PHARMACIST CE:

Updates on Glucagon-Like Peptide-Based Medications: Current, New, and Pipeline Agents

by Elizabeth A. Buckley, PharmD, CDCES, Francesca Napolitano Johnson, PharmD, MEd, Denise Walbrandt Pigarelli, PharmD, BC-ADM

CE FOR **PHARMACISTS**

COMPLETE ARTICLE AND CE EXAM AVAILABLE ONLINE: **WWW.PSWI.ORG**

Learning Objectives

- Compare and contrast the currently available glucagon-like peptide-1 receptor agonists (GLP1-RA)
- Describe the mechanism and advantages of tirzepatide
- Identify trends in pipeline GLP1-RA-based-medications

Finding the best therapeutic agent to help millions of people manage type 2 diabetes and hyperglycemia, reduce clinical and economic burden, and prevent macro- and microvascular complications continues to be a priority. It can be challenging to find an appropriate agent to help achieve glycemic goals and support heart and kidney risk reductions while limiting adverse drug reactions, intolerability and cost. Since the first glucagon-like peptide-1 receptor agonist (GLP1-RA) was approved in 2005, subsequent incretin agents have been developed with advantages such as extended dosing duration (once weekly) and cardiorenal risk reduction. The drug class has significantly and positively impacted the management of type 2 diabetes, as evidenced by its increasingly prominent role as an important therapeutic choice to decrease blood glucose, body weight, risk of major adverse cardiac events (MACE) in people at high risk for or established atherosclerotic cardiovascular disease (ASCVD), and risk of kidney dysfunction.[1] Current standards of care pathways and algorithms recommend specific agents in this class as first-line for people with these co-morbidities and risks, regardless of hemoglobin A1C (A1C) at diagnosis.[2,3] In addition, the American Diabetes Association (ADA) Standards of Care recommend initiating GLP1-RAs before prandial insulin due to their efficacy to lower glucose without the risks of hypoglycemia or weight gain. This article will review and compare the Federal Drug Administration (FDA)-approved indications, advantages, and disadvantages of current agents within this class; highlight the mechanisms and advantages of the newest incretin agent to enter the market; and preview pipeline agents.

