

Comparison of Low-Dose Liraglutide Use Versus Other GLP-1 Receptor Agonists in Patients Without Type 2 Diabetes

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Low-dose liraglutide (LD-L) (Victoza) is a glucagon-like peptide-1 receptor agonist (GLP-1 RA) approved in January 2010 as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes (T2D). It is available as a multidose pen that delivers doses of 0.6 mg, 1.2 mg, or 1.8 mg¹ liraglutide and it enjoys broad formulary access, in part because it was the first once-daily GLP-1 RA on the US market. While weight loss with LD-L in patients with diabetes was demonstrated in trials and in the real-world setting,^{2,3} LD-L is not indicated for weight management. Liraglutide 3 mg (Saxenda, high-dose liraglutide [HD-L]), approved in December 2014, is indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with an initial body mass index (BMI) of at least 30 kg/m² or at least 27 kg/m² in the presence of at least 1 weight-related comorbid condition. It is also available as a multidose pen that delivers doses of 0.6 mg, 1.2 mg, 1.8 mg, 2.4 mg, or 3.0 mg liraglutide.⁴ HD-L contains the same active ingredient as Victoza and is not indicated for the treatment of T2D. The introduction of Saxenda to the US market, with the subsequent promotional campaign initiated in April 2015, may have led to increased use of LD-L among patients who do not have T2D.

Based on a business analytics analysis of discrete monthly data from January 2014 to June 2015 (Optum Humedica Diabetes Database), the proportion of patients prescribed LD-L without a diagnosis of T2D increased nearly 2-fold during the first 6 months of 2015. Payers who do not offer favorable access to obesity treatments including HD-L may not be fully aware of LD-L use in patients without T2D, and therefore would be particularly interested in this proportion of patients who are prescribed and use LD-L most likely for weight loss. The objective of this study was to expand upon the previous analysis by evaluating prescribing patterns and prescription claims of LD-L compared with other GLP-1 RAs in 2 large national datasets from 2014 to 2016, which encompasses the approval and launch of HD-L.

Methods

This retrospective, repeated cross-sectional cohort study assessed information from patients in 2 databases. Prescription orders and

ABSTRACT

Objectives: The objective was to compare the use of low-dose liraglutide (LD-L) (Victoza) to the other glucagon-like peptide-1 receptor agonists (GLP-1 RAs) in patients without a type 2 diabetes (T2D) diagnosis in the post approval period for high-dose liraglutide (HD-L) (Saxenda), which is not indicated for T2D.

Study Design: This was a retrospective, repeated cross-sectional, cohort study.

Methods: Adult patients with T2D with more than 1 prescription for a GLP-1 RA in the Optum Humedica database between December 2014 and March 2016 were included. The proportions of patients without a T2D diagnosis who were prescribed LD-L versus the other GLP-1 RAs and within each cohort were computed. Logistic regression models estimated the predictive value of either treatment in those without a T2D diagnosis, controlling for multiple factors. To supplement these findings, administrative claims data were extracted from the Truven Health MarketScan database.

Results: Analyses identified 11,245 patients prescribed LD-L and 4134 patients prescribed other GLP-1 RAs. For the entire study period, Humedica data revealed that patients without T2D accounted for 2.7% of the GLP-1 RA cohort and 17.5% of the LD-L cohort. Multivariable logistic regression analyses identified that patients receiving LD-L were more than 6 times likely to have no indication of T2D relative to patients taking other GLP-1 RAs. Claims data from MarketScan corroborated the Humedica results.

Conclusions: In patients without a T2D diagnosis, LD-L use was significantly greater than that with other GLP-1 RAs within 6 months after approval of HD-L; differences persisted until the end of the study. Increased payer scrutiny of appropriate LD-L use is warranted.

