

GLP-1 Receptor Agonist Educational Needs Assessment

Executive Summary

Diabetes mellitus is a highly prevalent condition with comorbidities that affect mortality and quality of life. The International Diabetes Federation estimated that 537 million adults aged 20 to 79 years, or 10.5% of adults in that age range worldwide, had diabetes mellitus in 2021; the projected number was 783 million by 2045.¹ In the United States, the Centers for Disease Control and Prevention estimated that 38.4 million people, or 11.6% of the population, had diabetes mellitus in 2021.²

The economic burden of diabetes mellitus is substantial. In an age- and sex-adjusted United States analysis of 2017 costs, medical expenditures among people with diagnosed diabetes mellitus were approximately 2.3 times those expected in the absence of diabetes mellitus.³ Estimated global diabetes-related health expenditure was \$966 billion in 2021, and approximately 6.7 million deaths among adults aged 20 to 79 years were attributable to diabetes mellitus that year.¹ Diabetes mellitus causes microvascular and macrovascular complications, including kidney and cardiovascular disease, that affect survival and daily functioning. Lower health-related quality-of-life scores have also been associated with higher mortality in people with type 2 diabetes.⁴

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) offer benefits beyond glucose lowering. Selected agents reduce cardiovascular or kidney events in specified populations, promote weight loss, and improve outcomes in obesity-related heart failure and other cardiometabolic conditions. Injectable and oral formulations provide different treatment options, but efficacy, safety, indications, and administration requirements vary by agent. Clinicians need practical education to select appropriate treatment, support adherence, and integrate these therapies into individualized care.^{5,6}

Educational Gaps and Intended Outcomes

The assessment identifies 3 related gaps in clinician knowledge and treatment implementation. Each gap links a patient-care need to a measurable learning objective and a proposed clinical behavior. Root causes and supporting evidence follow the overview.

Category	Gap 1	Gap 2	Gap 3
Practice gap.	Endocrinology clinicians may not be fully aware of the efficacy, safety, dosing regimens, and indications of GLP-1 RAs and dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptor agonists for type 2 diabetes.	Endocrinology clinicians may not fully understand benefits beyond glycemic control, including weight loss, cardiovascular risk reduction, kidney protection, and potential effects on liver disease.	Endocrinology clinicians may be unfamiliar with evidence-based recommendations for integrating GLP-1 RAs into type 2 diabetes treatment.
Patient-care need.	Patients who could benefit from these treatments may not receive an appropriate agent, dose, or adherence support.	Patients with type 2 diabetes and related comorbidities may not receive treatment aligned with the demonstrated benefits of individual agents.	Delays in treatment, inappropriate patient selection, and failure to individualize therapy may limit glycemic and cardiorenal outcomes.
Learning objective.	Assess the mechanism of action, efficacy, safety, administration, and dosing of approved GLP-1 RAs and dual GIP and GLP-1 receptor agonists for type 2 diabetes.	Identify benefits beyond glucose lowering for patients with relevant comorbidities.	Incorporate GLP-1 RAs into type 2 diabetes treatment using evidence-based recommendations, patient and drug characteristics, and patient preferences.
Desired outcome.	Clinicians will select and incorporate treatment based on efficacy, safety, dosing, and patient characteristics.	Clinicians will integrate evidence-supported GLP-1 RA therapy into treatment plans for patients with type 2 diabetes and associated comorbidities.	Clinicians will identify eligible patients and individualize treatment for glycemic control, weight loss, cardiovascular risk reduction, and kidney protection.

Abbreviations: GIP, glucose-dependent insulinotropic polypeptide; GLP-1 RA, glucagon-like peptide-1 receptor agonist.

