Real-World Adherence and Persistence to Glucagon-Like Peptide-1 Receptor Agonists 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 through 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%)[a] and medication continuation through trial duration at over 90%.[5]
- GLP-1 utilization and costs during 2023 have increased dramatically in part due to increased obesity treatment and social media trends.[6]
- Current real-world data research describing obesity GLP-1 persistency and adherence will contribute to effectiveness evaluations, utilization forecasting and care management of the GLP-1 medication class.

OBJECTIVES

To measure adherence and persistence to GLP-1 therapy in a real-world cohort of commercially insured non-diabetic members newly initiating these drugs for the treatment of obesity.

OUTCOMES

- 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 365-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), except no additional GLP-1 claim was required after initial claim. Members with a PDC ≥80% were considered adherent, and those with PDC <80% were defined as non-adherent.
- Switches between GLP-1 products were defined as a change between GLP-1 products from one claim to the next for a given member.

METHODS

- This retrospective, observational cohort study analyzed the Prime Therapeutics' integrated pharmacy and medical claims data from 16 million commercially insured members covering all regions of the United States across the three-year period of January 1, 2020 through December 31, 2022.
- Members newly initiating GLP-1 therapy between January 1, 2021 and December 31, 2021 (identification period) 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 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 and other specified 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.

STATISTICAL METHODS

- The Kaplan-Meier method was used to estimate median and 95% confidence interval time-to-GLP-1 discontinuation for the three semaglutide products (Ozempic, Rybelsus and Wegovy) and liraglutide product (Saxenda).
- An overall log-rank test was used to compare differences in persistence across index GLP-1 products and across persistency gap definitions of 45, 60 and 90-days for sensitivity analysis. Pairwise comparisons in odds of nonpersistence were made between each GLP-1 product using a generalized linear model with a logit link and binomial distribution, and Tukey's Honest Significant Difference test was used to account for inflated Type 1 error rate.
- The same statistical modeling approach for the 365-day persistence outcome was used for the adherence outcome, with a generalized linear model assessing the log likelihood of achieving adherence over the post-period.
- The count of member-level product switches was divided into four categories (0, 1, 2, 3+), and the difference in switch rate across product was assessed using a chi-square test.
- Descriptive statistics compared member demographic and clinical characteristics between index GLP-1 products as well as for the overall study cohort. Analysis of variance (ANOVA) and chi-square tests were used to evaluate differences in demographic and clinical characteristics across products.

TABLE 1

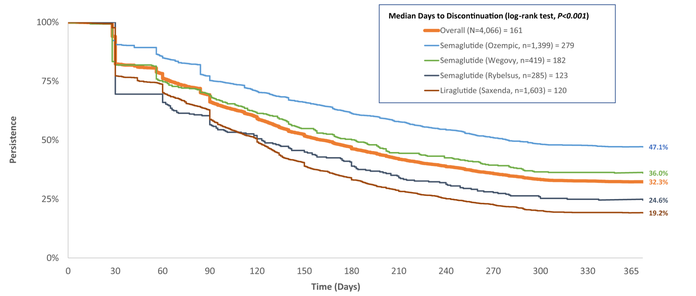
Demographics, Clinical Characteristics and Outcomes by Glucagon-Like Peptide-1 (GLP-1) Agonist Index Product[a]

	All Members N = 4,066 (100%)	Liraglutide (Saxenda) n =1,603 (39.4%)	Semaglutide (Ozempic) n = 1,399 (34.4%)	Semaglutide (Wegovy) n = 419 (10.3%)	Semaglutide (Rybelsus) n = 285 (7.0%)	Liraglutide (Victoza) n = 184 (4.5%)	Dulaglutide (Trulicity) n = 176 (4.3%)	P value[e]
Characteristic[b]								
Female, n (%)	3,299 (81.1)	1,346 (84.0)	1,116 (79.8)	328 (78.3)	224 (78.6)	152 (82.6)	133 (75.6)	0.004
Age, mean (SD), years	46.4 (10.1)	46.0 (10.0)	46.8 (10.2)	46.1 (9.6)	46.1 (10.4)	46.4 (10.1)	47.5 (9.5)	0.204
Charlson Comorbidity Index, mean (SD)	0.6 (1.5)	0.7 (1.6)	0.6 (1.4)	0.5 (1.3)	0.5 (1.3)	0.5 (1.2)	0.8 (1.8)	0.063
CVD, n (%)	223 (5.5)	76 (4.7)	88 (6.3)	24 (5.7)	14 (4.9)	10 (5.4)	11 (6.3)	0.566
Prediabetes, n (%)	653 (16.1)	155 (9.7)	314 (22.4)	46 (11.0)	54 (18.9)	33 (17.9)	51 (29.0)	<0.001
GLP-1 Outcome[c]								
Persistent without 60-day gap, n (%)	1,313 (32.3)	307 (19.2)	659 (47.1)	151 (36.0)	70 (24.6)	49 (26.6)	77 (43.8)	<0.001
Adherence (PDC), mean (SD)	51.0 (31.9)	40.8 (28.5)	63.1 (30.8)	52.5 (33.3)	44.5 (31.3)	46.5 (30.6)	60.7 (33.4)	<0.001
Adherent (PDC ≥80%), n (%)	1,106 (27.2)	241 (15.0)	561 (40.1)	132 (31.5)	56 (19.6)	43 (23.4)	73 (41.5)	<0.001
Number of Switches[d], n (%)								
0	3,615 (88.9)	1,386 (86.5)	1,319 (94.3)	357 (85.2)	246 (86.3)	148 (80.4)	159 (90.3)	<0.001
1	386 (9.5)	197 (12.3)	59 (4.2)	48 (11.5)	36 (12.6)	32 (17.4)	14 (8.0)	
2	50 (1.2)	15 (0.9)	14 (1.0)	14 (3.3)	1 (0.4)	4 (2.2)	2 (1.1)	
3+	15 (0.4)	5 (0.3)	7 (0.5)	0 (0)	2 (0.7)	0 (0)	1 (0.6)	

