suggests that close monitoring of those with diabetic retinopathy, or at risk for diabetic retinopathy, is prudent when using GLP-1RA therapy.

Injection site reactions

Injection site reactions are another known potential adverse event associated with the injectable GLP-1RAs. In trials, data on injection site reactions was variably absent or reported as the more generalized “injection site reaction” or more specifically “injection site nodule”, “injection site bruising” or “injection site pruritis”.[95] Trujillo et al. review this topic in detail.

Briefly, it appears that use of exenatide, particularly in the extended-release form, reliably results in more injection site reactions and injection site nodules in particular, as compared directly or indirectly to other GLP-1RAs.[10,13,22,96] Of note, a case series published in 2015 documented 27 cases reported to the FDA Adverse Event Reporting System (FAERS) in the

first 2 years after exenatide once weekly was approved consisting of significant injection site reactions. Some included large nodule formation at injection sites as well as cases that required hospitalization, surgical excision and medical intervention such as antibiotics, antihistamines or glucocorticoids.[97] There are multiple posited theories regarding the higher frequency of nodules associated with exenatide use including reactions to the microsphere excipient in the extended- release version and an anti-exenatide antibody response [98]. The Bydureon® (exenatide ER) drug label includes a warning regarding postmarking reports of reactions such as abscess, cellulitis and necrosis in association with/without subcutaneous nodules and isolated cases needing surgical intervention.[67]

In contrast, semaglutide, dulaglutide, liraglutide and tirzepatide appear to typically have low rates of injection site reactions.[1, 6, 10-14, 99-111] Higher doses of tirzepatide do appear to result in numerically higher rates of injection site reactions (4.5% for 15mg dose vs 1.9% for 5mg dose in SURPASS 2).[6]

Transitioning between medications

In clinical practice, transitioning amongst different GLP-1RAs is quite common, whether it be due to medication shortages, insurance formularies, desire for more potent effects on weight or HbA1c, side effects, differential cardiorenal benefits or other considerations. There is limited information in the literature on this topic. Almandoz et al. proposed dose equivalences based on available data and clinical experience in 2020.[112] Generally, if the transition is precipitated by side effects, it would be suggested to discontinue the original agent and let all side effects resolve prior to initiating a different agent at the lowest dose with subsequent titration. If the transition is pursued for other reasons, generally the first dose of a weekly medication can be administered the day after the last dose of a daily medication and the first dose of a weekly medication can be administered 7 days after the last dose of a weekly medication.

See table 3 for estimated approximate therapeutic interchanges to consider per review of the available literature.[5, 10-12, 16-17, 96, 113-115] Proposed interchange table differs from Almandoz et al. given inclusion of tirzepatide, inclusion of subsequently available higher doses of multiple agents, and interchanges suggested for exenatide (both BID and QW formulations).[112] If considering switch from agent with typically fewer side effects to agent with typically greater side effects (Figure 3), selecting a dose of the new agent that is of lower estimated equivalent

potency may be considered. It is important to recognize that switching agents without re-titration from initial dose of subsequent agent would be considered off label.

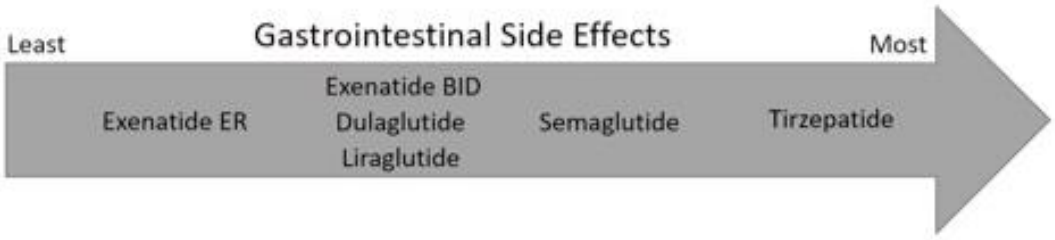

Figure 3: Comparative Gastrointestinal side effects between GLP-1RA medications.

Table 1: Available GLP-1RA Therapies.

Drug	Indication	Dose and Frequency	Route
Exenatide (Byetta®)	DM2	5-10 mcg twice daily	SC
Exenatide (Bydureon®)	DM2	2mg once weekly	SC
Lixisenatide* (Adlyxin®)	DM2	10-20mcg once daily	SC
Liraglutide (Victoza®)	DM2	0.6-1.8mg once daily	SC
Liraglutide (Saxenda®)	Obesity	0.6-3mg once daily	SC
Dulaglutide (Trulicity®)	DM2	0.75-4.5mg once weekly	SC
Semaglutide (Ozempic®)	DM2	0.25-2mg once weekly	SC
Semaglutide (Wegovy®)	Obesity	0.25-2.4mg once weekly	SC
Semaglutide (Rybelsus®)	DM2	3-14mg once daily	PO
Tirzepatide** (Mounjaro®)	DM2	2.5-15mg once weekly	SC

*Lixisenatide (Adlyxin) alone no longer available in US as of 1/1/23. Remains available in combination with insulin glargine as Soliqua.