Gap 1 Evidence and Root Causes

Barriers to Therapy Selection and Safe Prescribing

Supporting evidence and educational needs include:

- Concerns about adverse effects and unfamiliarity with newer agents contribute to underprescribing despite demonstrated clinical benefits.⁷⁻⁹
- Clinicians need practical guidance on tolerability, patient selection, and assessment of benefits and risks in patients with complex comorbidities.^{8,9}
- Initiating a GLP-1 RA in a patient receiving insulin requires reassessment of insulin dosing and hypoglycemia risk, which can create an educational need.^{6,10}

Approved GLP-1 RAs for type 2 diabetes include exenatide, liraglutide, lixisenatide, semaglutide, and dulaglutide. Tirzepatide is a dual GIP and GLP-1 receptor agonist approved for type 2 diabetes. These treatments differ in formulation, dosing, clinical evidence, and labeled indications.^{6,7}

Clinical trials and meta-analyses demonstrate that GLP-1 RAs improve glycemic control and promote weight loss in appropriate populations.¹¹⁻¹³ Several agents provide glycemic control comparable or superior to basal insulin, with less hypoglycemia and more favorable weight effects when used without other hypoglycemia-inducing medications. Changes in weight, blood pressure, and other cardiometabolic measures may inform treatment selection alongside agent-specific outcomes evidence.⁶

The most common adverse effects are gastrointestinal symptoms, including nausea, vomiting, and diarrhea. Starting at the recommended initiation dose, titrating according to the product label and tolerability, and providing dietary counseling can help patients continue treatment.¹⁴ Although hypoglycemia risk is low with GLP-1 RA monotherapy, concomitant insulin or insulin secretagogues may require dose reduction. Gastric emptying is delayed, and semaglutide is not recommended in patients with severe gastroparesis; suspected pancreatitis requires discontinuation and evaluation.¹⁵ Clinicians must assess contraindications, precautions, and dehydration-related kidney risk rather than interpret favorable average trial safety as absence of individual risk. Research on depressive symptoms does not establish GLP-1 RAs as treatments for depression or remove the need to evaluate new psychiatric symptoms.¹⁶

Investigational Therapies in the Original 2025 Assessment

Several investigational treatments were being evaluated for type 2 diabetes and obesity when this assessment was prepared. The following examples illustrate the need for clinicians to distinguish approved therapies from emerging agents. Development-stage descriptions below are historical and do not report subsequent trial results or regulatory decisions.

Cagrilintide, a long-acting amylin analog, was being studied alone and with semaglutide. In a 32-week phase 2 trial in 92 adults with type 2 diabetes, coadministered cagrilintide and semaglutide reduced glycated hemoglobin (HbA1c) by 2.2 percentage points, compared with 1.8 percentage points with semaglutide and 0.9 percentage points with cagrilintide. Fasting plasma glucose decreased by 3.3, 2.5, and 1.7 mmol/L, respectively; time in the target glucose range of 3.9 to 10.0 mmol/L at week 32 was 88.9%, 76.2%, and 71.7%, respectively.¹⁷ The HbA1c difference versus semaglutide alone was not statistically significant.¹⁷ Phase 3 development was underway in 2025.¹⁸

Retatrutide is an investigational agonist of GIP, GLP-1, and glucagon receptors. In a phase 2 trial in adults with type 2 diabetes, doses of 4 to 12 mg reduced HbA1c by approximately 1.30 to 2.02 percentage points at 24 weeks, compared with 1.41 percentage points with dulaglutide 1.5 mg; the 0.5-mg retatrutide dose produced a smaller reduction. Body weight decreased in a dose-dependent manner.¹⁹ Phase 3 programs in diabetes and

obesity, including populations with cardiovascular disease, were underway when the original assessment was prepared.¹⁸

Orforglipron is an investigational, once-daily, oral, nonpeptide GLP-1 RA. In a 26-week phase 2 trial in adults with type 2 diabetes, HbA1c decreased by up to 2.10 percentage points with orforglipron, compared with 1.10 percentage points with dulaglutide and 0.43 percentage points with placebo. Doses of 12 mg or higher also produced greater weight reductions than placebo or dulaglutide; adverse effects were predominantly gastrointestinal.²⁰ The oral formulation offered a potential alternative to injectable therapy, and phase 3 development was underway in 2025.¹⁸

Gap 2 Evidence and Root Causes

Recognizing Benefits Beyond Glucose Lowering

Supporting evidence and educational needs include:

