

WEGOVY, TRULICITY, OZEMPIC... OH MY!



Lauren Garfield, MD, PhD
OTR Associate Editor
RGA Reinsurance
Chesterfield, MO
lauren.garfield@rgare.com

Obesity in the US

In the US, the prevalence of obesity has been increasing over the last several decades. Approximately 30% of adults are classified as overweight (BMI 25-29.9), 42% as obese (BMI 30-40) and 9% as severely obese (BMI ≥ 40). Children in the US also have a high prevalence of obesity, with a combined 41% of children being classified as either overweight or obese. Comorbidities associated with obesity affect both morbidity and mortality, and include increased risk for Type 2 diabetes, hypertension, cardiovascular disease, stroke,³ musculoskeletal conditions, liver disease, gallbladder disease, some cancers and sleep apnea. The aggregate medical costs of obesity in the US was estimated to be over \$260 billion in 2016⁴ (see Figures 1 and 2, next page).

Glucagon-like Peptide-1 Receptor Agonists (GLP-1 RAs)

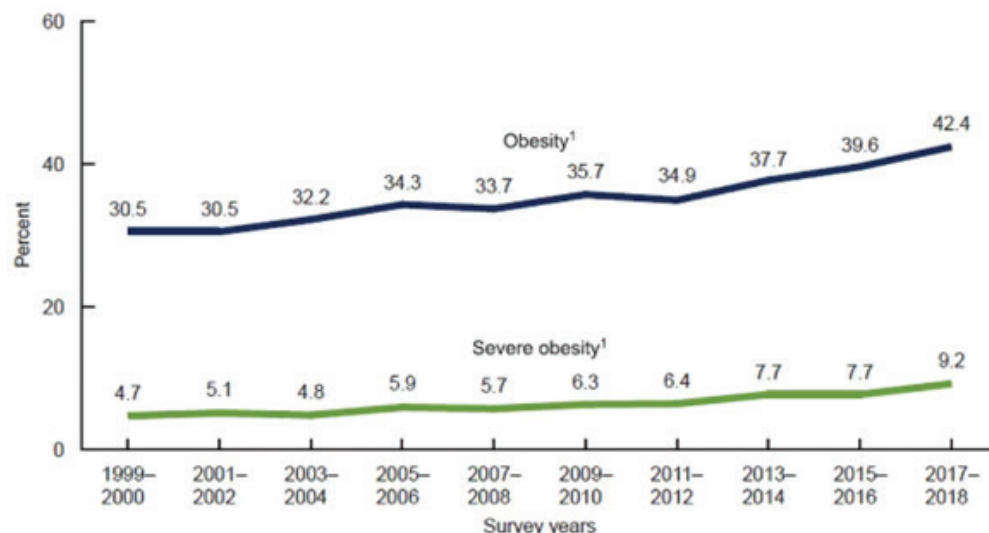
The class of drugs getting so much attention for weight loss are GLP-1 receptor agonists (GLP-1 RAs). They are synthetic analogues of GLP-1 that act to control diabetes in four main ways: they stimulate insulin release in response to glucose, reduce hepatic glucose production by inhibiting glucagon release, increase satiety and slow gastric emptying. Unlike natural GLP-1, which is degraded very quickly, the synthetic version tends to stick around longer.⁵

GLP-1 is an incretin hormone produced in the L cells of the small intestine and released upon eating. GLP-1 stimulates glucose-dependent-insulin release from the pancreas islets. GLP-1 receptors are located throughout the GI system in the pancreas, pancreatic ducts and gastric mucosa, and outside the GI system in the kidney, heart, lungs, skin, hypothalamus and immune cells.⁶

Executive Summary Recently, it has become difficult to avoid the buzz of print ads, commercials, social media postings and general discussion about the new weight loss drug Wegovy, a new indication of semaglutide also approved for treatment of Type 2 diabetes under the brand names Ozempic and Rybelsus. Whether it is discussion about drug shortages,¹ side effects or videos showing weight loss results, this class of drugs has been big news in the last year. One analysis from February 2023 estimates there was an increase of over 2000% in prescribing of semaglutide (Ozempic, Rybelsus, Wegovy) and tirzepatide (Mounjaro) for weight management between 2019 and 2022 (tirzepatide was approved in 2022). There was a 259% increase in prescriptions between 2021 and 2022 alone. In this analysis, one-fourth of prescriptions were for individuals without diabetes.² Finding a new, effective treatment for obesity has significant public health implications given the prevalence of overweight and obesity and associated comorbidities in the US.

