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Drug Class Literature Scan: GLP-1 Receptor Agonists and Dual GLP-1/GIP Receptor Agonists

Date of Review: April 2024

Date of Last Review: October 2022
Literature Search: 08/01/22 – 02/01/24

Current Status of PDL Class:
See **Appendix 1**.

Plain Language Summary:

- The purpose of this review is to look at new research for medicines called glucagon-like peptide-1 receptor agonists (GLP-1 RA) and dual GLP-1 RA/glucose-dependent insulinotropic polypeptides (GIP) agonists.
- There are 4 GLP-1 RAs that are available: dulaglutide, exenatide, liraglutide, and semaglutide.
- There is one FDA approved GLP-1/GIP agonist available: tirzepatide.
- These medicines lower blood sugars in people with type 2 diabetes (T2DM). Most of these medicines are injections. One of the medicines, semaglutide, can be taken by mouth or injected.
- These medicines have been shown to cause stomach upset, including nausea, vomiting and diarrhea.
- This review found that liraglutide, when added with metformin, can further lower blood sugars in children with diabetes.
- Either dulaglutide or liraglutide are recommended in children 10 years of age and older who have T2DM.
- Any of these medicines are recommended to further lower blood sugars in people with T2DM who have tried other medicines to lower blood sugars and still need additional sugar lowering. Many of them are very helpful in people with diabetes who also have heart disease or kidney disease, or if weight loss is desired.

Conclusions:

- One new high-quality systematic review, 5 high-quality clinical practice guidelines, one expanded Food and Drug Administration (FDA) indication, one updated FDA safety warning and 2 new randomized controlled trials (RCTs) were identified in this literature scan.
- The Canadian Agency for Drugs and Technologies in Health (CADTH) evaluated the evidence for the use of liraglutide in youth (ages 10-17 years) for the treatment of type 2 diabetes mellitus (T2DM).[1] Liraglutide demonstrated more hemoglobin (HbA1c) lowering than placebo in children. The estimated treatment difference (ETD) was -0.9% to -1.06% in trials lasting 5 to 26 weeks. Adverse events (AE) were similar to trials of liraglutide in adults with gastrointestinal (GI) AE being the most common.[1]

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- In young people with T2DM over the age of 10 years who require drug therapy, the National Institute for Health and Care Excellence (NICE) recommend metformin, dulaglutide, liraglutide or empagliflozin in addition to lifestyle modifications.[2]
- The 2023 NICE guideline recommends tirzepatide in adults with T2DM who are unable to achieve target HbA1C with metformin and 2 other oral antidiabetic drugs.[3]
- Recommendations for the management of adults with T2DM was provided by a 2023 Veterans Administration/Department of Defense (VA/DoD) Guideline. The use of GLP-1 RAs are strongly recommended for those with atherosclerotic cardiovascular (CV) disease. In patients with T2DM with chronic kidney disease (CKD), who are unable to take sodium- glucose co-transporter 2 (SGLT-2) inhibitors, the use of GLP-1 RAs are strongly recommended.[4]
- The Kidney Disease Improving Global Outcomes (KDIGO) group recommend GLP-1 RAs in people with T2DM and CKD after metformin and SGLT-2 inhibitors.[5]
- The 2024 American Diabetes Association (ADA) recommend GLP-1 RAs and dual GLP-1/GIP RAs for adults with T2DM who require weight reduction.[6]
- Dulaglutide received an expanded indication for children 10 years of age and older who have T2DM.[7,8]
- An FDA safety warning was added to oral semaglutide (RYBELSUS) after post-marketing reports identified dizziness and dysgeusia with use.[9]
- A trial found that insulin glargine and liraglutide were more effective than the other therapies at maintaining glucose control over 5 years.[10]

Recommendations:
- No changes to the preferred drug list (PDL) are recommended based on review of the evidence.
- Evaluate costs in the executive session.