- Cardiovascular and kidney benefits, weight loss, and selected liver and heart-failure outcomes broaden clinical relevance. Evidence varies by agent, population, and outcome.^{5,12,21-25}
- In a United States database study of 1,389,016 adults with type 2 diabetes, 97.5% had at least 1 assessed comorbidity; hypertension, overweight or obesity, hyperlipidemia, chronic kidney disease (CKD), and cardiovascular disease were common.²⁶
- In a Virginia community health system, only 17.4% of 22,060 adults with type 2 diabetes and atherosclerotic cardiovascular disease, heart failure, or CKD received either a sodium-glucose cotransporter 2 (SGLT2) inhibitor or GLP-1 RA during 2019 to 2021.²⁷
- Knowledge gaps, prescribing confidence, and clinical inertia can contribute to underuse. Cost, access, and fragmented care also require attention.^{8,9}

Endocrinology clinicians need to recognize the benefits and limitations of GLP-1 RAs beyond glycemic control. In an Alberta primary-care study using 2018 to 2019 data, GLP-1 RA use was 4.6% in patients with cardiorenal comorbidities and 11.0% in those without these comorbidities.²⁸ These observational findings do not by themselves establish why treatment was withheld. Education should connect each patient's comorbidities to agent-specific evidence and eligibility rather than imply that all agents provide identical protection.

Randomized trial evidence supports reductions in major cardiovascular events and adverse kidney outcomes with selected GLP-1 RAs.¹² Semaglutide has demonstrated benefits in specified populations with atherosclerotic cardiovascular disease, type 2 diabetes and CKD, and obesity-related heart failure with preserved ejection fraction.^{21,25,29} Tirzepatide has demonstrated benefits in obesity-related heart failure and obstructive sleep apnea.^{30,31} In a 176-week trial subgroup with obesity and prediabetes, type 2 diabetes developed in 1.3% of tirzepatide-treated participants and 13.3% of placebo-treated participants; this result should not be generalized to all patients with obesity or to established diabetes.³² Because multimorbidity is common, clinicians should consider these outcomes alongside glycemic and weight goals, safety, cost, and patient preferences.^{26,33}

The mechanisms underlying cardiovascular effects include systemic metabolic changes and may also involve direct tissue effects. Human heart studies detected GLP-1 receptor messenger ribonucleic acid in all 4 chambers, but precise localization and the contribution of direct cardiac receptor signaling remain incompletely defined.³⁴ Improvements in body weight, blood pressure, metabolic measures, and inflammatory pathways may contribute to clinical effects; mechanistic hypotheses should not be presented as proven explanations for every outcome.^{5,35}

Trials of semaglutide in obesity-related heart failure with preserved ejection fraction demonstrated improvements in symptoms, physical limitations, and exercise function.³⁶ In a separate randomized trial, tirzepatide reduced a composite of cardiovascular death or worsening heart failure in patients with obesity and preserved ejection fraction; the benefit was driven primarily by fewer worsening heart-failure events.³⁰ These

findings do not establish a mortality benefit for every GLP-1 RA or for all heart-failure phenotypes. Clinician education should distinguish these populations from those with reduced ejection fraction and reinforce agent-specific evidence.^{25,37}

The evidence base also includes metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic dysfunction-associated steatohepatitis (MASH). In a phase 2 trial, semaglutide increased steatohepatitis resolution without worsening fibrosis, but the between-group difference in fibrosis-stage improvement was not statistically significant.³⁸ Weight loss and metabolic effects are plausible contributors to liver benefit, whereas proposed direct immune and hepatic mechanisms require cautious interpretation.³⁹

Kidney outcomes also extend beyond glucose lowering. In a randomized trial in adults with type 2 diabetes and CKD, semaglutide reduced the risk of a composite of major kidney disease events and cardiovascular or kidney death by 24% relative to placebo.²⁹ Observational studies in advanced CKD or acute kidney disease have reported favorable associations, but these findings do not establish efficacy for acute kidney injury or replace individualized safety assessment.^{40,41} Clinical education should distinguish randomized outcomes from observational evidence and theoretical anti-inflammatory or antifibrotic mechanisms.

