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Off-label Uses of GLP-1 Receptor Agonists and Dual GLP-1/GIP Receptor Agonists

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Glucagon-like peptide-1 (GLP-1) receptor agonists (RAs) and dual GLP-1/glucose-dependent insulinotropic polypeptide (GIP) RAs have rapidly gained popularity for glucose lowering in patients with type 2 diabetes (T2D) and as weight management drugs. In addition to Food and Drug Administration (FDA) approved indications (**Table 1**), GLP-1 RAs are being used for additional off-label uses. This newsletter will review the evidence for off-label uses of GLP-1/GIP RAs and discuss important considerations when prescribing these medications.

Table 1. FDA Approved Indications for GLP-1 RAs and Dual GLP-1/ GIP Agonists

Drug*	Indication
Dulaglutide TRULICITY[1]	• Glucose lowering in adults and pediatrics with T2D • Reduce CV events in adults with T2D
Exenatide BYETTA[2]	• Glucose lowering in adults with T2D
Exenatide ER BYDUREON[3]	• Glucose lowering in adults and pediatrics with T2D
Liraglutide[4] SAXENDA[4]1/27/ 2025 12:07:00 PM	• Body weight reduction in the following: Adult patients with an initial body mass index (BMI) of: • 30 kg/m^2 or greater (obese), or • 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbid condition (e.g. hypertension, T2D, or dyslipidemia) Pediatric patients aged 12 years and older with: • body weight above 60 kg and • an initial BMI corresponding to 30 kg/m^2 for adults (obese) by international cut-offs
Liraglutide VICTOZA[5]	• Glucose lowering in adults and pediatrics with T2D • Reduce CV events in adults with T2D
Semaglutide OZEMPIC[6]	• Glucose lowering in adults with T2D • Reduce CV events in adults with T2D
Semaglutide RYBELSUS[7]	• Glucose lowering in adults with T2D
Semaglutide WEGOVY[8]	• Reduce CV events in adults with CV disease and overweight or obesity • Body weight reduction in adults and pediatric patients with obesity and adults with overweight in the presence of at least one weight-related comorbid condition
Tirzepatide+ MOUNJARO[9]	• Glucose lowering in adults with T2D
Tirzepatide+ ZEPBOUND[10]	• Body weight reduction in adults with obesity and overweight in the presence of at least one weight-related comorbid condition • Moderate to severe OSA in adults with obesity

Key: *All drugs are GLP-1 RAs unless indicated; + Dual GLP-1/GIP RA
Abbreviations: CV = cardiovascular; ER = extended release; OSA = obstructive sleep apnea; T2D = type 2 diabetes

Pharmacology of GLP-1 RAs and GLP-1/GIP RAs

GLP-1 RAs bind to the GLP-1 receptor in central (e.g., brain) and peripheral targets (e.g., lungs, pancreas, gastrointestinal tract, kidney, and heart) which triggers the effects of the GLP-1 hormone.[11] The physiological GLP-1 hormone stimulates insulin secretion, lowers glucagon secretion, and delays gastric emptying. Appetite regulation in the brain is also a function of the GLP-1 and GIP receptor.[9,12] Due to the widespread distribution of GLP-1 receptors there are multiple potential therapeutic uses. There is Medicaid compendia support (i.e., Micromedex)/evidence for use in fatty liver disease, polycystic ovary syndrome (PCOS), and heart failure with preserved ejection fraction and obesity. Additional indications where GLP-1/GIP RAs have demonstrated efficacy are: alcohol and substance use disorder (SUD)[11], prediabetes[13], epilepsy[14], Parkinson's disease (PD)[15], Alzheimer's disease (AD)[16], and obstructive sleep apnea (OSA)[17].

GLP-1 RAs use in Heart Failure

A recent trial studying semaglutide in patients with HF with preserved ejection fraction and obesity (STEP-HFpEF) provided evidence for use in this population.[18] Compared to placebo, semaglutide improved symptoms, as measured by the Kansas City Cardiomyopathy Questionnaire, with an estimated difference (ED) of 7.8 points (95% CI, 4.8 to 10.9 points) and reduced body weight (ED -10.7%; 95% confidence interval [CI], -11.9% to -9.4%). This trial provides moderate quality evidence of potential utility in the treatment of heart failure (HF).[19] Outcomes such as hospitalizations for HF, would provide valuable evidence to conclude benefit in this population.