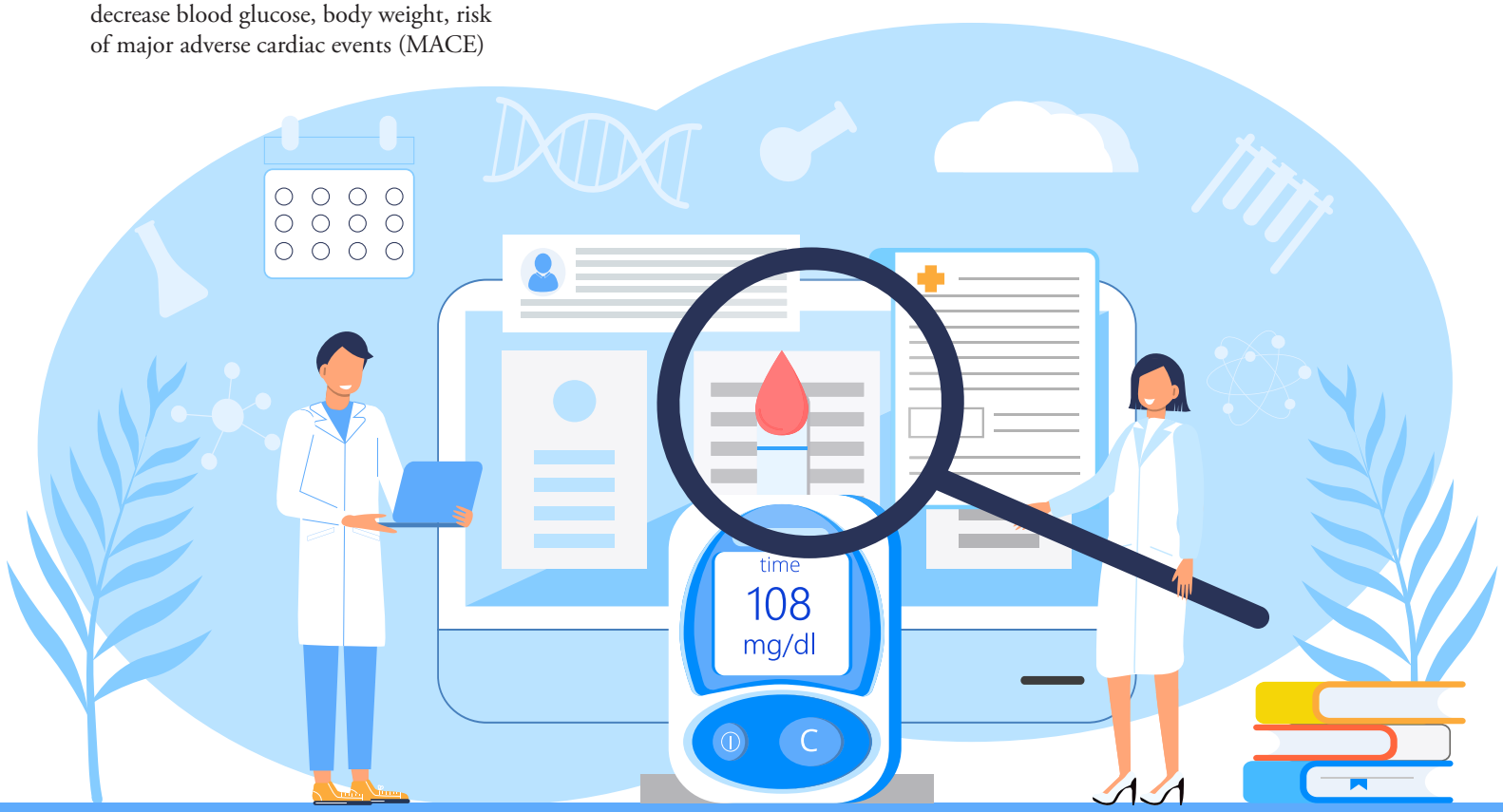

TABLE 1. Comparison of Currently Available GLP1-RA and GIP/GLP1-RA Medications[5,7–16]

Drug	Indication	Comparative Weight Loss	Efficacy ~A1C decrease	Frequency	Starting Dose (Sub-Q)	Titration schedule (As tolerated)	Approximate Similar Doses					
Tirzepatide (Mounjaro®)	T2DM - Adults	~ 11.2 kg	2.3%	Weekly	2.5 mg	Every 4 weeks	2.5 mg	5 mg	7.5 mg	10 mg	12.5 mg	15 mg
Dulaglutide (Trulicity®)	T2DM > 10 yo MACE reduction	~2.5-4.6kg	1.8%	Weekly	0.75 mg	Every 4 weeks		0.75 mg	1.5 mg	3 mg	4.5 mg	
Exenatide (Byetta®)	T2DM - Adults	~ 2 kg	0.9%	BID	5 mcg Before meals	Every 4 weeks	5 mcg	10 mcg				
Exenatide ER (Bydureon®)	T2DM > 10 yo	~ 2 kg	1.5%	Weekly	2 mg	No titration			2 mg			
Liraglutide Victoza®	T2DM MACE reduction	~ 2.5 kg	1.5%	Daily	0.6 mg	Weekly	0.6 mg	1.2 mg	1.8 mg			
Liraglutide Saxenda®	Obesity > 12yo	~ 9.5 kg		Daily	0.6 mg	Weekly	0.6 mg	1.2 mg	1.8 mg	2.4 mg	3 mg	
Semaglutide Ozempic®	T2DM MACE reduction	~ 4 kg	2.3%	Weekly	0.25 mg	Every 4 weeks		0.25 mg	0.5 mg	1 mg	2 mg	
Semaglutide Wegovy®	Obesity > 12yo	~ 16 kg		Weekly	0.25 mg	Every 4 weeks		0.25 mg	0.5 mg	1 mg	1.7 mg	2.4 mg
Oral semaglutide (Rybelsus®)	T2DM	~ 2.5 kg	1.3%	Daily	3 mg PO empty stomach	Every 30 days	3 mg	7 mg	14 mg			

Abbreviations: A1C = hemoglobin A1C, GIP = gastric inhibitory polypeptide, GLP1-RA = glucagon-like peptide-1 receptor agonist, MACE = major adverse cardiac events, Sub-Q = subcutaneous, T2DM = type 2 diabetes mellitus

Current GLP-1RAs

GLP1-RA agents mimic the action of endogenous GLP-1, a glucoregulatory hormone that is released from the gastrointestinal (GI) system in response to food ingestion.[4] GLP1-RA agents bind to the receptors on several organ systems and work in a multimodal manner to reduce blood glucose in response to food:

1. Pancreas - enhances beta cell insulin secretion and alpha cell glucagon suppression
2. Liver - decreases glucose production
3. Brain - increases satiety
4. Stomach - slows gastric emptying time
5. Peripheral tissue - increases insulin uptake via weight loss