Summary of Prior Reviews and Current Policy
- The GLP-1 and dual GLP-1/GIP RAs were last reviewed in October 2022.
- The dual GLP-1/GIP RAs were added to the GLP-1 RA prior authorization (PA) criteria (**Appendix 6**). Tirzepatide was reviewed and kept as a non-preferred on the PDL.
- Preferred GLP-1 RAs are dulaglutide, exenatide, and liraglutide. Semaglutide and tirzepatide are subject to PA approval (**Appendix 6**).
- There were over 300 hundred claims for the GLP-1 RAs and dual GLP-1/GIP RAs last quarter (October – December 2023). This class represents substantial cost to the Oregon Health Authority (OHA).

Methods:
A Medline literature search for new systematic reviews and RCTs assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. A summary of the clinical trials is available in **Appendix 2** with abstracts presented in **Appendix 3**. The Medline search strategy used for this literature scan is available in **Appendix 4**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:

CADTH – Liraglutide for Pediatric Patients with Type 2 Diabetes

In a Health Technology Review conducted by CADTH in 2023, the efficacy and safety of liraglutide in pediatric patients with T2DM was evaluated.[1] The literature was searched from January 2013 through June 2023. Two parallel-group, placebo-controlled RCTs met the inclusion criteria for evaluation. Patients were 10-17 years of age with a mean age of 14.6 years in one trial and 14.8 years in the second trial. Most of the patients were White and female.[1] Both trials allowed metformin as background therapy for all treatment groups. Follow up was 5 weeks (n=19) in one trial and 26 weeks in the second trial (n=135). The target maintenance dose for liraglutide was 1.8 mg weekly. The primary outcome was HbA1c changes from baseline compared to placebo.[1]

Both trials reported statistically significant decrease in HbA1c in those treated with liraglutide compared to placebo. In the 26-week follow-up study, HbA1c was reduced more with liraglutide than with placebo (ETD -1.06%; 95% CI, -1.65 to -0.46%; p<0.001); results were similar in the 5-week study versus placebo (-0.90%; 95% CI, -1.36 to -0.45%; p=0.0007).[1] Minor reductions in body weight with liraglutide were also reported relative to placebo (-0.5 kg and -1.91 kg). Hypoglycemia and gastrointestinal adverse events were more commonly reported with liraglutide than placebo.[1] This review provided moderate quality evidence that liraglutide, when combined with metformin, further decreases HbA1c in youth with T2DM versus metformin alone.[1]

After review, 5 systematic reviews were excluded due to poor quality, wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[11–15]

New Guidelines:

NICE – Management of Type 1 and Type 2 Diabetes Mellitus in Children

In 2023, NICE updated guidance on the treatment of young people with T1DM and T2DM. Literature was searched through February 2023.

- Maintenance of an HbA1c of 6.5% or less minimizes long-term complications.[2]
- Metformin is recommended as a first-line agent in children who require medication, in addition to dietary support.
- Basal-bolus insulin is recommended in children who present with ketosis without diabetic ketoacidosis (DKA).
- Review glucose monitoring 4 weeks after treatment is started.
- If a change in treatment is required for individuals 10 years and older with T2DM taking metformin monotherapy, offer liraglutide or dulaglutide if the following are met:
    - HbA1c remains at 6.5% or greater,
    - Plasma glucose greater than126 mg/dL? (4 or more days a week when fasting or before meals), or
    - Plasma glucose greater than 162 mg/dL? (on 4 or more days a week, 2 hours after meals).
- Empagliflozin may be added to metformin children 10 years or older with T2DM who are not able to tolerate liraglutide or dulaglutide or have a clear preference for empagliflozin.
- Insulin can be considered in young people with T2DM who are taking metformin, with or without liraglutide, dulaglutide, or empagliflozin, if an HbA1c of 6.5% cannot be obtained on current therapy.[2]
- In children on metformin and insulin, the addition of liraglutide or dulaglutide can be considered for those who are already on insulin therapy, instead of increasing insulin, if their HbA1c or glucose levels do not meet criteria (e.g., HbA1c ≥6.5%, plasma glucose level >126 mg/dL [4 or more days a week when fasting or before meals] or plasma glucose >162 mg/dL [on 4 or more days a week, 2 hours after meals]).