**Combination glucagon-like-peptide-1 receptor agonist and glucose-dependent insulinotropic polypeptide agonist (GLP-1RA/GIPRA) DM2, Type 2 Diabetes Mellitus; SC, Subcutaneous; PO, by mouth

Table 2: Dietary Patient Counseling to Minimize Gastrointestinal Side Effects on GLP-1RA/GIPRA Therapy.

Quantity	•Consider starting with half of typical portions •Stop eating when no longer hungry
Content	•Ensure hydration •Avoid or minimize: →Spicy (24) or highly flavored food →High fat foods[24,66] including greasy/fried food[59,61] and red meats →Large volume simple carbohydrates such as pasta →Sweets[24,59,61] →Alcohol and soda[24] →Temporary decrease in high fiber foods such as beans
Timing	• Eat slowly[24,59-60] •Avoid lying down after eating[24, 59-61]

Table 3: Conversion Between GLP-1RA Medications.

Medication							**Dosage**							
*Tirzepatide mg weekly SC (Mounjaro®)			2.5	2.5	2.5	2.5	2.5	5	5	5	7.5	10	12.5	15
Semaglutide mg weekly SC (Ozempic® or Wegovy®)			0.25	0.5			1	1.7	2	2.4				
Semaglutide mg daily PO (Rybelsus®)		3	7	14										
Dulaglutide mg weekly SC (Trulicity®)			0.75	1.5		3	4.5							
Liraglutide mg daily SC (Victoza® or Saxenda®)		0.6	1.2	1.8	2.4	3								
Exenatide mg weekly SC (Bydureon®)			2											
Exenatide BID mcg SC (Byetta®)	5	10												

*There is insufficient data to suggest dose equivalency between tirzepatide 2.5mg dose and available GLP-1RAs.

CONCLUSIONS

GLP-1RAs can be very effective tools for HbA1c and weight reduction. In addition, use of GLP-1RAs can result in CV and renal benefits in those with diabetes mellitus, separate from effects on glycemic control. However, there are potential adverse effects of GLP-1RA use that all medical practitioners should be aware of given the widespread use of GLP-1RA use across disciplines. In this review, we describe the available literature regarding GLP-1RA use in context of several common comorbidities to allow for more informed clinical shared decision making. In sum, GLP-1RAs have significantly changed the landscape of medications available for treatment of diabetes mellitus as well as obesity and will likely be a pillar of treatment for many years to come. Although adverse effects can sometimes be a hurdle to implementation of GLP-1RAs, at this time some of the largest hurdles are availability and cost. Given these factors, it is also important for medical practitioners to

become familiar with the various preparations and forms of GLP-1RAs and methods for conversion amongst agents in class when needed.

REFERENCES

1. Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA, et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. N Engl J Med, 2016; 375(19): 1834-44.
2. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med, 2016; 375(4): 311-22.
3. Gerstein HC, Colhoun HM, Dagenais GR, Diaz R, Lakshmanan M, Pais P, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. Lancet, 2019; 394(10193): 121-30.
4. ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, et al. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes-2023. Diabetes Care, 2023; 46(1): S140-s57.
5. Vadher K, Patel H, Mody R, Levine JA, Hoog M, Cheng AY, et al. Efficacy of tirzepatide 5, 10 and 15 mg versus semaglutide 2 mg in patients with type 2 diabetes: An adjusted indirect treatment comparison. Diabetes Obes Metab, 2022; 24(9): 1861-8.
6. Frías JP, Davies MJ, Rosenstock J, Pérez Manghi FC, Fernández Landó L, Bergman BK, et al. Tirzepatide versus Semaglutide Once Weekly in Patients with Type 2 Diabetes. N Engl J Med, 2021; 385(6): 503-15.
7. Trujillo JM, Nuffer W, Smith BA. GLP-1 receptor agonists: an updated review of head-to-head clinical studies. Ther Adv Endocrinol Metab, 2021; 12: 2042018821997320.
8. Buse JB, Rosenstock J, Sesti G, Schmidt WE, Montanya E, Brett JH, et al. Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6). Lancet, 2009; 374(9683): 39-47.
9. Drucker DJ, Buse JB, Taylor K, Kendall DM, Trautmann M, Zhuang D, et al. Exenatide once weekly versus twice daily for the treatment of type 2 diabetes: a randomised, open-label, non-inferiority study. Lancet, 2008; 372(9645): 1240-50.
10. Buse JB, Nauck M, Forst T, Sheu WH, Shenouda SK, Heilmann CR, et al. Exenatide once weekly versus liraglutide once daily in patients with type 2 diabetes (DURATION-6): a randomised, open-label study. Lancet, 2013; 381(9861): 117-24.