There are currently five FDA-approved GLP1-RA agents for the treatment of type 2 diabetes in the United States4 (Table 1). The medications are commonly differentiated by duration of action, with the shorter-acting agents having more of an effect on gastric emptying, thereby decreasing post-prandial glucose yet resulting in a higher incidence of GI effects.[4] The longer-duration agents (weekly injectables) affect both fasting and post-prandial glucose due to continuous receptor activation, which leads to greater reductions in A1C values. In general, the GLP1-RA with the highest efficacy to decrease A1C is semaglutide, followed by dulaglutide, liraglutide, and exenatide. In addition, exenatide is an exendin-4-derived agent that does not have the same effect on MACE outcomes as the other agents. The agents that do have evidence of improved cardiovascular outcomes are derived from modified human GLP-1, and include dulaglutide, liraglutide, and semaglutide. Interestingly, semaglutide was developed from modification of liraglutide to extend its duration of action. Each of these modified human GLP-1 agents has an FDA indication to reduce the risk of MACE in adults with type 2 diabetes and ASCVD. There is also strong published evidence that these agents can reduce MACE in adults with multiple risk factors for ASCVD, although at this time dulaglutide is the only agent to have an FDA-approved indication for it.[5,6]

Oral Formulation

As injectable incretin agents continue to come to market, there is only one oral GLP1 agonist currently available. In 2019, semaglutide (Rybelsus®) became the first oral GLP1 treatment approved by the FDA.[17] Although this dosage form is usually preferred over injectables, in order for it to be properly absorbed, it requires specific adherence to taking the tablet at least 30 minutes before the first intake of the day (food/beverages/medications) with no more than four ounces of plain water.[13] This is based on the addition of an absorption enhancer, Sodium-N-[8-(2-hydroxybenzoyl) amino] caprylate (SNAC), that works locally as a pH buffer in the stomach and enables the large structure of semaglutide to be absorbed orally before being degraded by gastric enzymes.[18] In addition, this dosage form does not have equal glycemic efficacy or data to support a reduction in cardiovascular or renal complications. However; there is currently a phase III study researching the effects on A1C and weight loss of oral semaglutide at 25 mg and 50 mg which may yield improved A1C and weight

loss potential.[19]

New Indications

A major focus of the updated joint ADA/European Association for the Study of Diabetes (EASD) and the stand-alone ADA Standards of Care 2023 is on the treatment of obesity as a health condition, with an emphasis on weight management being as important as glucose management in people with prediabetes and diabetes.[2] GLP1-RA agents have proven efficacy to reduce body weight in the majority of individuals that utilize this therapy.[4] This is related to their actions in the brain and the stomach. GLP1-RA mechanisms in the brain enhance hypothalamic satiety, reduce hunger, and suppress energy intake. GLP1-RA effects on the stomach slow GI motility and contribute to feeling full. However, the satiety and absorption delay signals can lead to nausea and vomiting, the most common side effects with agents in this class. Two of these agents, liraglutide and semaglutide, have separate, branded products and FDA-approved indications for the treatment of obesity/overweight in adolescents > 12 years old and adults (Table 1).[10,14] In general, based on clinical trial information, weight loss is as follows: semaglutide > liraglutide > dulaglutide > exenatide. The efficacy of these agents led to a shortage of all GLP1-RAs beginning in August 2022, which has prevented many people with diabetes from procuring their medications. Table 1 gives approximately similar doses of the agents and can be a useful tool in times of shortage or when switching between products for formulary issues. When making a switch, it is suggested to start with the approximately similar or a lower dose and titrate up as tolerated.[16]

Precautions

All agents within this class have similar adverse drug reaction profiles, warnings, and contraindications. Due to development of thyroid C-cell tumors in rats and mice during clinical trials, all GLP1-RAs are contraindicated in people with a personal or family history of medullary thyroid carcinoma (MTC) and multiple endocrine neoplasia syndrome type 2 (MEN 2), and all people taking GLP-1RA should be counseled on the symptoms of thyroid tumors.[5,7–14,20] Other warnings include monitoring for pancreatitis, hypoglycemia when used in combination with insulin or secretagogues, kidney impairment during dehydration, hypersensitivity reactions, and acute gallbladder disease.

TABLE 2. Incretin Effects at the Organ/Tissue Level[20,21]

Organ/Tissue	*GLP1*	*GIP*
CNS	Decreases caloric intake significantly	Decreases caloric intake
Heart	Increases in heart rate	
Pancreas – beta cells	Increases Insulin secretion	
Pancreas – alpha cells	Decreases glucagon secretion	Increases glucagon secretion
Stomach	Slows gastric emptying and chylomicron production	No prominent effect
Adipose Tissue	No prominent effect	Increases glucose uptake Increases triglyceride uptake and storage
Kidneys	Transient sodium excretion decreases	No prominent effect
Bones	Increases meal-associated bone remodeling	Increases meal-associated bone remodeling significantly
Liver (indirect effects)	Glucose uptake, glycogen increases, hepatic glucose production decreases	

CNS = central nervous system, GIP = gastric inhibitory polypeptide, GLP1 = glucagon-like peptide-1

Adverse Reactions

The most common adverse reactions within the class have some differences in frequency among agents: GI-related nausea, vomiting, diarrhea, decreased appetite, dyspepsia, and constipation.[5,9,11-13] Due to the mechanism of delaying gastric emptying, shorter-acting agents can affect the absorption of concomitantly administered oral medications, and people taking these medications should be educated on consistency of dosing intervals.