- The addition of empagliflozin is recommended, instead of increasing insulin, in children already on insulin if their HbA1c or glucose levels do not meet recommendations for reducing or stopping insulin (e.g., HbA1c ≥6.5%, plasma glucose level >126 mg/dL [4 or more days a week when fasting or before meals]) and they are not able to tolerate liraglutide or dulaglutide or if they specifically request empagliflozin.[2]
- The lowest dose of medications should be used that achieves target HbA1c and blood glucose levels.

NICE – Tirzepatide for Type 2 Diabetes Mellitus

The efficacy and safety evidence for tirzepatide was evaluated by NICE in 2023.[3] The recommendation was based off of policy that recommends that injectable treatment be considered after metformin and 2 other oral antidiabetic drugs have failed to reduce blood glucose to target levels, or alternatively the oral therapy are not tolerated or are contraindicated.

Direct evidence has demonstrated that tirzepatide decreases HbA1c and body mass index (BMI) more than semaglutide, insulin or placebo.[3] No studies have directly compared tirzepatide to other GLP-1 RAs.

NICE recommends tirzepatide for treatment of T2DM in adult patients in conjunction with diet and exercise if blood glucoses are not controlled with metformin and two other oral antidiabetic agents (or if oral therapy is not tolerated or contraindicated). Other criteria include:
- Patient has a BMI of 35 kg/m^2 or more and psychological or medical comorbidities associated with obesity;
- Patient has a BMI less than 35 kg/m^2 but insulin would impose significant occupational implications or weight loss would improve obesity-related complications; or
- Reduced BMI thresholds (e.g., reduce by 2.5 kg/m^2) should be considered for individuals from the following backgrounds: South Asian, Chinese, other Asian, Middle Eastern, Black African or African-Caribbean.[3]

Veteran Affairs/Department of Defense Clinical Practice Guideline for the Management of Type 2 Diabetes Mellitus

The VA/DoD published a clinical practice guideline for the treatment of T2DM in 2023.[4] Evidence was evaluated and graded from “Strong” to “Weak” based on the quality of evidence and not necessarily clinical importance. Recommendations for GLP-1 RAs are presented but recommendations for the use of GLP-1/GIP RAs (e.g., tirzepatide) were not included in the guideline.

The VA/DoD recommends:
- Targeting a HbA1c of 7.0% to 8.5% for most patients (weak recommendation).[4]
- GLP-1 RAs or SGLT-2 inhibitors that have demonstrated cardiovascular (CV) benefit in adults with T2DM and atherosclerotic CV disease (strong recommendation).
    - The evidence for the benefits of GLP-1 RAs on CV outcomes was conducted primarily in adults with CV disease, and less in those at high risk. Additionally, 71-82% of patients were also taking metformin.[4]
- GLP-1 RAs or SGLT-2 inhibitors that have demonstrated CV benefit in adults with T2DM who are at high risk for atherosclerotic CV disease (e.g., chronic kidney disease (CKD), left ventricular hypertrophy, heart failure) (weak recommendation).[4]
    - There was insufficient high quality evidence on the benefits of GLP-1 RAs on CV outcomes for those who are at low risk for CV disease.
- GLP-1 RAs with proven renal protection to improve macroalbuminuria for adults with T2DM who have CKD and are not able to take SGLT-2 inhibitors (strong recommendation).

- This recommendation was based on evidence that GLP-1 RAs benefit kidney outcomes in adults with T2DM (Hazard Ratio: 0.79 vs. placebo; 95% CI: 0.73–0.87).[4] Renal benefits of GLP-1 RAs (e.g., liraglutide, semaglutide, dulaglutide) are primarily driven by a decrease in new onset macroalbuminuria.