GLP-1 RAs use in Polycystic Ovary Disease

Elevated insulin levels are a known contributor to PCOS. The underlying cause of PCOS is insulin resistance which results in hyperinsulinemia. This leads to exaggerated insulin effects in

the ovary due to the excess insulin levels. The American Society for Reproductive Medicine recommends antidiabetic therapies, such as GLP-1 RAs, as an option for patient with PCOS and obesity.[20] In women with PCOS and overweight or obesity, a meta-analysis of 6 studies (n=327), found liraglutide to be superior to metformin for weight loss.[21] The combination of liraglutide and metformin, compared to placebo, were found to improve body mass index (BMI), fasting blood sugar, and fasting insulin more than metformin alone at 12 weeks.[21] In a second meta-analysis of 176 patients, GLP-1 RAs (i.e., semaglutide and liraglutide) were compared to placebo in women with PCOS and found that GLP-1 RAs statistically significantly reduced BMI (mean difference [MD] -2.42; 95% confidence interval [CI], -3.10 to -1.74); p<0.00001) and serum triglycerides (MD -0.20; 95% CI, -0.30 to -0.11; p<0.00001) and non-significantly total testosterone levels (MD -1.33; 95% CI, -0.10 to 0.01; p=0.15).[20] Results are suggestive of a favorable option for people with PCOS, with additional randomized controlled trials (RCT) studying outcomes such as restoration of ovulatory menstrual cycles and hyperandrogenism, needed to verify benefit.

GLP-1 RAs in Substance Use Disorder

GLP-1 RAs may have utility in the management of alcohol and other substance use disorders (SUD). While most of the evidence is in alcohol use disorder (AUD), research has also been conducted in patients taking psychostimulants, opioids and nicotine.[11] The suggested mechanism of efficacy is related to reward processing, cognitive function, stress adaption and satiety. One prospective, RCT (n=127) found extended-release exenatide had no effect on alcohol consumption in patients with AUD.[22]

Low quality evidence has found no benefit of GLP-1 RAs in those with cocaine use disorder.[11] Preliminary results from one, unpublished trial studying the use of liraglutide in patients with opioid use disorder reported a reduction in cravings in patients receiving liraglutide. GLP-1 RA use for nicotine has been suggested as having potential benefits but additional studies need to be performed.[11]

GLP-1 RAs and GLP-1/GIP RAs and Liver Disease

In 2023, the American Association for the Study of Liver Diseases (AASLD) introduced new nomenclature for fatty liver disease. The terms metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic dysfunction-associated steatohepatitis (MASH) were introduced in place of nonalcoholic fatty liver disease (NAFLD) and its subcategory nonalcoholic steatohepatitis (NASH). MASLD affects 30% of people worldwide and can progress to more severe forms of liver disease such cirrhosis or MASH and an increased risk of cardiovascular (CV) disease.[23, 24] MASLD has been linked to insulin resistance, and the suggested hepatic benefits of GLP-1 RAs are most likely due to weight loss.

Studies in adults with overweight and MASLD have demonstrated GLP-1 RA and GLP-1/GIP RA benefits in liver inflammation, fibrosis and potential reversal of steatohepatitis with weight loss of 7% or more.[25,26] Results of phase 2 studies of semaglutide and tirzepatide in the treatment of MASH are presented below (**Table 2**). Liraglutide was also studied in a double-blind, phase 2 RCT (n=52) which demonstrated more resolution of definite non-alcoholic steatohepatitis compared to placebo, 39% versus 9% (relative risk [RR] 4.3%; 95% CI, 1.0 to 17.7; p=0.019).[27]

The American Association of Clinical Endocrinology (AACE) recommends semaglutide or liraglutide for people with MASLD and who have a BMI of at least 27 kg/m^2 who are not able to obtain weight management goals with lifestyle modifications.[25]

For a more detailed review on the use of GLP-1/GIP RAs in the treatment of liver disease, visit our newsletter at: https://www.orpdl.org/durm/newsletter/osdr_articles/volume14/osdr_v14_i10.pdf.