Since the first GLP-1 RA medication became available in 2005, several additional medications have been added to this class. They were initially developed as treatments for Type 2 diabetes⁷ and have demonstrated significant reductions in A1c in individuals with Type 2, minimal risk of hypoglycemia, and favorable effect on weight. Additionally, dulaglutide, liraglutide and semaglutide (injectable) have shown evidence for reduction in major cardiovascular events. Use of the GLP-1 RAs may be limited by high cost, need for injection of most of the agents, and adverse gastrointestinal (GI) effects in some individuals.⁸

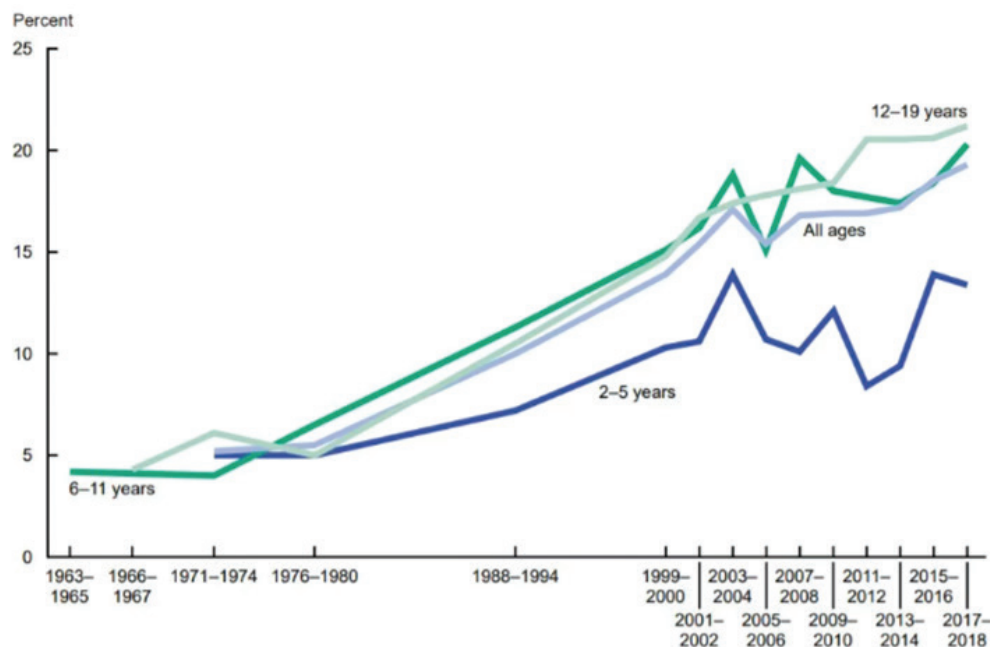
Figure 1. Trends in Age-Adjusted Obesity and Severe Obesity Prevalence Among Adults Ages 20 and Over: US, 1999-2000 Through 2017-2018.



Note: Estimates were age adjusted by the direct method to the 2000 US Census population using the age groups 20-39, 40-59, and 60 and over.

Source: www.niddk.nih.gov/health-information/health-statistics/overweight-obesity.

Figure 2. Trends in Obesity Among Children and Adolescents Ages 2-19 Years, By Age: US, 1963-1965 Through 2017-2018.



Note: Obesity is defined as body mass index (BMI) at or above the 95th percentile from the sex-specific BMI-for-age 2000 CDC Growth Charts.

Source: www.niddk.nih.gov/health-information/health-statistics/overweight-obesity.

Table 1. Summary of GLP-1 RAs available in the US.					
Generic Name	Brand Name(s)	Formulation	FDA Approval	Highlights	Contraindications
Semaglutide ⁹	Wegovy ¹⁰	2.4 mg weekly injection	Approved 6/2021 for weight management in adults and children age 12+.	Approved for weight loss. Approved in teens.	Personal or family history of medullary thyroid cancer or MEN 2A.
	Ozempic ¹¹	0.5, 1.0, 2.0 mg weekly injection	Approved 12/2017 to improve blood glucose in adults with Type 2 diabetes and to reduce major CVD events in people with Type 2 and CVD.	Approved for both Type 2 and to reduce major CVD events in Type 2.	
	Rybelsus ¹²	7.0, 14.0 mg daily tablet	Approved 9/2019 for blood glucose control in adults with Type 2 diabetes.	First oral GLP-1 drug available in the US.	
Tirzepatide ¹³	Mounjaro	2.5, 5, 7.5, 10, 12.5, 15 mg weekly injection	Approved 5/2022 to improve blood glucose control in adults with Type 2 diabetes.	Activates both GLP-1 and GIP.	Personal or family history of medullary thyroid cancer or MEN 2A.
Liraglutide	Victoza ¹⁴⁻¹⁶	1.2, 1.8 mg daily injection	Approved 1/2010 (original approval) for type 2 in adults. Additional approval 8/2017 to reduce CVD events in Type 2. Approved 6/2019 to treat patients 10+ with Type 2 diabetes.	Approved to treat type 2 in kids ages 10 and up. Also approved to reduce CVD events in adults with Type 2 diabetes.	Personal or family history of medullary thyroid cancer or MEN 2A.
	Saxenda ^{17,18}	3 mg daily injection	Approved 12/2014 for chronic weight management in adults. Approved 12/2020 for kids age ≥12.	Approved for weight loss in kids ages 12-17.	