11. Wysham C, Blevins T, Arakaki R, Colon G, Garcia P, Atisso C, et al. Efficacy and safety of dulaglutide added onto pioglitazone and metformin versus exenatide in type 2 diabetes in a randomized controlled trial (AWARD-1). Diabetes Care, 2014; 37(8): 2159-67.
12. Dungan KM, Povedano ST, Forst T, González JG, Atisso C, Sealls W, et al. Once-weekly dulaglutide versus once-daily liraglutide in metformin-treated patients with type 2 diabetes (AWARD-6): a randomised, open-label, phase 3, non-inferiority trial. Lancet, 2014; 384(9951): 1349-57.
13. Ahmann AJ, Capehorn M, Charpentier G, Dotta F, Henkel E, Lingvay I, et al. Efficacy and Safety of Once-Weekly Semaglutide Versus Exenatide ER in Subjects With Type 2 Diabetes (SUSTAIN 3): A 56-Week, Open-Label, Randomized Clinical Trial. Diabetes Care, 2018; 41(2): 258-66.
14. Pratley RE, Aroda VR, Lingvay I, Lüdemann J, Andreassen C, Navarria A, et al. Semaglutide versus dulaglutide once weekly in patients with type 2 diabetes (SUSTAIN 7): a randomised, open-label, phase 3b trial. Lancet Diabetes Endocrinol, 2018; 6(4): 275-86.
15. Capehorn MS, Catarig AM, Furberg JK, Janez A, Price HC, Tadayon S, et al. Efficacy and safety of once-weekly semaglutide 1.0mg vs once-daily liraglutide 1.2mg as add-on to 1-3 oral antidiabetic drugs in subjects with type 2 diabetes (SUSTAIN 10). Diabetes Metab, 2020; 46(2): 100-9.
16. Pratley R, Amod A, Hoff ST, Kadowaki T, Lingvay I, Nauck M, et al. Oral semaglutide versus subcutaneous liraglutide and placebo in type 2 diabetes (PIONEER 4): a randomised, double-blind, phase 3a trial. Lancet, 2019; 394(10192): 39-50.
17. Yabe D, Nakamura J, Kaneto H, Deenadayalan S, Navarria A, Gislum M, et al. Safety and efficacy of oral semaglutide versus dulaglutide in Japanese patients with type 2 diabetes (PIONEER 10): an open-label, randomised, active-controlled, phase 3a trial. Lancet Diabetes Endocrinol, 2020; 8(5): 392-406.
18. Frías JP, Auerbach P, Bajaj HS, Fukushima Y, Lingvay I, Macura S, et al. Efficacy and safety of once-weekly semaglutide 2·0 mg versus 1·0 mg in patients with type 2 diabetes (SUSTAIN FORTE): a double-blind, randomised, phase 3B trial. Lancet Diabetes Endocrinol, 2021; 9(9): 563-74.
19. Pi-Sunyer X, Astrup A, Fujioka K, Greenway F, Halpern A, Krempf M, et al. A Randomized, Controlled Trial of 3.0 mg of Liraglutide in Weight Management. N Engl J Med, 2015; 373(1): 11-22.

20. Wilding JPH, Batterham RL, Calanna S, Davies M, Van Gaal LF, Lingvay I, et al. Once-Weekly Semaglutide in Adults with Overweight or Obesity. N Engl J Med, 2021; 384(11): 989-1002.
21. Eli Lilly and Company. The Effect of Tirzepatide Versus Dulaglutide on Major Adverse Cardiovascular Events in Patients With Type 2 Diabetes (SURPASS-CVOT) 2023 [Available from: https://clinicaltrials.gov/ct2/show/NCT04255433.
22. Blevins T, Pullman J, Malloy J, Yan P, Taylor K, Schulteis C, et al. DURATION-5: exenatide once weekly resulted in greater improvements in glycemic control compared with exenatide twice daily in patients with type 2 diabetes. J Clin Endocrinol Metab, 2011; 96(5): 1301-10.
23. Wharton S, Davies M, Dicker D, Lingvay I, Mosenzon O, Rubino DM, et al. Managing the gastrointestinal side effects of GLP-1 receptor agonists in obesity: recommendations for clinical practice. Postgrad Med, 2022; 134(1): 14-9.
24. Gorgojo-Martínez JJ, Mezquita-Raya P, Carretero-Gómez J, Castro A, Cebrián-Cuenca A, de Torres-Sánchez A, et al. Clinical Recommendations to Manage Gastrointestinal Adverse Events in Patients Treated with Glp-1 Receptor Agonists: A Multidisciplinary Expert Consensus. J Clin Med, 2022; 12(1).
25. Garvey WT, Batterham RL, Bhatta M, Buscemi S, Christensen LN, Frias JP, et al. Two-year effects of semaglutide in adults with overweight or obesity: the STEP 5 trial. Nat Med, 2022; 28(10): 2083-91.
26. Novo Nordisk A/S. Ozempic, 2023. [Available from: https://www.ozempic.com/.
27. Novo Nordisk A/S. Wegovy, 2023. [Available from: https://www.wegovy.com/.
28. Novo Nordisk A/S. Rybelsus, 2022 [Available from: https://www.rybelsus.com/.
29. Shetty R, Basheer FT, Poojari PG, Thunga G, Chandran VP, Acharya LD. Adverse drug reactions of GLP-1 agonists: A systematic review of case reports. Diabetes Metab Syndr, 2022; 16(3): 102427.
30. FDA. Information for Healthcare Professionals: Exenatide (Marketed as Byetta), 2008. [Available from: http://wayback.archive-it.org/7993/20161022204529/http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124713.htm.
31. Nauck MA. A critical analysis of the clinical use of incretin-based therapies: The benefits by far outweigh the potential risks. Diabetes Care, 2013; 36(7): 2126-32.