Table 2. Selected GLP-1 RAs and GLP-1/GIP RAs phase 2 studies*[28,29]

	MASH Resolution	Fibrosis Improvement
Semaglutide 0.1 mg daily injection	40% OR 3.36 (95% CI 1.29-8.86)	49% OR 1.96 (95% CI 0.86-4.51)
Semaglutide 0.2 mg daily injection	36% OR 2.71 (95% CI 1.06-7.56)	32% OR 1.00 (95% CI 0.43-2.32)
Semaglutide 0.4 mg daily injection	59% OR 6.87 (95% CI 2.60-17.63)	43% OR 1.42 (95% CI 0.62-3.28)
Placebo	17%	33%
Tirzepatide 5 mg injection	44% Difference 34% (95% CI 17-50)	55% Difference 25% (95% CI 5-46)
Tirzepatide 10 mg injection	56% Difference 46% (95% CI 29-62)	51% Difference 22% (95% CI 1-42)
Tirzepatide 15 mg injection	62% Difference 53% (95% CI 36-69)	51% Difference 21% (95% CI 1-42)
Placebo	10%	30%

* Results from unique studies; not for direct comparison.
Abbreviations: CI = confidence interval; MASH = metabolic dysfunction-associated steatohepatitis; OR = odds ratio.

Prediabetes and GLP-1 RAs

Weight loss has demonstrated efficacy in preventing progression to T2D in adults who have prediabetes (hemoglobin A1c [HbA1c) of ≥ 5.7%]).[13] Certain GLP-1 RAs

(i.e., liraglutide, semaglutide and tirzepatide) have been associated with clinically significant weight loss ranging from 5.2 kg to 19 kg in studies lasting around one year.[13] Due to the weight loss benefits demonstrated with the use of GLP-1 RAs and GLP-1/GIP RAs, studies have shown reductions in the development of diabetes. The most evidence is for liraglutide and semaglutide. In a post-hoc analysis of 3 studies (n=3375) evaluating semaglutide for weight loss, the STEP 1-3 trials, glucose level were studied. In patients with prediabetes at baseline, normoglycemia was found to be higher with semaglutide compared to placebo at week 68, (STEP 1, 84.1% vs. 47.8%; STEP 3, 89.5% vs. 55.0%; STEP 4, 89.8% vs. 70.4%; all $P < 0.0001$).[30]

In a double blind, placebo controlled RCT, liraglutide 3.0 mg injected daily in patients with prediabetes and a BMI of 30 kg/m^2, or at least 27 kg/m^2 with comorbidities, was found to decrease the risk of developing diabetes (absolute risk reduction [ARR] 4%; number needed to treat [NNT] 25 over 160 weeks). The study was limited by high dropout rates.[31]

GLP-1 RAs and Epilepsy

There is some preliminary evidence that GLP-1 RAs may decrease neurodegeneration and improve neuroinflammation in people with epilepsy. A recent meta-analysis and systematic review in late-onset epilepsy (those diagnosed after the age of 55 years) compared glucose lowering therapies to placebo.[32] The trials were designed to access long-term CV and renal outcomes. Seizures and epilepsy prevention were analyzed from adverse event outcomes from trial data. In an analysis of 8 RCTs, GLP-1 RAs, compared to placebo, reduced the risk for the composite outcome of epilepsy and seizures with a relative risk of 0.67 (95% CI, 0.46 to 0.98).[32] Results were similar for the newer glucose drugs, sodium-glucose cotransporter-2 (SGLT-2) inhibitors and dipeptidyl peptidase-4 (DPP-4) inhibitors. Additional research is needed to confirm these benefits.

Parkinson's disease and GLP-1 RA

GLP-1 RAs may have efficacy in preventing or treating PD. Neuronal metabolism and repair and synaptic efficacy is influenced by insulin signaling in the brain. The proposed mechanism of the role of GLP-1 RAs is prevention of insulin desensitization in the brain which is often seen in patients with PD. A Cochrane review evaluating exenatide compared to placebo in 2 studies (n=104) found low-quality evidence that motor impairment, accessed by the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III, was improved in the off-medication state (12-weeks after exenatide discontinuation) in patients who took exenatide compared to people who took placebo.[15] In one study, the difference compared to placebo and GLP-1 RAs was small and results were not clinically meaningful (i.e., a clinically meaningful change is defined as a change of -3.25 or more) (MD -3.10; 95% CI, -6.11 to -0.09).[15] In the second study (n=44), exenatide was superior to no treatment with results that were considered clinically meaningful (MD -4.5; 95% CI, -8.64 to -0.36).[15] There is a lack of evidence to determine a definitive benefit and additional research is needed.