- GLP-1 RAs or SGLT-2 inhibitors for adults with T2DM who have CV disease or renal disease even if they have already achieved target blood glucose levels on baseline medication (weak recommendation).[4]
  - There is evidence that GLP-1 RAs may improve CV and renal outcomes independent of glucose lowering.
- Classes of antidiabetic therapies besides insulin, sulfonylureas or meglitinides in adults, especially those 65 years and older, to reduce risk of hypoglycemia (weak recommendation).

Kidney Disease Improving Global Outcomes Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease

The KDIGO updated guidance in 2022 for management of individuals with diabetes mellitus with CKD.[5] The strength of the recommendation was either Level 1 (strong), which are *recommendations*, and Level 2 (weak) which are *suggestions*. The quality of evidence is graded from A (high) to D (low). The evidence for the use of GLP-1 RAs and GLP-1 RA/GIPs in CKD will be presented.

- In patients with T2DM and CKD (without dialysis and estimated glomerular filtration rate [EGFR] of ≥30 ml/min/1.73 m^2), metformin with a SGLT-2 inhibitor is recommended (1A recommendation).[5]
- Long-acting GLP-1 RAs with CV benefit are recommended for patients requiring additional medications for glucose lowering or who cannot tolerate metformin and/or SGLT-2 inhibitors (1B recommendation).
  - GLP-1 RAs are also preferred for those patients desiring weight loss, have heart failure, high-risk of atherosclerotic cardiovascular disease (ASCVD), and wish to avoid hypoglycemia.[5]
  - The combined use of GLP-1 RAs and DDP-4 inhibitors should not be used.
  - If GLP-1 RAs are used with sulfonylureas or insulin, the dose of those products should be reduced to reduce the risk of hypoglycemia.

American Diabetes Association: Standards of Care in Diabetes

The ADA updates guidance for diabetes care every year. In the 2024 guidance, the use of GLP-1 RAs and GLP-1 RA/GIPs are evaluated and recommendations are graded based on the evidence.[6]

- Combination therapy upon initiation is recommended if needed to meet glucose goals (Grade A).
- GLP-1 or dual GLP-1/GIP RAs are preferred for patients with T2DM who would benefit from weight management (Grade A).
- GLP-1 RAs should be considered independent of HbA1c in adults with T2DM and established CV disease, who are at high risk of CV disease, HF, or CKD, because of evidence of benefit in these populations. (Grade A).[6]
- GLP-1 RAs are preferred in adults with T2DM and advanced CKD (eGFR <30 mL/min per 1.73 m^2). GLP-1 RAs are preferred for glucose lowering because of evidence of reduced CV risk and hypoglycemia in this population. (Grade B).[6]
- GLP-1 and dual GLP-1 /GIP RAs are recommended over insulin in people with T2DM because of the beneficial effect on weight and hypoglycemic risk (Grade A).[6]

New Formulations:

Dulaglutide (TRULICITY): In November 2022, dulaglutide received the expanded indication to improve glycemic control in pediatric patients 10 years of age or older with T2DM, as an adjunct to diet and exercise. The expanded indication was based on one placebo-controlled, RCT in 154 children (**Appendix 2**).

New FDA Safety Alerts:

Table 1. Description of New FDA Safety Alerts

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Semaglutide[9]	RYBELSUS	January 2024	Adverse Drug Reactions – post-marketing reports	Nervous system disorders: dizziness and dysgeusia

References:

1. Kaulback K, Walter M. Liraglutide for Pediatric Patients With Type 2 Diabetes. *Canadian Agency for Drugs and Technology in Health*. 2023;3(7). doi:10.51731/cjht.2023.698.

2. National Institute for Health and Care Excellence. Diabetes (type 1 and type 2) in Children and Young People: Diagnosis and Management. *NICE Guideline*. May 2023. Available at: https://www.nice.org.uk/guidance/ng18. Accessed January 20, 2024.

3. National Institute for Health and Care Excellence. Tirzepatide for Treating Type 2 Diabetes. *Technology Appraisal Guidance*. October 2023. Available at: nice.orgl.uk/guidance/ta924. Accessed January 30, 2024.