New Incretin

Addition of GIP to GLP-1 RA: Tirzepatide

Tirzepatide (Mounjaro®) was FDA approved in 2022 and is an agonist at both the glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptors.[7] It is the first "twincretin" to come to market, based on evidence from the SURPASS trials. For more details on the SURPASS trials, please see the "Review of Effect of Tirzepatide on Glycemic Control and Weight Loss" article in this issue. GIP is another incretin secreted from the intestines in response to ingestion of carbohydrates.[20] The activation of GIP receptors enhances GLP-1RA effectiveness and further decreases A1C and body weight in people with type 2 diabetes. See Table 2 for comparative effects on the body. People with type 2 diabetes have a reduced incretin effect, with a slight GLP1 impairment and an almost complete lack of GIP response.[20] Initially, GIP did not seem to have the same effectiveness as GLP1 on increasing insulin secretion, so it did not progress as a therapeutic agent until research showed the synergistic effect of using them together.

Tirzepatide is a once-weekly subcutaneous injection that has a higher efficacy (A1C reduction > 2%) and a more profound weight loss (> 10 kg on average) than comparators of semaglutide 1 mg weekly (not maximum dose), insulin degludec, insulin glargine, and combination therapy in persons with increased cardiovascular (CV) risk.[7] The side effects, contraindications, and precautions for tirzepatide are similar to other agents in the GLP1-RA class.[7] In addition, due to the effect on gastric emptying, labeling for tirzepatide includes a precaution about potential reduced efficacy of oral contraceptives, and recommends a backup form of contraception for the first four weeks of use. Drugs with a narrow therapeutic window such as warfarin

and levothyroxine should be monitored carefully, and people taking acetaminophen should be educated on the possibility of decreased efficacy and delayed time for pain relief. There is a positive impact on CV-associated risk factors such as weight, blood pressure, and lipids. However, the medication's impacts on MACE and prevention of adverse kidney outcomes will be determined via results from ongoing trials.[22] A sub-analysis of SURPASS-4 did show a significant decrease in albuminuria, estimated glomerular filtration (eGFR) rate of decline, and risk of end stage kidney disease.[23]

Pipeline Incretin Medications

The following sections will highlight incretin agents that are currently being studied in phase II or III clinical trials.

Pipeline Oral Incretins

Orforglipron (LY3502970) is a once-daily oral GLP1-RA in the pipeline that completed Phase II studies in fall of 2022.[24] During phase I trials, the medication was found to have pharmacodynamic profiles similar to injectable GLP1-RA, pharmacokinetics enabling once daily administration, and up to a 3.6 kg weight reduction in 29 days.[25] Although finalized data from phase II has not been formally released, preliminary results shared during the investor meeting demonstrated a dose-dependent A1C reduction of up to 2.1% and weight loss of up to 9.6% in patients with diabetes over a 26 week period, and Eli Lilly and Company plan to move this medication into phase III studies in 2023.[26]

Danuglipron (PF-06882961) is a twice daily oral GLP1-RA in the pipeline for which Pfizer Inc. presented phase II study results at the 2022 EASD Annual Meeting.[27] The phase 2a results found mean A1C reductions up to 1.57% and body weight reductions up to 5.38 kg over 16 weeks and had efficacy and safety data in line with phase II data for other GLP1-RAs. The phase 2b results found a mean A1C reduction of up to 1.15%, mean fasting plasma glucose reductions of up to 31.93 mg/dl, and mean weight loss of up to 4.6 kg over 16 weeks.

