Real-World Adherence and Persistence to Glucagon-Like Peptide-1 Receptor Agonists at Two Years among Non-Diabetic Obese Commercially Insured Adults

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Background

- The National Health and Nutrition Examination Survey (NHANES) estimates U.S. obesity prevalence at 41.9% from 2017 to March 2020, with the Centers for Disease Control and Prevention (CDC) reporting U.S. total obesity-related health care costs at nearly $173 billion annually.[1]
- In 2014, the U.S. Food & Drug Administration (FDA) approved the first glucagon-like peptide-1 agonist (GLP-1) product, liraglutide injection, for obesity treatment,[2] followed by semaglutide injection in 2021.[3]
- GLP-1 clinical trials for products to treat obesity report significant weight loss (6.1%-17.4%)[4] and medication continuation through a three-year randomized controlled trial duration at over 85%.[5]
- Current real-world GLP-1 obesity treatment adherence and persistence research is limited to one year with findings indicating one-third stay on GLP-1 therapy and 27% were adherent.[6]
- Understanding real-world GLP-1 obesity treatment persistence and adherence rates beyond one year is important to forecasting expected clinical effectiveness, utilization, and financial risk.

Objectives

To measure adherence, persistence, and GLP-1 product switching over two years in a real-world cohort of commercially insured non-diabetic members newly initiating a GLP-1 drug for the treatment of obesity

Methods

- The methods have been published in the *Journal of Managed Care & Specialty Pharmacy*.[6] Prime Therapeutics analyzed integrated pharmacy and medical claims data from 16.5 million commercially insured members. Study inclusion was limited to members with a GLP-1 claim (index date) between Jan. 1, 2021, and Dec. 31, 2021, with continuous enrollment 12 months before (pre-period) and 24 months after (post-period) the index date, and no GLP-1 drug claim during the pre-period.
- Members newly initiating GLP-1 therapy between Jan. 1, 2021, and Dec. 31, 2021, were identified for the following GLP-1 products: injectable semaglutide for diabetes (Ozempic), oral semaglutide (Rybelsus), dulaglutide (Trulicity), injectable liraglutide for obesity (Saxenda), injectable semaglutide for obesity (Wegovy), and injectable liraglutide for diabetes (Victoza).
- Date of first GLP-1 pharmacy claim in the identification period was labeled as index date from which members were required to be continuously enrolled one year before (pre-period) and two years after (post-period) index date.
- During the pre-period, members were required to have a medical claim with diagnosis indicating obesity, defined as ICD-10-CM codes E660-E669, except for E663, or ICD-10-CM codes Z683-Z684.
- To reduce the possibility of GLP-1 use for diabetes, members were excluded if they had a medical claim with a diabetes diagnosis (T1DM, T2DM, gestational diabetes, diabetes due to underlying condition, chemical-induced diabetes, or other specificied diabetes) or a pharmacy claim for an antidiabetic medication during the pre-period.
- Also excluded were members with diagnoses for HIV/AIDS, hemophilia, sickle cell disease, malignant cancer or end-stage renal disease as identified by diagnosis codes in medical claims during the 365 days before study index date. The clinical classifications software refined (CCSR) for ICD-10-CM diagnoses was used to specify diabetes and the above clinical conditions.
- The study primary outcome of persistence and secondary outcomes of adherence and GLP-1 switching were reported by the initial GLP-1 product dispensed. Switching GLP-1 products was allowed, and persistency and adherence measurements were calculated at the GLP-1 category level.
- Members were considered persistent if they did not have a 60-day gap in therapy and were censored at the end of the 730-day period. The last day of supply before gap was defined as the member's discontinuation date for those nonpersistent.
- Adherence was measured using the proportion of days covered (PDC) method endorsed by the Pharmacy Quality Alliance (PQA) and used by Centers for Medicare & Medicaid Services (CMS) in their Part C and D Star Ratings with three differences: (1) all members were naive to GLP-1 therapy with no GLP-1 claim history in the prior 365 days, (2) a single GLP-1 claim allowed a member to be included in the adherence measurement, whereas CMS requires two claims, and (3) all members were continuously enrolled. Members with a PDC ≥80% were considered adherent, and those with PDC <80% were defined as nonadherent.
- Switches between GLP-1 products were defined as a change between GLP-1 products from one claim to the next for a given member. For example, if a member initiated Ozempic and switched to Wegovy, that would count as a GLP-1 product switch, even though both are semaglutide products.
- The Kaplan-Meier method with a log-rank test was used to estimate median time-to-GLP-1 discontinuation for the three semaglutide products (Ozempic, Rybelsus and Wegovy), dulaglutide (Trulicity), and liraglutide products (Saxenda and Victoza).
- Descriptive statistics were used to describe adherence rates and the count of members with a GLP-1 product switch, by product.