[a] Commercially insured adults without diabetes newly initiating a GLP-1 during calendar year 2021 and with a diagnosis indicating obesity medical claim
[b] Clinical characteristics measured in 365-day period prior to GLP-1 initiation (pre-period). Age and gender ascertained at first day of member's pre-period
[c] Measured in 365-day post GLP-1 initiation (post-period)
[d] Count of member-level product switches
[e] P values for continuous variables is the F-test resulting from ANOVA; P values for categorical variables is derived from the chi-square test
CVD = Cardiovascular disease; GLP-1 = Glucagon-like peptide-1 agonist; PDC = Proportion of days covered

FIGURE 1

Glucagon-Like Peptide-1 (GLP-1) Agonists: Kaplan-Meier One-Year Therapy Persistence, Overall and for Top Four Study Index Drugs



Note: Kaplan-Meier curves represent obese commercially insured adults without diabetes initiating one of the following GLP-1 products during calendar year 2021: semaglutide (Ozempic), semaglutide (Wegovy), semaglutide (Rybelsus) or liraglutide (Saxenda).

RESULTS

- A total of 4,066 non-diabetic commercially insured adults with obesity who newly initiated GLP-1 therapy during calendar year 2021 met the requisite inclusion and exclusion criteria. **(Table 1)**
- The mean age was 46.4 years, 81.1% were female, and prevalence of CVD and pre-diabetes was 5.5% and 16.1%, respectively.
- The three most common index GLP-1 drugs by share of total analyzed members were liraglutide (Saxenda) 39.4%, semaglutide (Ozempic) 34.4% and semaglutide (Wegovy) 10.3%.
- One-year GLP-1 persistence using a 60-day gap definition was 32.3% for entire study population and ranged from 19.2% in the liraglutide (Saxenda) cohort to 47.1% in the semaglutide (Ozempic) cohort. During the one-year follow-up, median time to GLP-1 discontinuation was significantly different (P<0.001) across the top four studied GLP-1 drugs **(Table 1 and Figure 1).**
- Median time to discontinuation ranged from 279 days (95% CI: 255 to 336) in the semaglutide (Ozempic) cohort to 120 days (95% CI: 111 to 125) in the liraglutide (Saxenda) cohort.
- Persistence sensitivity analysis showed consistent trends across the full study population **(Table 1).** Pairwise comparisons across products find that semaglutide (Ozempic) and dulaglutide (Trulicity) persistence was significantly higher than for all other products.
- Mean PDC was lowest in the liraglutide (Saxenda) cohort (40.8% [SD=28.5]) and highest in the semaglutide (Ozempic) cohort (63.1% [SD=30.8]).
- Overall, 27.2% (range: 15.0% to 41.5%) of members were adherent to GLP-1 therapy during follow-up. Adherence rates varied by product, with members significantly more adherent to semaglutide (Ozempic) and dulaglutide (Trulicity) than to other products.
- The number of GLP-1 switches varied by GLP-1 product with >80% of members in each cohort not having a switch during study follow-up.

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 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 they were not available during the 2021 study identification and one-year post-index measurement period.
- 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 one-year persistence (32.3%) and adherence (27.2%), as compared to clinical trials data.
- Low adherence and persistence may be due to adverse effects, lack of perceived benefit, member cost share and drug shortages.
- Participation in a comprehensive weight loss treatment program, including a care manager, may improve GLP-1 therapy persistency.
- 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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Academy of Managed Care Pharmacy (AMCP) Annual Meeting, April 15 – 18, 2024, New Orleans, LA

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Sponsorship: Prime Therapeutics LLC