32. Butler PC, Elashoff M, Elashoff R, Gale EA. A critical analysis of the clinical use of incretin-based therapies: Are the GLP-1 therapies safe? Diabetes Care, 2013; 36(7): 2118-25.
33. Steinberg WM, Rosenstock J, Wadden TA, Donsmark M, Jensen CB, DeVries JH. Impact of Liraglutide on Amylase, Lipase, and Acute Pancreatitis in Participants With Overweight/Obesity and Normoglycemia, Prediabetes, or Type 2 Diabetes: Secondary Analyses of Pooled Data From the SCALE Clinical Development Program. Diabetes Care, 2017; 40(7): 839-48.
34. Elashoff M, Matveyenko AV, Gier B, Elashoff R, Butler PC. Pancreatitis, pancreatic, and thyroid cancer with glucagon-like peptide-1-based therapies. Gastroenterology, 2011; 141(1): 150-6.
35. Li L, Shen J, Bala MM, Busse JW, Ebrahim S, Vandvik PO, et al. Incretin treatment and risk of pancreatitis in patients with type 2 diabetes mellitus: systematic review and meta-analysis of randomised and non-randomised studies. Bmj, 2014; 348: 2366.
36. Monami M, Dicembrini I, Nardini C, Fiordelli I, Mannucci E. Glucagon-like peptide-1 receptor agonists and pancreatitis: a meta-analysis of randomized clinical trials. Diabetes Res Clin Pract, 2014; 103(2): 269-75.
37. Storgaard H, Cold F, Gluud LL, Vilsbøll T, Knop FK. Glucagon-like peptide-1 receptor agonists and risk of acute pancreatitis in patients with type 2 diabetes. Diabetes Obes Metab, 2017; 19(6): 906-8.
38. Nreu B, Dicembrini I, Tinti F, Mannucci E, Monami M. Pancreatitis and pancreatic cancer in patients with type 2 diabetes treated with glucagon-like peptide-1 receptor agonists: an updated meta-analysis of randomized controlled trials. Minerva Endocrinol, 2020.
39. Aroda VR, Ahmann A, Cariou B, Chow F, Davies MJ, Jódar E, et al. Comparative efficacy, safety, and cardiovascular outcomes with once-weekly subcutaneous semaglutide in the treatment of type 2 diabetes: Insights from the SUSTAIN 1-7 trials. Diabetes Metab, 2019; 45(5): 409-18.
40. Kushner RF, Calanna S, Davies M, Dicker D, Garvey WT, Goldman B, et al. Semaglutide 2.4 mg for the Treatment of Obesity: Key Elements of the STEP Trials 1 to 5. Obesity (Silver Spring), 2020; 28(6): 1050-61.
41. Aroda VR, Bauer R, Christiansen E, Haluzík M, Kallenbach K, Montanya E, et al. Efficacy and safety of oral semaglutide by subgroups of patient characteristics in the PIONEER phase 3 programme. Diabetes Obes Metab, 2022; 24(7): 1338-50.