Treatment with GLP-1 RAs promotes weight loss through effects on appetite, satiety, and gastrointestinal motility. Clinically meaningful weight reduction can improve glycemic control and cardiometabolic risk, although responses vary across agents and patients.^{6,13} In patients with CKD and obesity, weight loss may support broader treatment goals, but suitability for kidney transplant depends on the individual and the transplant program. Clinicians need education on maintaining nutrition, monitoring tolerability, and setting realistic weight goals.⁴²

Pulmonary outcomes require similar distinctions. Tirzepatide reduced apnea-hypopnea frequency in randomized trials of adults with moderate to severe obstructive sleep apnea and obesity, and United States approval for this population was granted in December 2024.^{31,43} Observational evidence also associated GLP-1 RA use with fewer asthma attacks among patients with type 2 diabetes, but this does not establish an approved asthma indication or a causal treatment effect.⁴⁴

Historically, GLP-1 RAs were often introduced after other glucose-lowering therapies. The 2025 treatment framework emphasizes earlier selection according to cardiovascular, kidney, weight, and other patient-specific needs rather than a uniform late-stage position.⁶ Clinical inertia and limited coordination among specialties may delay implementation. Education should combine evidence-based patient selection with practical initiation, tolerability, access, and interdisciplinary communication strategies.^{9,33}

Gap 3 Evidence and Root Causes

Applying the 2025 Treatment Recommendations

Supporting evidence and educational needs include:

- Updated recommendations require clinicians to select therapies according to comorbidities and patient priorities rather than HbA1c alone.⁶
- National and primary-care studies document persistent underuse of GLP-1 RAs and SGLT2 inhibitors in patients at high cardiorenal risk.^{28,45,46}
- In a United States cohort of adults with type 2 diabetes and CKD, GLP-1 RA use was below 10% across estimated glomerular filtration rate categories, while insulin use increased as kidney function declined.⁴⁷

The 2025 American Diabetes Association (ADA) Standards of Care expanded guidance relevant to GLP-1 RA prescribing. Recommendations address cardiovascular and kidney risk, body weight, and other comorbidities in addition to glycemic control. Applying these recommendations requires careful selection of an agent with evidence relevant to the patient.⁶

For adults with type 2 diabetes and established or high risk of atherosclerotic cardiovascular disease, the ADA recommends a GLP-1 RA or SGLT2 inhibitor with demonstrated cardiovascular benefit, irrespective of HbA1c. For heart failure, SGLT2 inhibitors remain recommended to prevent hospitalization; a GLP-1 RA with demonstrated benefit is recommended for symptoms and physical limitations in patients with obesity and symptomatic heart failure with preserved ejection fraction. These recommendations should not be interpreted as a universal cardiovascular mortality indication for every GLP-1 RA.⁶

In type 2 diabetes with MASLD and overweight or obesity, the 2025 recommendations support considering a GLP-1 RA or dual GIP and GLP-1 receptor agonist alongside healthy lifestyle interventions. For biopsy-proven MASH or high risk of liver fibrosis, selected glucose-lowering therapies may be preferred because of potential MASH benefits. The recommendation does not establish that every listed therapy reverses fibrosis.^{6,48}

Evidence supporting treatment for obesity-related heart failure includes improvements in symptoms, exercise function, and physical limitations.^{30,36} Nevertheless, clinical implementation has lagged behind trial evidence. In a University of Mississippi cohort of 21,173 patients with type 2 diabetes and cardiovascular disease studied from January 2013 through June 2019, 1.4% received an SGLT2 inhibitor and 1.6% received a GLP-1 RA.⁴⁹ These historical, single-center findings illustrate a treatment gap but are not current national prescribing rates.

For type 2 diabetes with CKD, the 2025 recommendations favor agents with demonstrated kidney and cardiovascular benefits. In advanced CKD, defined as an estimated glomerular filtration rate below 30 mL/min/1.73 m², a GLP-1 RA is preferred for glycemic treatment because of lower hypoglycemia risk and cardiovascular benefit; selection must still account for agent-specific labeling.^{6,42} Historical prescribing data show substantial underuse, including GLP-1 RA use below 10% across kidney-function categories in a United States cohort studied from 2016 to 2018.⁴⁷