4. VA/DoD Clinical Practice Guideline. (2023). Management of Type 2 Diabetes Mellitus. Washington, DC: U.S. Government Printing Office. Available at: https://www.healthquality.va.gov/guidelines/CD/diabetes/VADoD-Diabetes-CPG_Final_508.pdf. Accessed January 30, 2024.

5. Rossing P, Caramori ML, Chan JCN, et al. KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. *Kidney International*. 2022;102(5):S1-S127. doi:10.1016/j.kint.2022.06.008.

6. ElSayed N, Allepo G, Aroda V, et al. Pharmacological Approaches to Glycemic Treatment: Standards of Care in Diabetes - 2023. *Diabetes Care.* 2023;46: S140-S157.

7. TRULICITY (dulaglutide) [prescribing information]. Indianapolis, IN; Eli Lily and Company. November 2022.

8. Arslanian SA, Hannon T, Zeitler P, et al. Once-Weekly Dulaglutide for the Treatment of Youths with Type 2 Diabetes. *N Engl J Med*. 2022;387(5):433-443. doi:10.1056/NEJMoa2204601.

9. Food and Drug Administration. Drug Safety-related Labeling Changes: Rybelsus. Available at: https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/index.cfm?event=searchdetail.page&DrugNameID=2456. Accessed February 2, 2024.

10. GRADE Study Research Group. Glycemia Reduction in Type 2 Diabetes — Glycemic Outcomes. *NEJM.* 2022; 387:1063-74.

11. Mannucci E, Gallo M, Giaccari A, et al. Effects of glucose-lowering agents on cardiovascular and renal outcomes in subjects with type 2 diabetes: An updated meta-analysis of randomized controlled trials with external adjudication of events. *Diabetes, Obesity and Metabolism*. 2023;25(2):444-453. doi:10.1111/dom.14888.

12. The Grade Study Group. Glycemia Reduction in Type 2 Diabetes — Microvascular and Cardiovascular Outcomes. *New England Journal of Medicine*. 2022;387(12):1075-1088. doi:10.1056/NEJMoa2200436.

13. Guo X, Sang C, Tang R, et al. Effects of glucagon-like peptide-1 receptor agonists on major coronary events in patients with type 2 diabetes. *Diabetes Obes Metab*. 2023;25 Suppl 1:53-63. doi:10.1111/dom.15043.

14. Yang XY, Yin S, Yu YF, et al. Is tirzepatide 15 mg the preferred treatment strategy for type 2 diabetes? A meta-analysis and trial-sequence-analysis. *Eur Rev Med Pharmacol Sci*. 2023;27(15):7164-7179. doi:10.26355/eurrev_202308_33290.

15. Jahagirdar D, Mahood Q. Semaglutide for Type 2 Diabetes (2 mg). *Canadian Agency for Drugs and Technology in Health*. 2023;3(10). doi:10.51731/cjht.2023.752.

Appendix 1: Current Preferred Drug List

Generic	Brand	Form	PDL	Route
dulaglutide	TRULICITY	PEN INJCTR	Y	Subcutaneous
exenatide	BYETTA	PEN INJCTR	Y	Subcutaneous
liraglutide	VICTOZA 2-PAK	PEN INJCTR	Y	Subcutaneous
liraglutide	VICTOZA 3-PAK	PEN INJCTR	Y	Subcutaneous
exenatide microspheres	BYDUREON BCISE	AUTO INJCT	N	Subcutaneous
semaglutide	OZEMPIC	PEN INJCTR	N	Subcutaneous
semaglutide	RYBELSUS	TABLET	N	Oral
tirzepatide	MOUNJARO	PEN INJCTR	N	Subcutaneous

Appendix 2: New Comparative Clinical Trials

A total of 45 citations were manually reviewed from the initial literature search. After further review, 42 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). The remaining 3 trials are summarized in the table below. Full abstracts are included in **Appendix 3**.