TABLE 3. Pipeline Dual- and Tri- Agonists in Phase II or III[33–35]

Medication	Route, Frequency, and MOA	Company	Current Status and Relevant Publications/Studies
BI 456906	Subcutaneous once to twice weekly GCGR/GLP1-R dual agonist	Zealand Pharma	Phase II Completed 11/14/2021 https://clinicaltrials.gov/ct2/show/NCT04153929
Oxyntomodulin (OPK88003)	Weekly subcutaneous GCGR/GLP1-R dual agonist	OPKO Health	Phase II Completed 6/27/2019 https://clinicaltrials.gov/ct2/show/NCT03406377
Retatrutide (LY3437943)	Weekly subcutaneous GIP/GLP1/GCGR tri-agonist	Eli Lilly	Phase II completed 12/28/2020 https://doi.org/10.2337/db21-104-OR https://doi.org/10.1016/S0140-6736(22)02033-5 https://doi.org/10.2337/db22-340-OR

GCGR = glucagon receptor, GIP = gastric inhibitory polypeptide, GLP1-R = glucagon-like peptide-1 receptor, MOA = mechanism of Action

PIPELINE Incretin Combinations with Semaglutide

Novo Nordisk currently has two incretin combinations in phase II that utilize a combination with semaglutide both orally and subcutaneously. CarigSema is a once weekly subcutaneous injection that includes cagrilinitide and semaglutide, with a phase II trial that was completed in July 2022.[28]

Cagrilintide is a long-acting acylated amylin analogue that agonizes amylin and calcitonin receptors.[28] Amylin is a peptide hormone secreted from the pancreatic β-cell in addition to insulin that can function similarly to GLP1 by inhibiting glucagon secretion, delaying gastric emptying, and causing satiety.[29] What differentiates the action of amylin from a GLP1RA is that it does not cause beta-cell insulin release.

When utilized alone, the investigational amylin agonist cagrilintide has been found to reduce food intake and weight in a dose-dependent manner in people with excess body weight without diabetes who experienced weight reductions up to 10.8% in 26 weeks; however, there was no change in A1C or fasting glucose from baseline to week 26.[30] Although the phase II trial results for weight loss efficacy of CarigSema are not available yet, there seems to be a potential for significant weight loss with the combination of cagrilintide with semaglutide as compared to GLP1-RA monotherapy, while maintaining A1C lowering due to the inclusion of semaglutide.

FDC Sema – OW GIP (NNC0480-0389) is a once weekly subcutaneous injection that includes a novel GIP agonist in combination with semaglutide. A phase II trial of this investigational combination agent for people with type 2 diabetes began in November 2021, and study completion is expected in March 2023.[31] Little information is currently available about this product; however, in the future, it may provide people with type 2 diabetes additional A1C and weight loss efficacy, compared to a GLP1-RA alone.

Pipeline GLP1, GIP, GCGR Dual- and Tri- Agonists

With the success of GLP1-RA agents and the introduction of a dual GLP1/GIP RA into the market, there are additional dual, triple, or other unique modifications of the glucagon receptor (GCGR) on the horizon.[32] Agonizing GCGR can reduce appetite, increase energy expenditure to promote weight loss, decrease gastrointestinal motility, enhance hepatic fatty acid oxidation and lipolysis, and stimulate insulin secretion during times of hyperglycemia.[33]

Studies demonstrating the synergistic weight-loss mechanisms of GLP-1 and glucagon have led to development of dual-agonists.[32] Several candidates have been in the pipeline for treatment of type 2 diabetes; however, a recent review of pharmaceutical companies' pipeline websites revealed that the intended use for many of these agents has been changed to treatment of nonalcoholic fatty liver disease (NAFLD) and/or obesity. Three agents for type 2 diabetes are currently in phase II or beyond, as described in Table 3.

Tri-agonism of GLP1-R, GIP-R, and GCGR in pre-clinical and clinical

studies demonstrated weight reductions and improved glycemic parameters.[32,34,35] Multiple agents are being explored for obesity and NAFLD, and one tri-agonist has completed a phase II trial for type 2 diabetes, as seen in Table 3. Results from the phase II trial of retatrutide demonstrated a mean A1C reduction of up to 1.9% and mean weight loss of up to 8.65 kg (10.1% decrease from baseline) at 12 weeks, which could be a competitive addition to the market.[33]

Conclusion

This is a dynamic time for diabetes pharmacotherapeutics. The introduction of GLP1-based medications into the market has been transformative in providing effective A1C and weight reductions for people with Type 2 diabetes. Additionally, the most recent ADA guidelines highlight weight management as a compelling factor when selecting diabetes pharmacotherapy. Several GLP1-based therapies are currently available, and there are additional, exciting products in the pipeline.

Elizabeth Buckley is a Professor of Pharmacy Practice at Concordia University Wisconsin School of Pharmacy in Mequon, WI. Francesca Napolitano Johnson is an Assistant Professor of Pharmacy Practice at Concordia University Wisconsin School of Pharmacy in Mequon, WI. Denise Walbrandt Pigarelli is an Associate Professor of Pharmacy (CHS) at the University of Wisconsin-Madison School of Pharmacy in Madison, WI.

PR *This article has been peer-reviewed. The contribution in reviewing is greatly appreciated!*

Disclosure: The authors declare no real or potential conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria.