42. Blonde L, Russell-Jones D. The safety and efficacy of liraglutide with or without oral antidiabetic drug therapy in type 2 diabetes: an overview of the LEAD 1-5 studies. Diabetes Obes Metab, 2009; 11, 3: 26-34.
43. Ard J, Cannon A, Lewis CE, Lofton H, Vang Skjøth T, Stevenin B, et al. Efficacy and safety of liraglutide 3.0 mg for weight management are similar across races: subgroup analysis across the SCALE and phase II randomized trials. Diabetes Obes Metab, 2016; 18(4): 430-5.
44. Jendle J, Grunberger G, Blevins T, Giorgino F, Hietpas RT, Botros FT. Efficacy and safety of dulaglutide in the treatment of type 2 diabetes: a comprehensive review of the dulaglutide clinical data focusing on the AWARD phase 3 clinical trial program. Diabetes Metab Res Rev, 2016; 32(8): 776-90.
45. Grimm M, Han J, Weaver C, Griffin P, Schulteis CT, Dong H, et al. Efficacy, safety, and tolerability of exenatide once weekly in patients with type 2 diabetes mellitus: an integrated analysis of the DURATION trials. Postgrad Med, 2013; 125(3): 47-57.
46. Klonoff DC, Buse JB, Nielsen LL, Guan X, Bowlus CL, Holcombe JH, et al. Exenatide effects on diabetes, obesity, cardiovascular risk factors and hepatic biomarkers in patients with type 2 diabetes treated for at least 3 years. Curr Med Res Opin, 2008; 24(1): 275-86.
47. Haal S, Guman MSS, Bruin S, Schouten R, van Veen RN, Fockens P, et al. Risk Factors for Symptomatic Gallstone Disease and Gallstone Formation After Bariatric Surgery. Obes Surg, 2022; 32(4): 1270-8.
48. Yuan S, Gill D, Giovannucci EL, Larsson SC. Obesity, Type 2 Diabetes, Lifestyle Factors, and Risk of Gallstone Disease: A Mendelian Randomization Investigation. Clin Gastroenterol Hepatol, 2022; 20(3): e529-e37.
49. Monami M, Nreu B, Scatena A, Cresci B, Andreozzi F, Sesti G, et al. Safety issues with glucagon-like peptide-1 receptor agonists (pancreatitis, pancreatic cancer and cholelithiasis): Data from randomized controlled trials. Diabetes Obes Metab, 2017; 19(9): 1233-41.
50. Nauck MA, Muus Ghorbani ML, Kreiner E, Saevereid HA, Buse JB. Effects of Liraglutide Compared With Placebo on Events of Acute Gallbladder or Biliary Disease in Patients With Type 2 Diabetes at High Risk for Cardiovascular Events in the LEADER Randomized Trial. Diabetes Care, 2019; 42(10): 1912-20.
51. He L, Wang J, Ping F, Yang N, Huang J, Li Y, et al. Association of Glucagon-Like Peptide-1 Receptor Agonist Use With Risk of Gallbladder and Biliary Diseases: A

Systematic Review and Meta-analysis of Randomized Clinical Trials. JAMA Intern Med, 2022; 182(5): 513-9.

52. Drucker DJ. The biology of incretin hormones. Cell Metab, 2006; 3(3): 153-65.
53. Drucker DJ. GLP-1 physiology informs the pharmacotherapy of obesity. Mol Metab, 2022; 57: 101351.
54. Nauck MA, Kemmeries G, Holst JJ, Meier JJ. Rapid tachyphylaxis of the glucagon-like peptide 1-induced deceleration of gastric emptying in humans. Diabetes, 2011; 60(5): 1561-5.
55. van Can J, Sloth B, Jensen CB, Flint A, Blaak EE, Saris WH. Effects of the once-daily GLP-1 analog liraglutide on gastric emptying, glycemic parameters, appetite and energy metabolism in obese, non-diabetic adults. Int J Obes (Lond), 2014; 38(6): 784-93.
56. Linnebjerg H, Park S, Kothare PA, Trautmann ME, Mace K, Fineman M, et al. Effect of exenatide on gastric emptying and relationship to postprandial glycemia in type 2 diabetes. Regul Pept, 2008; 151(1-3): 123-9.
57. Beti C, Stratmann B, Bokman G, Dreier J, Hauber M, Lee-Barkey YH, et al. Exenatide Delays Gastric Emptying in Patients with Type 2 Diabetes Mellitus but not in Those with Gastroparetic Conditions. Horm Metab Res, 2019; 51(4): 267-73.
58. Kalas MA, Dang TQ, Galura G, Alvarado L, Dwivedi AK, Deoker A, et al. Frequency of GLP-1 receptor agonists use in diabetic patients diagnosed with delayed gastric emptying and their demographic profile. J Investig Med, 2023; 71(1): 11-6.
59. OZEMPIC® (semaglutide) injection [Package Insert]. Plainsboro, NJ: NovoNordisk, 2017.
60. WEGOVY® (semaglutide) injection [Package Insert]. Plainsboro, NJ: NovoNordisk, 2017.
61. RYBELSUS® (semaglutide) tablets [Package Insert]. Plainsboro, NJ: NovoNordisk, 2017.
62. Victoza® (liraglutide) [Package Insert]. Plainsboro, NJ: NovoNordisk, 2010.
63. SAXENDA® (liraglutide) injection 3mg [Package Insert]. Plainsboro, NJ: NovoNordisk, 2010.
64. BYETTA™ exenatide injection [Package Insert]. San Diego, CA: Amylin Pharmaceuticals, Inc, 2005.
65. TRULICITY (dulaglutide) injection [Package Insert]. Indianapolis, IN: Eli Lilly, 2014.
66. MOUNJARO (tirzepatide) Injection [Package Insert] Indianapolis, IN: Eli Lilly, 2022.