Table 1. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results	Notes/Limitations
Arslanian, et al[8] DB, PC, PG, Phase 3	1. Dulaglutide 0.75 mg once weekly 2. Dulaglutide 1.5 mg once weekly 3. Placebo 26 weeks	-Age 10 to <18 y -BMI >85th percentile - Lifestyle modification -Metformin with or without basal insulin (n=154)	Change in HbA1c at 26 weeks	1. -0.6% 2. -0.9% 3. 0.6% <u>Dulaglutide 0.75 vs. placebo:</u> -1.2% (95% CI, -1.8 to -0.6%; P<0.001) <u>Dulaglutide 1.5 vs. placebo:</u> -1.5 % (95% CI, -2.1 to -0.9%; P<0.001)	Mean age 14 years; 71% female; 55% White; Mean BMI 34; 63% on metformin monotherapy. Most common AE: GI
GRADE Study Research Group[10] DB, PG, Phase 3	1. Insulin glargine U-100 initiated at 20 units and titrated according to glucose levels while avoiding hypoglycemia 2. Glimepiride 1-2 mg, titrated up to 8 mg daily in divided doses 3. Liraglutide 0.6 mg daily titrated up to 1.8 mg daily 4. Sitagliptin 100 mg daily, adjusted to renal function	-Adults -T2DM duration <10 y (diagnosed at age 30 y or later) -Metformin 500 mg/d -HbA1c 6.8-8.5%	Failure rate (defined as HbA1c ≥7.0% (evaluated quarterly)† † Metformin was increased to ≥1000 mg/day with target dose of 2000 mg/day during run-in phase	<u>Failure rate at 5 years:</u> 1. Glargine: 67% 2. Glimepiride: 72% 3. Liraglutide: 68% 4. Sitagliptin: 77% <u>Glargine vs. sitagliptin:</u> HR 0.71 (95% CI, 0.64 to 0.78; P≤0.001) ARR 10%/NNT 10 <u>Glargine vs. glimepiride:</u> HR 0.89 (95% CI, 0.81 to 0.98; P≤0.05) <u>Liraglutide vs. sitagliptin:</u> HR 0.69 (95% CI, 0.63 to 0.76; P≤0.001) ARR 9%/NNT 11 <u>Glimepiride vs. sitagliptin:</u>	Mean age 57 y; 63.6% male; 65.7% White, 19.8% Black; Mean BMI 34.3; Mean duration of T2DM 4 y Glargine and liraglutide had less failure rates over 5 years than glimepiride and sitagliptin.

				HR 0.79 (95% CI, 0.72 to 0.88; P≤0.001) ARR 5%/NNT 20	

Abbreviations: AE = adverse events; ARR = absolute risk reduction; BMI = body mass index; DB = double-blind; CI = confidence interval; CV = cardiovascular; GI = gastrointestinal; HbA1c = hemoglobin A1c; HR = hazard ratio; MI = myocardial infarction; NI = non-inferiority; NNT = number needed-to-treat; PC = placebo-controlled; PG = parallel group; RCT = randomized clinical trial; SC = subcutaneous; T2DM = type 2 diabetes mellitus.

Appendix 3: Abstracts of Comparative Clinical Trials

Once-Weekly Dulaglutide for the Treatment of Youths with Type 2 Diabetes

Silva Arslanian, Tamara Hannon, Philip Zeitler, Lily C Chao , Claudia Boucher-Berry, Margarita Barrientos-Pérez, Elise Bismuth, Sergio Dib, Jang Ik Cho, David Cox; AWARD-PEDS Investigators

Background: The incidence of type 2 diabetes mellitus is increasing among youths. Once-weekly treatment with dulaglutide, a glucagon-like peptide-1 receptor agonist, may have efficacy with regard to glycemic control in youths with type 2 diabetes.