Corresponding Author: *Elizabeth Buckley - Beth.Buckley@cuw.edu*

References

1. ElSayed NA, Aleppo G, Aroda VR, et al. 9. Pharmacologic approaches to glycemic treatment: standards of care in diabetes—2023. *Diabetes Care*. 2023;46(Suppl 1):S140-S157. doi:10.2337/dc23-S009
2. ElSayed NA, Aleppo G, Aroda VR, et al. Standards of care in diabetes—2023. *Diabetes Care.* 2023;46(Suppl 1):S1-S291. doi:10.2337/dc23-S001
3. Blonde L, Umpierrez GE, Reddy SS, et al. American Association of Clinical Endocrinology clinical practice guideline: developing a diabetes mellitus comprehensive care plan—2022 Update. *Endocr Pract*. 2022;28(10):923-1049. doi: 10.1016/j.eprac.2022.08.002
4. Cornell S. A review of GLP-1 receptor agonists in type 2 diabetes: A focus on the mechanism of action of once-weekly agents. *J Clin Pharm Ther.* 2020;45 (Suppl 1):17-27. doi:10.1111/jcpt.13230
5. Trulicity. Prescribing information. Eli Lilly and Company; 2014, 2022. Accessed January 17, 2023. https://pi.lilly.com/us/trulicity-uspi.pdf
6. Marx N, Husain M, Lehrke M, Verma S, Sattar N. GLP-1 receptor agonists for the reduction of atherosclerotic cardiovascular risk in patients with type 2 diabetes. *Circulation*. 2022;146(24):1882-1894. doi:10.1161/CIRCULATIONAHA.122.059595
7. Mounjaro. Prescribing information. Eli Lilly and Company; 2022. Accessed January 17, 2023. https://pi.lilly.com/us/mounjaro-uspi.pdf?s=pi
8. Byetta. Prescribing information. AstraZeneca Pharmaceuticals LP. Accessed January 17, 2023. https://den8dhaj6zs0e.cloudfront.net/50fd68b9-106b-4550-b5d0-12b045f8b184/ce8afab9-2b45-436d-957c-a73978d09e93/ce8afab9-2b45-436d-957c-a73978d09e93_viewable_rendition__v.pdf
9. BydureonBCise. Prescribing information. AstraZeneca Pharmaceuticals LP. Accessed January 17, 2023. https://den8dhaj6zs0e.cloudfront.net/50fd68b9-106b-4550-b5d0-12b045f8b184/df5ddbd6-546b-43da-b794-56f711189aba/df5ddbd6-546b-43da-b794-56f711189aba_viewable_rendition__v.pdf
10. Saxenda. Prescribing information. Novo Nordisk. Accessed January 17, 2023. https://www.novo-pi.com/saxenda.pdf
11. Victoza. Prescribing information. Novo Nordisk. Accessed January 17, 2023. https://www.novo-pi.com/victoza.pdf
12. Ozempic. Prescribing information. Novo Nordisk. Accessed January 17, 2023. https://www.novo-pi.com/ozempic.pdf
13. Rybelsus. Prescribing information. Novo Nordisk. Accessed January 17, 2023. https://www.novo-pi.com/rybelsus.pdf
14. Wegovy. Prescribing information. Novo Nordisk. Accessed January 17, 2023. https://www.novo-pi.com/wegovy.pdf
15. Jellin JM, Gregory P, Batz F, et al. Pharmacist's Letter. Drugs for type 2 diabetes (United States). Resource 380701. Stockton, CA: Therapeutic Research Faculty. Accessed on January 17, 2023. https://pharmacist.therapeuticresearch.com
16. 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. doi: 10.2337/cd19-0100
17. FDA. FDA approves first oral GLP-1 treatment for type 2 diabetes. March 24, 2020. Accessed January 17, 2023. https://www.fda.gov/news-events/press-announcements/fda-approves-first-oral-glp-1-treatment-type-2-diabetes
18. RYBELSUS® semaglutide tablets mechanism of action. novoMEDLINK. Accessed January 17, 2023. https://www.novomedlink.com/diabetes/products/treatments/rybelsus/about/mechanism-of-action.html
19. Novo Nordisk A/S. Efficacy and safety of once-daily oral semaglutide 25 mg and 50 mg compared with 14 mg in subjects with type 2 diabetes. clinicaltrials.gov. Accessed January 16, 2023. https://clinicaltrials.gov/ct2/show/NCT04707469