67. BYDUREON BCISE- exenatide injection [Package Insert]. Wilmington, DE: AstraZeneca Pharmaceuticals, 2005.
68. Bjerre Knudsen L, Madsen LW, Andersen S, Almholt K, de Boer AS, Drucker DJ, et al. Glucagon-like Peptide-1 receptor agonists activate rodent thyroid C-cells causing calcitonin release and C-cell proliferation. Endocrinology, 2010; 151(4): 1473-86.
69. Madsen LW, Knauf JA, Gotfredsen C, Pilling A, Sjögren I, Andersen S, et al. GLP-1 receptor agonists and the thyroid: C-cell effects in mice are mediated via the GLP-1 receptor and not associated with RET activation. Endocrinology, 2012; 153(3): 1538-47.
70. Hale PM, Ali AK, Buse JB, McCullen MK, Ross DS, Sabol ME, et al. Medullary Thyroid Carcinoma Surveillance Study: A Case-Series Registry. Thyroid, 2020; 30(10): 1397-8.
71. Liang C, Bertoia ML, Ding Y, Clifford CR, Qiao Q, Gagne JJ, et al. Exenatide use and incidence of pancreatic and thyroid cancer: A retrospective cohort study. Diabetes Obes Metab, 2019; 21(4): 1037-42.
72. Alves C, Batel-Marques F, Macedo AF. A meta-analysis of serious adverse events reported with exenatide and liraglutide: acute pancreatitis and cancer. Diabetes Res Clin Pract, 2012; 98(2): 271-84.
73. Cao C, Yang S, Zhou Z. GLP-1 receptor agonists and risk of cancer in type 2 diabetes: an updated meta-analysis of randomized controlled trials. Endocrine, 2019; 66(2): 157-65.
74. Mali G, Ahuja V, Dubey K. Glucagon-like peptide-1 analogues and thyroid cancer: An analysis of cases reported in the European pharmacovigilance database. J Clin Pharm Ther, 2021; 46(1): 99-105.
75. Funch D, Mortimer K, Ziyadeh NJ, J DS, Zhou L, Ng E, et al. Risk of Thyroid Cancer Associated with Use of Liraglutide and Other Antidiabetic Drugs in a US Commercially Insured Population. Diabetes Metab Syndr Obes, 2021; 14: 2619-29.
76. Bezin J, Gouverneur A, Pénichon M, Mathieu C, Garrel R, Hillaire-Buys D, et al. GLP-1 Receptor Agonists and the Risk of Thyroid Cancer. Diabetes Care, 2023; 46(2): 384-90.
77. Thompson CA, Stürmer T. Putting GLP-1 RAs and Thyroid Cancer in Context: Additional Evidence and Remaining Doubts. Diabetes Care, 2023; 46(2): 249-51.
78. Pappa T. GLP-1 Receptor Agonists and the Risk of Thyroid Cancer. Clinical Thyroidology, 2023; 35(1): 18-20.
79. Hu W, Song R, Cheng R, Liu C, Guo R, Tang W, et al. Use of GLP-1 Receptor Agonists and Occurrence of Thyroid Disorders: a Meta-Analysis of Randomized Controlled Trials. Front Endocrinol (Lausanne), 2022; 13: 927859.