Methods: In a double-blind, placebo-controlled, 26-week trial, we randomly assigned participants (10 to <18 years of age; body-mass index [BMI], >85th percentile) being treated with lifestyle modifications alone or with metformin, with or without basal insulin, in a 1:1:1 ratio to receive once-weekly subcutaneous injections of placebo, dulaglutide at a dose of 0.75 mg, or dulaglutide at a dose of 1.5 mg. Participants were then included in a 26-week open-label extension study in which those who had received placebo began receiving dulaglutide at a weekly dose of 0.75 mg. The primary end point was the change from baseline in the glycated hemoglobin level at 26 weeks. Secondary end points included a glycated hemoglobin level of less than 7.0% and changes from baseline in the fasting glucose concentration and BMI. Safety was also assessed.

Results: A total of 154 participants underwent randomization. At 26 weeks, the mean glycated hemoglobin level had increased in the placebo group (0.6 percentage points) and had decreased in the dulaglutide groups (-0.6 percentage points in the 0.75-mg group and -0.9 percentage points in the 1.5-mg group, P<0.001 for both comparisons vs. placebo). At 26 weeks, a higher percentage of participants in the pooled dulaglutide groups than in the placebo group had a glycated hemoglobin level of less than 7.0% (51% vs. 14%, P<0.001). The fasting glucose concentration increased in the placebo group (17.1 mg per deciliter) and decreased in the pooled dulaglutide groups (-18.9 mg per deciliter, P<0.001), and there were no between-group differences in the change in BMI. The incidence of gastrointestinal adverse events was higher with dulaglutide therapy than with placebo. The safety profile of dulaglutide was consistent with that reported in adults.

Conclusions: Treatment with dulaglutide at a once-weekly dose of 0.75 mg or 1.5 mg was superior to placebo in improving glycemic control through 26 weeks among youths with type 2 diabetes who were being treated with or without metformin or basal insulin, without an effect on BMI. (Funded by Eli Lilly; AWARD-PEDS ClinicalTrials.gov number, NCT02963766.).

Glycemia Reduction in Type 2 Diabetes - Glycemic Outcomes

GRADE Study Research Group; David M Nathan, John M Lachin, Ashok Balasubramanyam, Henry B Burch, John B Buse, Nicole M Butera, Robert M Cohen, Jill P Crandall, Steven E Kahn, Heidi Krause-Steinrauf, Mary E Larkin, Neda Rasouli, Margaret Tiktin, Deborah J Wexler, Naji Younes

Abstract

Background: The comparative effectiveness of glucose-lowering medications for use with metformin to maintain target glycated hemoglobin levels in persons with type 2 diabetes is uncertain.

Methods: In this trial involving participants with type 2 diabetes of less than 10 years' duration who were receiving metformin and had glycated hemoglobin levels of 6.8 to 8.5%, we compared the effectiveness of four commonly used glucose-lowering medications. We randomly assigned participants to receive insulin glargine U-100 (hereafter, glargine), the sulfonylurea glimepiride, the glucagon-like peptide-1 receptor agonist liraglutide, or sitagliptin, a dipeptidyl peptidase 4 inhibitor. The primary metabolic outcome was a glycated hemoglobin level, measured quarterly, of 7.0% or higher that was subsequently confirmed, and the secondary metabolic outcome was a confirmed glycated hemoglobin level greater than 7.5%.

Results: A total of 5047 participants (19.8% Black and 18.6% Hispanic or Latinx) who had received metformin for type 2 diabetes were followed for a mean of 5.0 years. The cumulative incidence of a glycated hemoglobin level of 7.0% or higher (the primary metabolic outcome) differed significantly among the four groups ($P<0.001$ for a global test of differences across groups); the rates with glargine (26.5 per 100 participant-years) and liraglutide (26.1) were similar and lower than those with glimepiride (30.4) and sitagliptin (38.1). The differences among the groups with respect to a glycated hemoglobin level greater than 7.5% (the secondary outcome) paralleled those of the primary outcome. There were no material differences with respect to the primary outcome across prespecified subgroups defined according to sex, age, or race or ethnic group; however, among participants with higher baseline glycated hemoglobin levels there appeared to be an even greater benefit with glargine, liraglutide, and glimepiride than with sitagliptin. Severe hypoglycemia was rare but significantly more frequent with glimepiride (in 2.2% of the participants) than with glargine (1.3%), liraglutide (1.0%), or sitagliptin (0.7%). Participants who received liraglutide reported more frequent gastrointestinal side effects and lost more weight than those in the other treatment groups.