For adults with type 2 diabetes without evidence of insulin deficiency, a GLP-1 RA, including a dual GIP and GLP-1 receptor agonist, is preferred to insulin; insulin remains appropriate for symptomatic or severe hyperglycemia and other indications.⁶ Glycemic targets are individualized, with HbA1c below 7% appropriate for many nonpregnant adults; 6.5% is not a universal target.⁵⁰ Improved glycemia during medication treatment should not be described as diabetes remission without meeting accepted remission criteria.⁵¹ When insulin and a GLP-1 RA are combined, insulin dosing and hypoglycemia risk require reassessment.⁶ In a national United States analysis from 2015 to 2020, 9.0% of adults with diabetes mellitus used either a GLP-1 RA or SGLT2 inhibitor, while 4.8% used a GLP-1 RA; use did not differ significantly by high versus lower cardiovascular-kidney risk.⁴⁶

Bone health is another consideration in treatment selection. The 2025 ADA review described a generally neutral effect of GLP-1 RAs on bone health and a theoretical potential benefit of GIP receptor agonism, but clinical bone-outcome data for tirzepatide were not yet available. Avoiding hypoglycemia is particularly important in older adults because falls can increase fracture risk.⁴⁸

The broader assessment of comorbidities includes sleep apnea, depression, disordered eating, and cognitive function. Evidence for tirzepatide in obstructive sleep apnea is supported by randomized trials, whereas psychiatric and cognitive effects of GLP-1 RAs remained investigational in the original assessment.^{31,48} Reported associations or small changes in symptom scores should not be framed as established indications for depression, disordered eating, or prevention of cognitive decline. Clinicians should continue appropriate screening and condition-specific care.^{16,48}

These developments increase the need for focused clinician education. Educational activities should clarify treatment eligibility, evidence strength, practical prescribing, and the distinction between approved indications and emerging applications. The intended outcome is more consistent, individualized, guideline-informed care rather than indiscriminate expansion of prescribing.^{6,9}

Conclusion

Therapies targeting GLP-1, alone or together with GIP, have an important role in type 2 diabetes treatment and selected cardiometabolic conditions. Clinical benefits extend beyond glucose lowering, but the evidence must be applied by agent, population, and outcome. Persistent knowledge gaps, clinical inertia, treatment burden, cost, and access barriers support targeted education on patient selection, safe initiation, monitoring, and interdisciplinary care. Linking these skills to case-based practice can help clinicians implement evidence-based treatment and improve patient-centered outcomes.^{6,8,9}

Proposed Educational Design

Agenda for 90 Minutes

Welcome and introduction | 5 minutes

Benefits beyond glucose lowering | 15 minutes. Mechanisms and multisystem effects of GLP-1 RAs and dual GIP and GLP-1 receptor agonists, supported by explanatory animations.

Key clinical trial evidence | 15 minutes. Efficacy, safety, dosing, and routes of administration for available agents, including exenatide, liraglutide, lixisenatide, semaglutide, dulaglutide, and tirzepatide; distinguish approved agents from investigational therapies.

Case-based implementation | 40 minutes. Expert and audience discussion applying evidence, guideline recommendations, and patient preferences to treatment decisions.

Audience questions and discussion | 15 minutes. Expert responses to clinical challenges and practical implementation questions.

6 Clinical Case Discussions

1. Patient with newly diagnosed type 2 diabetes and cardiovascular risk factors: apply recommendations and select an appropriate GLP-1 RA.
2. Patient receiving insulin who is gaining weight: assess the role of a GLP-1 RA and reassess insulin dosing.
3. Patient with type 2 diabetes and kidney disease: apply recommendations and agent-specific prescribing considerations.
4. Patient who frequently misses GLP-1 RA doses: identify barriers and support adherence.
5. Patient who does not tolerate a GLP-1 RA: assess symptoms, titration, dietary measures, and whether treatment should be modified.
6. Patient receiving a GLP-1 RA who has a planned surgical procedure: coordinate individualized perioperative assessment and preparation.

Questions raised during the activity, including those not answered live, will be addressed in a follow-up question-and-answer resource for participants.

Faculty Qualifications

Faculty should have clinical, research, or publication experience in endocrinology and the use of incretin-based therapies. Selection should emphasize evidence-based, balanced, and unbiased education.

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