80. Leehey DJ, Rahman MA, Borys E, Picken MM, Clise CE. Acute Kidney Injury Associated With Semaglutide. Kidney Med, 2021; 3(2): 282-5.
81. Yin WL, Bain SC, Min T. The Effect of Glucagon-Like Peptide-1 Receptor Agonists on Renal Outcomes in Type 2 Diabetes. Diabetes Ther, 2020; 11(4): 835-44.
82. Kristensen SL, Rørth R, Jhund PS, Docherty KF, Sattar N, Preiss D, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet Diabetes Endocrinol, 2019; 7(10): 776-85.
83. Sattar N, Lee MMY, Kristensen SL, Branch KRH, Del Prato S, Khurmi NS, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials. Lancet Diabetes Endocrinol, 2021; 9(10): 653-62.
84. Steven S, Jurk K, Kopp M, Kröller-Schön S, Mikhed Y, Schwierczek K, et al. Glucagon-like peptide-1 receptor signalling reduces microvascular thrombosis, nitro-oxidative stress and platelet activation in endotoxaemic mice. Br J Pharmacol, 2017; 174(12): 1620-32.
85. Sternkopf M, Nagy M, Baaten C, Kuijpers MJE, Tullemans BME, Wirth J, et al. Native, Intact Glucagon-Like Peptide 1 Is a Natural Suppressor of Thrombus Growth Under Physiological Flow Conditions. Arterioscler Thromb Vasc Biol, 2020; 40(3): e65-e77.
86. Li ZX, Wu SS, Yang ZR, Zhan SY, Sun F. [Impact of glucagon-like peptide-1 receptor agonists on nasopharyngitis and upper respiratory tract infection among patients with type 2 diabetes: a network meta-analysis]. Beijing Da Xue Xue Bao Yi Xue Ban, 2016; 48(3): 454-9.
87. Wang T, Lu W, Tang H, Buse JB, Stürmer T, Gower EW. Assessing the Association Between GLP-1 Receptor Agonist Use and Diabetic Retinopathy Through the FDA Adverse Event Reporting System. Diabetes Care, 2019; 42(2): e21-e3.
88. Zheng D, Li N, Hou R, Zhang X, Wu L, Sundquist J, et al. Glucagon-like peptide-1 receptor agonists and diabetic retinopathy: nationwide cohort and Mendelian randomization studies. BMC Med, 2023; 21(1): 40.
89. Douros A, Filion KB, Yin H, Yu OH, Etminan M, Udell JA, et al. Glucagon-Like Peptide 1 Receptor Agonists and the Risk of Incident Diabetic Retinopathy. Diabetes Care, 2018; 41(11): 2330-8.
90. Bethel MA, Diaz R, Castellana N, Bhattacharya I, Gerstein HC, Lakshmanan MC. HbA(1c) Change and Diabetic Retinopathy During GLP-1 Receptor Agonist

Cardiovascular Outcome Trials: A Meta-analysis and Meta-regression. Diabetes Care, 2021; 44(1): 290-6.

91. Yoshida Y, Joshi P, Barri S, Wang J, Corder AL, O'Connell SS, et al. Progression of retinopathy with glucagon-like peptide-1 receptor agonists with cardiovascular benefits in type 2 diabetes - A systematic review and meta-analysis. J Diabetes Complications, 2022; 36(8): 108255.
92. Hernández C, Bogdanov P, Corraliza L, García-Ramírez M, Solà-Adell C, Arranz JA, et al. Topical Administration of GLP-1 Receptor Agonists Prevents Retinal Neurodegeneration in Experimental Diabetes. Diabetes, 2016; 65(1): 172-87.
93. Shu X, Zhang Y, Li M, Huang X, Yang Y, Zeng J, et al. Topical ocular administration of the GLP-1 receptor agonist liraglutide arrests hyperphosphorylated tau-triggered diabetic retinal neurodegeneration via activation of GLP-1R/Akt/GSK3β signaling. Neuropharmacology, 2019; 153: 1-12.
94. Novo Nordisk A/S. A Research Study to Look at How Semaglutide Compared to Placebo Affects Diabetic Eye Disease in People With Type 2 Diabetes (FOCUS), 2023. [Available from: https://clinicaltrials.gov/ct2/show/NCT03811561.
95. Trujillo J. Safety and tolerability of once-weekly GLP-1 receptor agonists in type 2 diabetes. J Clin Pharm Ther, 2020; 45, 1(1): 43-60.
96. Buse JB, Drucker DJ, Taylor KL, Kim T, Walsh B, Hu H, et al. DURATION-1: exenatide once weekly produces sustained glycemic control and weight loss over 52 weeks. Diabetes Care, 2010; 33(6): 1255-61.
97. Jones SC, Ryan DL, Pratt VS, Niak A, Brinker AD. Injection-Site Nodules Associated With the Use of Exenatide Extended-Release Reported to the U.S. Food and Drug Administration Adverse Event Reporting System. Diabetes Spectr, 2015; 28(4): 283-8.
98. Hearn EB, Sherman JJ. Injection-Site Nodules Associated With Once-Weekly Subcutaneous Administration of Semaglutide. Diabetes Spectr, 2021; 34(1): 73-5.
99. Giorgino F, Benroubi M, Sun JH, Zimmermann AG, Pechtner V. Efficacy and Safety of Once-Weekly Dulaglutide Versus Insulin Glargine in Patients With Type 2 Diabetes on Metformin and Glimepiride (AWARD-2). Diabetes Care, 2015; 38(12): 2241-9.
100. Umpierrez G, Tofé Povedano S, Pérez Manghi F, Shurzinske L, Pechtner V. Efficacy and safety of dulaglutide monotherapy versus metformin in type 2 diabetes in a randomized controlled trial (AWARD-3). Diabetes Care, 2014; 37(8): 2168-76.
101. Blonde L, Jendle J, Gross J, Woo V, Jiang H, Fahrbach JL, et al. Once-weekly dulaglutide versus bedtime insulin glargine, both in combination with prandial insulin

lispro, in patients with type 2 diabetes (AWARD-4): a randomised, open-label, phase 3, non-inferiority study. Lancet, 2015; 385(9982): 2057-66.