GLP-1 RAs and Alzheimer's disease

It is known that T2D is a risk factor for developing AD. GLP-1 RAs cross the blood-brain barrier and may improve cognitive function by reducing oxidative stress and neuroinflammation and suppressing neurotoxicity.[16] Modification of the underlying disease process is measured by Aß and tau accumulation.[14] In a systematic review of 3 studies, there was no treatment difference between GLP-1 RAs (i.e., liraglutide and exenatide) and placebo.[16] A second systematic review and meta-analysis found similar results, suggesting that additional research is needed to determine any benefit for the use of GLP-1 RAs in people with AD.[33] There may also be a preventative role of GLP-1 RAs in the development of AD, based on retrospective data in patients with T2D; however, due to the high risk of bias associated with retrospective data, randomized controlled trials need to be done to determine if there is any actual benefit .[25]

Obstructive Sleep Apnea and GLP-1 RAs and GLP-1/GIP RAs

Obstructive sleep apnea is associated with obesity, T2D, and increased risk of CV disease. Intermittent hypoxia associated with OSA can lead to a variety of detrimental physiological changes including weight gain, cognitive impairment and CV events. Weight loss in adults with obesity-associated OSA can decrease or eliminate OSA.[17] The weight loss benefits demonstrated with GLP-1 RAs and GLP-1/GIP RAs, as well as improvement in OSA associated impaired glucose metabolism, suggests a therapeutic use of GLP-1 RAs for the treatment of OSA. A systematic review and meta-analysis of 6 studies demonstrated reductions in the apnea-hypopnea index (AHI) with the use of GLP-1 RAs with an estimated treatment difference of -9.48 events per hour (95% CI, -12.56 to -6.40).[17] In indirect comparisons, tirzepatide was superior to liraglutide with a mean difference in AHI reductions of -21.86 events per hour versus -5.10 events per hour.[17]

Tirzepatide (ZEPBOUND) is FDA-approved for use in OSA associated with obesity based on two RCTs demonstrating reductions in AHI of -20 (95% CI, -25.8 to -14.2) and -23.8

(95% CI, -29.6 to -17.9) in patients with moderate to severe OSA and obesity, based on moderate quality of evidence.[10]

GLP-1 RAs Adverse Reactions

The most common adverse reactions with GLP-1 RAs are gastrointestinal (GI) in nature and include nausea, vomiting, diarrhea, constipation and abdominal pain.[12] Starting at low doses and increasing gradually may help to alleviate GI issues.

Certain patients should may not be candidates for take GLP-1 RAs, including the following[12]:

- Personal or family history of medullary thyroid cancer or multiple endocrine neoplasia type 2
- Gut motility issues or inflammatory bowel disease
- Renal impairment with an estimated glomerular filtration rate (eGFR) of 30 mL/min/1.73 m^2.
- Pregnancy

Additional Considerations

Due to the high demand, high out of pocket costs for some patients, and drug shortages in some cases, patients have sought to obtain GLP-1 RAs by alternative means, such as unapproved, compounded versions.[34] The FDA has advised against the use of these products because they are not regulated for safety and efficacy, and complications and deaths have been reported in users of compounded products. Compounded versions of semaglutide and tirzepatide have been reported to cause hospitalizations related to dosing errors.[34] Dosing errors range from patients administering the wrong dose, being prescribed excessive doses, and miscalculated doses by healthcare professionals.

Counterfeit versions of semaglutide have been marketed in the United States and could potentially contain the incorrect ingredients, or product that is not intended for human use. Illegal online sales of semaglutide and tirzepatide have also been identified and may contain harmful or incorrect ingredients.[34] GLP-1 RAs should only be purchased from state-licensed pharmacies that dispense FDA-regulated products. Adverse events or quality problems should be reported to the FDA at: www.accessdata.fda.gov/scripts/medwatch/index.cfm.

It is also important to note that GLP-1 RAs and GLP-1/GIP RAs used for weight management require lifelong use to maintain weight loss. Studies have demonstrated weight regain when the medication is discontinued.

Conclusion

The existing evidence for GLP-1 RAs and GLP-1/GIP RAs use for off-label indications is limited and mostly low-quality. Most of the current evidence is from small studies that are often not powered to detect differences between groups. Additional studies are needed to verify efficacy and safety for these conditions. GLP-1 RA use for off-label uses is not covered for fee-for-service (FFS) patients, except for MASH patients who meet specifications outlined in the prior authorization criteria available at: https://www.oregon.gov/oha/HSD/OHP/Tools/Oregon%20Medicaid%20PA%20Criteria%20January%201,%202025%20KH.pdf.

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