Dulaglutide	Trulicity ¹⁹⁻²¹	.75, 1.5, 3.0, 4.5 mg weekly injection	Approved 9/2014 to improve glycemic control in adults with Type 2 diabetes and to reduce risk of CVD events in adults with Type 2. The 11/2022 approval was extended to kids age 10+ for Type 2 diabetes.	Approved for both Type 2 diabetes and to reduce major CVD events in Type 2 diabetes. Approved for use in kids ages 10 and up for Type 2 diabetes.	Personal or family history of medullary thyroid cancer or MEN 2A.
Exenatide	Byetta ^{22,23}		Approved 4/2005 as adjunctive therapy for blood sugar control in patients with Type 2 diabetes who have not achieved control with metformin and/or a sulfonylurea. Approved 11/2009 as standalone treatment for Type 2 diabetes. Approved 10/2011 for use with insulin glargine.	This was the first approval in the class. Can be used with insulin.	Personal or family history of medullary thyroid cancer or MEN 2A.
	Bydureon BCise ^{24,25}	2 mg extended release weekly injection	Approved 1/2012 for adults with Type 2 diabetes (injectable suspension). Pre-filled, single-use pen injector approved 3/2014. Approved 4/2018 as add-on therapy for use with basal insulin in adults with Type 2 diabetes and inadequate glycemic control. Approved 7/21 for ages 10+.	First weekly treatment for Type 2 diabetes. Can be used with insulin. Approved for Type 2 diabetes for kids ages 10+_ as of 7/2021.	

Lixisenatide ^{26,27}	Adlyxin	na	Approved 7/2016 for adults with Type 2 diabetes. Discontinued 1/2023.	Discontinued 1/1/23 in US market for business reasons. <i>Soliqua</i> – a formulation that contains insulin glargine and lixisenatide – is still available. ²⁸	na
----------------------------------	---------	----	---	---	----

Use for Weight Loss

While the GLP-1 RAs were initially developed to treat Type 2 diabetes, their weight-loss effects are currently getting more attention. All have shown some effect on weight, though their effectiveness varies (see Table 2). So far, only semaglutide (Wegovy) and liraglutide (Saxenda) have FDA approval as therapy for weight loss. Both Wegovy and Saxenda are approved for teens (ages 12 and older) and adults. Wegovy is a weekly injection while Saxenda is a daily injection. In terms of efficacy, the STEP 8 randomized clinical trial compared use of semaglutide 2.4 mg weekly injection with liraglutide 3.0 mg daily injection in overweight and obese adults. After 68 weeks, those in the semaglutide group achieved a mean weight change of -15.8% and those in the liraglutide group a mean weight change of -6.4%. Both led to weight loss, but semaglutide led to greater weight loss.²⁹ Tirzepatide is not currently FDA-approved for weight loss but has received the FDA Fast Track designation³⁰ to accelerate the path to approval. In a Phase 3 trial³¹ of obese adults receiving tirzepatide weekly for 72 weeks at doses of 5-15 mg, the mean weight change was -15% across groups, with 85% of participants reducing their weight at least 5%. It is important to

note that because all the medications in this class have effects on weight, there is evidence that they are being prescribed off-label for weight loss.³²

What Does This Mean for Underwriting?