102. Skrivanek Z, Gaydos BL, Chien JY, Geiger MJ, Heathman MA, Berry S, et al. Dose-finding results in an adaptive, seamless, randomized trial of once-weekly dulaglutide combined with metformin in type 2 diabetes patients (AWARD-5). Diabetes Obes Metab, 2014; 16(8): 748-56.
103. Tuttle KR, Lakshmanan MC, Rayner B, Busch RS, Zimmermann AG, Woodward DB, et al. Dulaglutide versus insulin glargine in patients with type 2 diabetes and moderate-to-severe chronic kidney disease (AWARD-7): a multicentre, open-label, randomised trial. Lancet Diabetes Endocrinol, 2018; 6(8): 605-17.
104. Dungan KM, Weitgasser R, Perez Manghi F, Pintilei E, Fahrbach JL, Jiang HH, et al. A 24-week study to evaluate the efficacy and safety of once-weekly dulaglutide added on to glimepiride in type 2 diabetes (AWARD-8). Diabetes Obes Metab, 2016; 18(5): 475-82.
105. Pozzilli P, Norwood P, Jódar E, Davies MJ, Ivanyi T, Jiang H, et al. Placebo-controlled, randomized trial of the addition of once-weekly glucagon-like peptide-1 receptor agonist dulaglutide to titrated daily insulin glargine in patients with type 2 diabetes (AWARD-9). Diabetes Obes Metab, 2017; 19(7): 1024-31.
106. Ludvik B, Frías JP, Tinahones FJ, Wainstein J, Jiang H, Robertson KE, et al. Dulaglutide as add-on therapy to SGLT2 inhibitors in patients with inadequately controlled type 2 diabetes (AWARD-10): a 24-week, randomised, double-blind, placebo-controlled trial. Lancet Diabetes Endocrinol, 2018; 6(5): 370-81.
107. Rosenstock J, Wysham C, Frías JP, Kaneko S, Lee CJ, Fernández Landó L, et al. Efficacy and safety of a novel dual GIP and GLP-1 receptor agonist tirzepatide in patients with type 2 diabetes (SURPASS-1): a double-blind, randomised, phase 3 trial. Lancet, 2021; 398(10295): 143-55.
108. Ludvik B, Giorgino F, Jódar E, Frias JP, Fernández Landó L, Brown K, et al. Once-weekly tirzepatide versus once-daily insulin degludec as add-on to metformin with or without SGLT2 inhibitors in patients with type 2 diabetes (SURPASS-3): a randomised, open-label, parallel-group, phase 3 trial. Lancet, 2021; 398(10300): 583-98.
109. Del Prato S, Kahn SE, Pavo I, Weerakkody GJ, Yang Z, Doupis J, et al. Tirzepatide versus insulin glargine in type 2 diabetes and increased cardiovascular risk (SURPASS-4): a randomised, open-label, parallel-group, multicentre, phase 3 trial. Lancet, 2021; 398(10313): 1811-24.

110. Dahl D, Onishi Y, Norwood P, Huh R, Bray R, Patel H, et al. Effect of Subcutaneous Tirzepatide vs Placebo Added to Titrated Insulin Glargine on Glycemic Control in Patients With Type 2 Diabetes: The SURPASS-5 Randomized Clinical Trial. Jama, 2022; 327(6): 534-45.
111. Jastreboff AM, Aronne LJ, Ahmad NN, Wharton S, Connery L, Alves B, et al. Tirzepatide Once Weekly for the Treatment of Obesity. N Engl J Med, 2022; 387(3): 205-16.
112. Almandoz JP, Lingvay I, Morales J, Campos C. Switching Between Glucagon-Like Peptide-1 Receptor Agonists: Rationale and Practical Guidance. Clin Diabetes, 2020; 38(4): 390-402.
113. Pratley RE, Catarig AM, Lingvay I, Viljoen A, Paine A, Lawson J, et al. An indirect treatment comparison of the efficacy of semaglutide 1.0 mg versus dulaglutide 3.0 and 4.5 mg. Diabetes Obes Metab, 2021; 23(11): 2513-20.
114. Lingvay I, Bauer R, Baker-Knight J, Lawson J, Pratley R. An Indirect Treatment Comparison of Semaglutide 2.0 mg vs Dulaglutide 3.0 mg and 4.5 mg Using Multilevel Network Meta-regression. J Clin Endocrinol Metab, 2022; 107(5): 1461-9.
115. O'Neil PM, Birkenfeld AL, McGowan B, Mosenzon O, Pedersen SD, Wharton S, et al. Efficacy and safety of semaglutide compared with liraglutide and placebo for weight loss in patients with obesity: a randomised, double-blind, placebo and active controlled, dose-ranging, phase 2 trial. Lancet, 2018; 392(10148): 637-49.