20. Nauck MA, Quast DR, Wefers J, Pfeiffer AFH. The evolving story of incretins (GIP and GLP-1) in metabolic and cardiovascular disease: A pathophysiological update. *Diabetes Obes Metab.* 2021;23(S3):5-29. doi:10.1111/dom.14496
21. Nakatani Y, Kawabe A, Matsumura M, et al. Effects of GLP-1 receptor agonists on heart rate and the autonomic nervous system using holter electrocardiography and power spectrum analysis of heart rate variability. *Diabetes Care.* 2015;39(2):e22-e23. doi:10.2337/dc15-1437
22. Eli Lilly and Company. The effect of tirzepatide versus dulaglutide on major adverse cardiovascular events in patients with type 2 diabetes (SURPASS-CVOT). clinicaltrials.gov. Accessed February 22, 2023. https://clinicaltrials.gov/ct2/show/NCT04255433
23. American College of Cardiology. Tirzepatide versus insulin glargine in type 2 diabetes and increased cardiovascular risk.. Accessed January 17, 2023. https://www.acc.org/Latest-in-Cardiology/Clinical-Trials/2021/11/01/03/42/http%3a%2f%2fwww.acc.org%2fLatest-in-Cardiology%2fClinical-Trials%2f2021%2f11%2f01%2f03%2f42%2fSURPASS-4
24. Eli Lilly and Company. A phase 2 study of once-daily LY3502970 compared with placebo and once-weekly dulaglutide in participants with type 2 diabetes mellitus. clinicaltrials.gov. Accessed January 16, 2023. https://clinicaltrials.gov/ct2/show/NCT05048719
25. Pratt EJ, Ma X, Liu R, Rbins DH, Sloop K, Benson C. 336-OR: A first-in-human single- and multiple-ascending dose study evaluating safety, tolerability, pharmacokinetics, and pharmacodynamics of a novel oral nonpeptide GLP-1 receptor agonist in healthy subjects. *Diabetes*. 2022;71(Suppl 1):336-OR. https://doi.org/10.2337/db22-336-OR
26. Eli Lilly. Lilly announces 2023 financial guidance, plans to launch up to four new medicines. Lilly Investors. December 13, 2022. Accessed January 17, 2023. https://investor.lilly.com/news-releases/news-release-details/lilly-announces-2023-financial-guidance-plans-launch-four-new
27. Saxena AR, Frias J, Brown LS, Gorman DN, Tsamandouras N, Birnbaum MJ. Oral small molecule GLP-1 receptor agonist danuglipron (PF-06882961) results in glucose lowering and body weight loss over 16 weeks in adults with type 2 diabetes mellitus. Paper presented at: Hybrid 58th EASD Annual Meeting; September 20, 2022; Session SO 43 Glucose lowering agents.
28. Novo Nordisk A/S. Efficacy and safety of co-administration of cagrilintide s.c. 2.4 mg and Semaglutide s.c. 2.4 mg once weekly in subjects with type 2 diabetes. clinicaltrials.gov. Accessed January 16, 2023. https://clinicaltrials.gov/ct2/show/NCT04982575
29. Schmitz O, Brock, B, Rungby J. Amylin agonists: a novel approach in the treatment of diabetes . *Diabetes.* 2004;53(Suppl 3):S233-S238. doi: 10.2337/diabetes.53.suppl_3.s233
30. Lau DCW, Erichsen L, Francisco AM, et al. Once-weekly cagrilintide for weight management in people with overweight and obesity: a multicentre, randomised, double-blind, placebo-controlled and active-controlled, dose-finding phase 2 trial. *Lancet.* 2021;398(10317):2160-2172. doi:10.1016/S0140-6736(21)01751-7
31. Novo Nordisk A/S. Investigation of the safety and efficacy of semaglutide s.c. in combination with NNC0480-0389 in participants with type 2 diabetes - a dose finding study. clinicaltrials.