Table 1

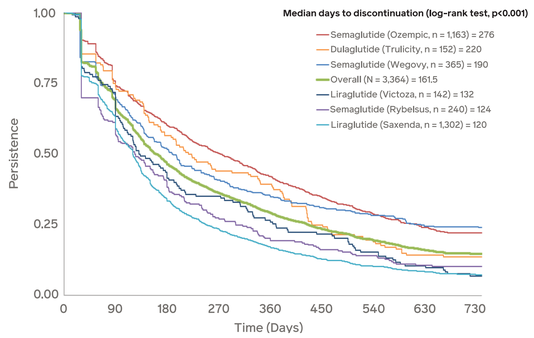
Sample selection

Study selection criteria – Glucagon-Like Peptide-1 (GLP-1) obesity therapy	16.5 million average monthly commercially insured members in 2021
2021 GLP-1 claim (first GLP-1 claim in 2021 is the member's index GLP-1 claim)	280,298
Newly initiated GLP-1 in 2021 (no GLP-1 claim in 365 days prior to index GLP-1 claim)	148,564
Obesity medical claim or Z-code BMI ≥ 30 (in past 365 days from index GLP-1 claim)	57,948
Continuously enrolled (one-year pre & post index GLP-1 claim)	36,189
≥ 19 years old at GLP-1 index date	36,070
No diabetes medical or pharmacy claim (in 365 days prior to and including GLP-1 index date)	4,154
No malignant cancer, HIV/AIDS, hemophilia, sickle cell disease, or end-stage renal disease	4,066 one-year cohort
Continuously enrolled 2 years from GLP-1 new start	3,364 (83%) of 4,066

GLP-1 therapy = semaglutide (Ozempic), semaglutide (Rybelsus), dulaglutide (Trulicity), liraglutide (Saxenda), semaglutide (Wegovy), and liraglutide (Victoza); HIV/AIDS = human immunodeficiency virus/acquired immunodeficiency syndrome. Note: tirzepatide was FDA approved May 2022.

Figure 1

Glucagon-like peptide-1 (GLP-1) agonists: Kaplan-Meier two-year obesity therapy persistence (n= 3,364) and median days to discontinuation



Kaplan-Meier curve represents 3,364 obese commercially insured adults without diabetes initiating one of the following GLP-1 products during calendar year 2021: semaglutide (Ozempic), semaglutide (Wegovy), semaglutide (Rybelsus), dulaglutide (Trulicity), liraglutide (Victoza), or liraglutide (Saxenda). Members were considered persistent if they did not have a 60-day gap in GLP-1 therapy and were censored at the end of the 730-day period. All persistency measurements allowed for GLP-1 product switching. Note: tirzepatide was FDA approved May 2022.

Table 2

Two-year glucagon-like peptide-1 (GLP-1) agonists: obesity therapy adherence, persistence and GLP-1 product switch rates

2-year obesity treatment GLP-1 users	% persistent (no 60-day gap)	% adherent (PDC >/= 80%)	% with GLP-1 product switch
Overall (N=3,364)	14.8%	16.6%	25.8%
Wegovy (n=365 [11%)	24.1%	24.1%	23.0%
Ozempic (n=1,163 [34%])	22.2%	24.8%	17.1%
Trulicity (n=152 [5%)	13.8%	17.8%	38.8%
Rybelsus (n=240 [7%])	10.4%	10.4%	28.3%
Saxenda (n=1,302 [39%])	7.4%	8.9%	30.7%
Victoza (n=142 [4%])	7.0%	10.6%	40.1%