Overweight and obesity are very common in the US, and their comorbidities are associated with some of the most common causes of increased morbidity and mortality.³³ While long-term data is lacking for these treatments, reduction in overweight and obesity should theoretically lead to improvement in downstream outcomes. However, this is speculative, and more research is needed over the next decade to study the effectiveness of these therapies over the long term. Currently, in underwriting, it is important to understand that use of this class of medications does not necessarily indicate that a PI is a Type 2 diabetic. It is also important to note that there is a warning about using these medications in individuals at risk for medullary thyroid cancer or MEN 2A. This is a rapidly evolving landscape with many trials underway as drug companies seek indication for weight loss (see tirzepatide), so underwriters will continue to see more of this class of medications with additional changes to come.

Table 2. Comparison of GLP-1 RAs: Effect on Weight Based on Phase III Studies	
Drug	Effect on Weight Compared to Other GLP-1 RAs
Dulaglutide (Trulicity)	Intermediate
Exenatide Twice daily (Byetta) XR (Bydureon BCise)	Low Low
Liraglutide (Saxenda, Victoza)	High
Lixisenatide (Adlyxin) #	Low
Semaglutide Oral (Rybelsus) Injection (Ozempic, Wegovy)	Highest Highest

Note: Analyses for this table did not include tirzepatide. #Discontinued in US Market in 2023.²⁶
Source: Trujillo et al. 2021.³²