gov. Accessed January 16, 2023. https://clinicaltrials.gov/ct2/show/NCT05144984
32. Patil M, Deshmukh NJ, Patel M, Sangle GV. Glucagon-based therapy: past, present and future. *Peptides.* 2020;127:170296. doi:10.1016/j.peptides.2020.170296
33. Coskun T, Urva S, Roell WC, et al. LY3437943, a novel triple glucagon, GIP, and GLP-1 receptor agonist for glycemic control and weight loss: From discovery to clinical proof of concept. *Cell Metab.* 2022;34(9):1234-1247.e9. doi:10.1016/j.cmet.2022.07.013
34. Brandt SJ, Kleinert M, Tschöp MH, Müller TD. Are peptide conjugates the golden therapy against obesity? *J Endocrinol.* 2018;238(2):R109-R119. doi:10.1530/JOE-18-0264
35. De Block CEM, Dirinck E, Verhaegen A, Van Gaal LF. Efficacy and safety of high-dose glucagon-like peptide-1, glucagon-like peptide-1/glucose-dependent insulinotropic peptide, and glucagon-like peptide-1/glucagon receptor agonists in type 2 diabetes. *Diabetes Obes Metab.* 2022;24(5):788-805. doi:10.1111/dom.14640

Assessment Questions

1. Which of the following is true regarding the mechanism of GLP1-RA?
   a. Decreases beta cell insulin secretion in the pancreas
   b. Decreases glucose production in the liver
   c. Decreases satiety
   d. Increases gastric emptying time

2. **True or False:** Once daily GLP1-RA medications are more effective than once weekly
   a. True
   b. False

3. Patient MR is a 45-year-old male with type 2 diabetes. He was previously well managed on metformin 1000 mg BID and Farxiga 10 mg daily, however his A1C today was elevated at 8 %. MR has had the following BMI values over the last year: 32.4 kg/m^2 (today's visit), 30.2 kg/m^2 (6 months ago), 28.6 kg/m^2 (12 months ago). Due to his rising BMI, you would like to start a GLP1-RA. Assuming no contraindications to therapy or insurance barriers, which GLP1-RA would have the best efficacy for weight loss?
   a. Dulaglutide
   b. Exenatide
   c. Liraglutide
   d. Semaglutide

4. Which of the following is NOT approved for use in adolescents WITH diabetes?
   a. Dulaglutide
   b. Tirzepatide
   a. Liraglutide
   b. Semaglutide

5. Which of the follow medications do NOT have an FDA approval for MACE
   a. Dulaglutide
   b. Exenatide
   a. Liraglutide
   b. Semaglutide

6. Which of the following is unique about the mechanism of GIP compared to GLP1?
   a. GIP does not affect the kidneys
   b. GIP slows gastric emptying
   c. GIP increases glucagon secretion
   d. GIP does not affect the adipose tissue

7. Which of the following is an advantage of tirzepatide compared to other GLP1-RA medications?
   a. Oral administration
   b. Once monthly administration
   c. Lower risk of drug interactions
   d. More effective for weight loss

8. The common adverse gastrointestinal reactions of nausea, vomiting, diarrhea or constipation are primarily due to which mechanism of GLP1-RAs?
   a. Delayed gastric emptying
   b. Change in intestinal biome
   c. Increased insulin secretion and uptake in peripheral tissues
   d. Increased satiety in the CNS

9. Which of the following is TRUE about the ORAL formulation of semaglutide?
   a. It has higher efficacy
   b. It has a more profound weight loss
   c. It needs to be taken on an empty stomach with up to 4 ounces of water
   d. It can be taken with food if it causes nausea

10. **True or False:** Including GCGR agonism in combination with GLP1/GIP-RA can increase weight loss potential due to increased energy expenditure.
    a. True
    b. False

11. Did the activity meet the stated learning objectives? (if you answer no, please email sarahs@pswi.org to explain)
    a. Yes
    b. No

12. On a scale of 1 – 10 (1-no impact; 10-strong impact), please rate how this program will impact the medication therapy management outcomes or safety of your patients.

13. On a scale of 1 – 10 (1-did not enhance; 10-greatly enhanced), please rate how this program enhanced your competence in the clinical areas covered.

12. On a scale of 1 – 10 (1-did not help; 10-great help), please rate how this program helped to build your management and leadership skills.

14. How useful was the educational material?
    a. Very useful
    b. Somewhat useful
    c. Not useful

15. How effective were the learning methods used for this activity?
    a. Very effective
    b. Somewhat effective
    c. Not effective

16. Learning assessment questions were appropriate.
    a. Yes
    b. No

17. Were the authors free from bias?
    a. Yes
    b. No

18. If you answered "no" to question 17, please comment (email info@pswi.org).

19. Please indicate the amount of time it took

CE FOR **PHARMACISTS**

Continuing Education Credit Information

The Pharmacy Society of Wisconsin is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. Continuing education credit can be earned by completing the self assessment questions. Questions may be completed online. Participants receiving a score of 70% or better will be granted 1 hour (0.1 CEU) credit through CPE Monitor. Accurate birth date (MMDD) and CPE Monitor ID must be provided in order to receive this credit as required by ACPE. This CE offering is offered free-of-charge to all PSW members. Nonmembers are charged $25.

May/June 2023
Updates on Glucagon-Like Peptide-Based Medications: Current, New, and Pipeline Agents

ACPE Universal Activity Number: 0175-0000-23-017-H01-P

Target Audience: Pharmacists & Technicians
Activity Type: Knowledge-based
Release Date: May 1, 2023
(No longer valid for CE credit after May 1, 2026)

Submit Your CE Online
www.pswi.org/Education/Journal-CE