3,364 obese commercially insured adults without diabetes initiating one of the following GLP-1 products during calendar year 2021: semaglutide (Ozempic), semaglutide (Wegovy), semaglutide (Rybelsus), dulaglutide (Trulicity), liraglutide (Victoza), or liraglutide (Saxenda). Members were considered persistent if they did not have a 60-day gap in therapy and were censored at the end of the 730-day period. Adherence was measured using proportion of days covered (PDC) over two years, further defined in the Methods section. All adherence and persistency measurements were conducted at the GLP-1 product level allowing for GLP-1 product switching. Note: tirzepatide was FDA approved May 2022.

Results

- Among 16.5 million commercially insured members, a total of 3,364 members were identified as newly-initiating GLP-1 therapy and were continuously enrolled for two years after beginning their GLP-1 obesity therapy **(Table 1).**
- The mean age of individuals included in the study was 46.5 and 81.0% were women.
- Overall, GLP-1 persistence was 47.1% at 180 days, 28.9% at one year, and 14.8% at two years **(Figure 1).**
- The median days to discontinuation was significantly different between products with the weekly semaglutide products having higher median days to discontinuation than daily injection liraglutide products and the oral semaglutide product **(Figure 1).**
- Utilizers of the weekly injection semaglutide products (Wegovy at 24.1% and Ozempic at 22.2%) had the highest two-year persistency rates, and the daily injection liraglutide products (Saxenda at 7.4% and Victoza at 7.0%) had the lowest persistence rates **(Table 2).**
- Overall, 16.6% were adherent to their GLP-1 obesity treatment during the two years, with an average adherence PDC of 40.7%. Semaglutide product adherence was 24.8% for Ozempic and 24.1% for Wegovy **(Table 2).**
- 25.8% switched GLP-1 products during the two years **(Table 2).**

Limitations

- Although outcome calculations allowed for product switching, product shortages may have impacted persistence and adherence rates.
- Members switching to compounded GLP-1 therapy or paying out of pocket for their GLP-1 product may have reduced observed persistence and adherence, as this utilization was not recorded in insurance claims data.
- Using medical and pharmacy claims to exclude members without a diabetes diagnosis or by drug therapy, and to identify those with obesity, may misclassify cohort members.
- Tirzepatide products were not included in this analysis as a GLP-1 new initiator group, as they were not available during the 2021 study identification. However, switching to tirzepatide was allowed and included in the persistence and adherence assessments.
- Our study examined a commercially insured membership and, therefore, are not generalizable to Medicare or Medicaid populations.
- The impact of a member's cost sharing, other diagnoses, social determinants of health or other member characteristics are outside the scope of this analysis and are worthy of future consideration.

Conclusions

- This real-world analysis of GLP-1 products used for weight loss, among obese members without diabetes, found poor two-year persistence 1 in 7 members remaining on GLP-1 therapy, and 1 in 6 adherent, as compared to three-year clinical trial data of greater than 85%[5].
- Weekly injected semaglutide products were found to have higher persistency and adherence at approximately 1 in 4 remaining on therapy over the two-year assessment.
- Product switching was common with 25.8% switching GLP-1 products during the two-year assessment.
- Low adherence and persistence, as well as product switching, may be due to adverse effects, lack of perceived benefit, member cost share, and drug shortages.
- These findings highlight substantial GLP-1 therapy investment risk due to waste.
- Participation in a comprehensive weight loss treatment program, including a care manager, may improve GLP-1 therapy adherence and persistence.
- Understanding real-world persistence and adherence to current GLP-1 products, when used for weight loss, will aid in assessing product cost-effectiveness, understanding obesity care management program needs, forecasting future GLP-1 utilization and cost trends, and negotiating GLP-1 pharmaceutical manufacturer value-based purchasing agreements.
- Additional research is needed to understand reasons for treatment discontinuation and long-term cost-effectiveness of these products.

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