Notes

1. Drug Shortage Detail: Semaglutide Injection. Accessed June 8, 2023. www.ashp.org/Drug-Shortages/Current-Shortages/Drug-Shortage-Detail.aspx?id=813.
2. Prescriptions for Trendy Diabetes and Weight-Loss Drugs Increased Over 2,000% Since 2019. Accessed June 8, 2023. www.komodohealth.com/insights/prescriptions-for-trendy-diabetes-and-weight-loss-drugs-increased-over-2000-since-2019.
3. Overweight & Obesity Statistics - NIDDK. National Institute of Diabetes and Digestive and Kidney Diseases. Accessed June 8, 2023. www.niddk.nih.gov/health-information/health-statistics/overweight-obesity.
4. Cawley J, Biener A, Meyerhoefer C, et al. Direct medical costs of obesity in the US and the most populous states. *JMCP*. 2021;27(3):354-366. doi:10.18553/jmcp.2021.20410.
5. Lathief S. Getting to know GLP-1 receptor agonists. Accessed June 8, 2023. <https://acpinternist.org/archives/2023/03/getting-to-know-glp-1-receptor-agonists.htm>.
6. Glucagon-like peptide 1-based therapies for the treatment of type 2 diabetes mellitus - UpToDate. Accessed June 8, 2023. www.uptodate.com/contents/glucagon-like-peptide-1-based-therapies-for-the-treatment-of-type-2-diabetes-mellitus.
7. GLP-1 receptor agonists: Breaking down the hype and demand. American Pharmacists Association. Accessed June 8, 2023. <http://pharmacist.com/Publications/Pharmacy-Today/Article/glp-1-receptor-agonists-breaking-down-the-hype-and-demand>.
8. GLP-1 receptor agonists: An updated review of head-to-head clinical studies - Jennifer M. Trujillo, Wesley Nuffer, Brooke A. Smith, 2021. Accessed June 8, 2023. <https://journals.sagepub.com/doi/10.1177/2042018821997320#table1-2042018821997320>.
9. Semaglutide Responsible Use | Official Website. novoMEDLINK. Accessed June 8, 2023. www.novomedlink.com/semaglutide.html, www.novomedlink.com/semaglutide.html.
10. Commissioner O of the FDA Approves New Drug Treatment for Chronic Weight Management, First Since 2014. FDA. Published June 21, 2021. Accessed June 8, 2023. www.fda.gov/news-events/press-announcements/fda-approves-new-drug-treatment-chronic-weight-management-first-2014.
11. Research C for DE and Drug Trial Snapshot: Ozempic. FDA. Published online August 20, 2020. Accessed June 8, 2023. www.fda.gov/drugs/drug-approvals-and-databases/drug-trial-snapshot-ozempic.
12. Commissioner O of the FDA approves first oral GLP-1 treatment for type 2 diabetes. FDA. Published March 24, 2020. Accessed June 8, 2023. www.fda.gov/news-events/press-announcements/fda-approves-first-oral-glp-1-treatment-type-2-diabetes.
13. Commissioner O of the FDA Approves Novel, Dual-Targeted Treatment for Type 2 Diabetes. FDA. Published May 13, 2022. Accessed June 8, 2023. www.fda.gov/news-events/press-announcements/fda-approves-novel-dual-targeted-treatment-type-2-diabetes.
14. Commissioner O of the FDA approves new treatment for pediatric patients with type 2 diabetes. FDA. Published March 24, 2020. Accessed June 8, 2023. www.fda.gov/news-events/press-announcements/fda-approves-new-treatment-pediatric-patients-type-2-diabetes.
15. Victoza Non-Insulin | Victoza (liraglutide) injection 1.2mg or 1.8mg. Accessed June 8, 2023. www.victoza.com.
16. Victoza (liraglutide) FDA Approval History - Drugs.com. Accessed June 8, 2023. www.drugs.com/history/victoza.html.
17. Prescription Weight-Loss Medicine | Saxenda (liraglutide) injection 3mg. Accessed June 8, 2023. www.saxenda.com.
18. Research C for DE and FDA approves weight management drug for patients aged 12 and older. FDA. Published online September 30, 2021. Accessed June 8, 2023. www.fda.gov/drugs/news-events-human-drugs/fda-approves-weight-management-drug-patients-aged-12-and-older.
19. Type 2 Diabetes & Cardiovascular Disease Treatment | Trulicity (dulaglutide) Once Weekly Injection. Accessed June 8, 2023. www.trulicity.com.
20. OptumRx Memo on Trulicity (dulaglutide) Expanded Indication. Accessed June 8, 2023. https://professionals.optumrx.com/content/dam/optum3/professional-optumrx/news/rxnews/clinical-updates/clinicalupdate_trulicity_2022-1118.pdf.
21. Amylin and Lilly Announce FDA Approval of BYETTA (Exenatide) Injection | Eli Lilly and Company. Accessed June 8, 2023. <https://investor.lilly.com/news-releases/news-release-details/amylin-and-lilly-announce-fda-approval-byettatm-exenatide>.
22. Byetta (exenatide) FDA Approval History - Drugs.com. Accessed June 8, 2023. www.drugs.com/history/byetta.html.
23. Type 2 Diabetes Treatment | BYDUREON BCise (exenatide extended-release) injectable suspension. Accessed June 8, 2023. www.bydureon.com/bydureon-bcise.html.
24. Bydureon BCise (exenatide) FDA Approval History - Drugs.com. Accessed June 8, 2023. www.drugs.com/history/bydureon-bcise.html.
25. OptumRx Memo on Sanofi – Discontinuation of Adlyxin (lixisenatide). Accessed on June 8, 2023. https://professionals.optumrx.com/content/dam/optum3/professional-optumrx/news/rxnews/drug-withdrawals/drugwithdrawal_adlyxin_2023-0117.pdf.
26. Commissioner O of the FDA approves Adlyxin to treat type 2 diabetes. FDA. Published March 24, 2020. Accessed June 8, 2023. www.fda.gov/news-events/press-announcements/fda-approves-adlyxin-treat-type-2-diabetes.
27. Dosing and Titration | SOLIQUA 100/33 (insulin glargine & lixisenatide) injection 100 Units/mL & 33 mcg/mL. Accessed June 8, 2023. www.soliqua100-33.com/hcp/dosing-and-titration.
28. Rubino DM, Greenway FL, Khalid U, et al. Effect of Weekly Subcutaneous Semaglutide vs. Daily Liraglutide on Body Weight in Adults With Overweight or Obesity Without Diabetes: The STEP 8 Randomized Clinical Trial. *JAMA*. 2022;327(2):138-150. doi:10.1001/jama.2021.23619.
29. Lilly receives US FDA Fast Track designation for tirzepatide for the treatment of adults with obesity, or overweight with weight-related comorbidities | Eli Lilly and Company. Accessed June 8, 2023. <https://investor.lilly.com/news-releases/news-release-details/lilly-receives-us-fda-fast-track-designation-tirzepatide>.
30. Tirzepatide Once Weekly for the Treatment of Obesity | *NEJM*. Accessed June 8, 2023. www.nejm.org/doi/full/10.1056/NEJMoa2206038.
31. For Weight Loss, Off-Label GLP-1s Are Increasingly the Chosen Ones | AMCP 2023. Managed Healthcare Executive. Published March 24, 2023. Accessed June 8, 2023. www.managedhealthcareexecutive.com/view/for-weight-loss-the-glp-1s-are-the-ones-amcp-2023.
32. Trujillo JM, Nuffer W, Smith BA. GLP-1 receptor agonists: an updated review of head-to-head clinical studies. *Therapeutic Advances in Endocrinology*. 2021;12:2042018821997320. doi:10.1177/2042018821997320.
33. FastStats. Published January 18, 2023. Accessed June 8, 2023. www.cdc.gov/nchs/fastats/leading-causes-of-death.htm.