Conclusions**:** All four medications, when added to metformin, decreased glycated hemoglobin levels. However, glargine and liraglutide were significantly, albeit modestly, more effective in achieving and maintaining target glycated hemoglobin levels. (Funded by the National Institute of Diabetes and Digestive and Kidney Diseases and others; GRADE ClinicalTrials.gov number, NCT01794143.).

Appendix 4: Medline Search Strategy

Database(s): **Ovid MEDLINE(R) ALL** 1946 to February 01, 2024

Search Strategy:

#	Searches	Results
1	dulaglutide.mp.	777
2	exenatide.mp. or Exenatide/	3898
3	liraglutide.mp. or Liraglutide/	4283
4	semaglutide.mp.	1551
5	tirzepatide.mp.	390
6	limit 5 to (english language and humans and yr="2022 -Current")	231
7	limit 6 to (clinical trial, phase iii or guideline or meta analysis or practice guideline or "systematic review")	45

Appendix 5: Key Inclusion Criteria

Population	Patients with type-2 diabetes mellitus (T2DM)
Intervention	GLP-1 receptor agonists (injectable and oral)
Comparator	Placebo or active treatment
Outcomes	HbA1c, cardiovascular death, myocardial infarction, stroke, chronic kidney disease, hypoglycemia
Setting	Outpatient

Glucagon-like Peptide-1 (GLP-1) Receptor Agonists and Glucose Dependent Insulinotropic Polypeptide (GIP) Receptor Agonists

Goal(s):

- Promote cost-effective and safe step-therapy for management of type 2 diabetes mellitus (T2DM).

Length of Authorization:

- Up to 12 months

Requires PA:

- All non-preferred GLP-1 receptor agonists and GLP-1 receptor + GIP agonists. Preferred products do not require PA when prescribed as second-line therapy in conjunction with metformin.

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Does the patient have a diagnosis of Type 2 diabetes mellitus?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness.
3. Will the prescriber consider a change to a preferred product? Message: • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives in class	**No:** Go to #4

Approval Criteria		
4. Has the patient tried and failed to meet hemoglobin A1C goals with metformin or have contraindications to metformin? (document contraindication, if any)	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness. Recommend trial of metformin. See below for metformin titration schedule.

Initiating Metformin

1.	Begin with low-dose metformin (500 mg) taken once or twice per day with meals (breakfast and/or dinner) or 850 mg once per day.
2.	After 5-7 days, if gastrointestinal side effects have not occurred, advance dose to 850 mg, or two 500 mg tablets, twice per day (medication to be taken before breakfast and/or dinner).
3.	If gastrointestinal side effects appear with increasing doses, decrease to previous lower dose and try to advance the dose at a later time.
4.	The maximum effective dose can be up to 1,000 mg twice per day. Modestly greater effectiveness has been observed with doses up to about 2,500 mg/day. Gastrointestinal side effects may limit the dose that can be used.

Nathan, et al. Medical management of hyperglycemia in Type 2 Diabetes: a consensus algorithm for the initiation and adjustment of therapy. *Diabetes Care*. 2008; 31;1-11.

P&T Review: *4/24 (KS), 10/22 (KS), 8/20 (KS), 6/20), 3/19, 7/18, 9/17; 1/17; 11/16; 9/16; 9/15; 1/15; 9/14; 9/13; 4/12; 3/11*
Implementation: *1/1/23; 9/1/20; 5/1/19; 8/15/18; 4/1/17; 2/15; 1/14*