Am J Manag Care. 2018;24:S156-S164

For author information and disclosures, see end of text.

clinical data were extracted from the Humedica Diabetes Integrated Database, which included EMR and claims data for approximately 6.8 million patients between 2014 and 2016. Clinical data were provided by integrated delivery networks that were composed of hospitals, physician offices, small group practices, and multi-specialty practices. Clinical data included medication orders and prescriptions, medications administered, laboratory results, vital signs, body measurements, diagnoses, and procedures. The EMR dataset was linked to Optum claims, which included medical and pharmacy claims data from Optum affiliated health plans. Patients were included if they had data in both datasets based on direct patient matching through a trusted third party, and had diabetes, as defined by meeting 1 or more of the following criteria: diagnosis code for type 1 or type 2 diabetes mellitus (*International Classification of Diseases, Ninth Version [ICD-9]*: 249.0-249.9 and 250.0-250.9); a medication order or prescription claim for an antihyperglycemic medication; a documented glycated hemoglobin (A1C) level of 5.7% or greater; or a fasting plasma glucose of 100 mg/dL or greater.

In the Humedica dataset, we focused on identifying GLP-1 RA prescribing patterns; thus, we limited assessment of GLP-1 RA use to prescription orders. To identify patients whose GLP-1 RA prescriptions were filled and reimbursed by a third-party payer and to improve generalizability, we supplemented findings from the Humedica data with administrative claims data from the Truven Health MarketScan Commercial Claims and Encounters (Commercial) and Medicare Supplemental and Coordination of Benefits (Medicare Supplemental) databases (hereafter referred to as MarketScan). These data included enrollment information, demographic information and inpatient medical, outpatient medical, and outpatient pharmacy claims data from more than 300 large self-insured US employers and more than 25 US health plans.⁵

The Humedica and MarketScan databases satisfy the conditions set forth in Sections 164.514 (a) to (b)iii of the Health Insurance Portability and Accountability Act (HIPAA) of 1996 privacy rule regarding the determination and documentation of statistically de-identified data. Thus, the study did not require external institutional review board or ethics review.

Patient inclusion criteria for the study were: (1) age at least 18 years as of the index date; (2) at least 12 months of database enrollment; (3) at least 1 prescription order (in Humedica) or prescription claim (in MarketScan) for LD-L or another GLP-1 RA issued between January 2014 and December 2016 (for the Humedica Database) or September 2016 (for the MarketScan Database); and (4) had never received GLP-1 RA treatment, as evidenced by no GLP-1 RA prescriptions ordered or filled in the 12 months prior to the index date. (The date of the first such prescription was identified as the index date, and censoring by the date of the most recent update differed between the 2 databases). Patient exclusion criteria were:

(1) receipt of insulin at any time during the study period; (2) a diagnosis of type 1 diabetes (T1D), as determined by diagnosis codes for T1D at any time pre- or postindex date; and (3) evidence of subsequent switching between LD-L and another GLP-1 RA following the index date.

Study variables were measured from the databases using enrollment records, *International Classification of Diseases, Ninth and Tenth Revisions* (depending on calendar time), *Clinical Modification (ICD-9-CM/ICD-10-CM)* codes, Current Procedural Technology 4th Edition (CPT-4) codes, Healthcare Common Procedure Coding System (HCPCS) codes, and National Drug Codes (NDCs), as appropriate. The dependent variable in this study was evidence of T2D diagnosis, which was determined in a hierarchical manner by the presence of at least 1 of the following: an ICD-9 or ICD-10 code for T2D with a diagnosis prior to the index date; prescription order or claim for an oral antihyperglycemic medication at any time; or a fasting plasma glucose level greater than 126 mg/dL or an A1C level greater than 6.5% prior to the index date.

Baseline characteristics captured to describe the study cohorts included demographic data (age, sex, US region of residence), comorbidities, and use of weight loss medications. BMI was also captured from the Humedica data. Diagnosis code searches were identified for any position. NDCs were searched to identify diabetes medications for inclusion/exclusion criteria, and weight loss medications. Additionally, searches of drug name and generic name fields were conducted in addition to NDC searches when identifying index medications for the Humedica analysis. To control for disease severity, values for Charlson Comorbidity Index (CCI)⁶ and Diabetes Complication Severity Index (DCSI) were calculated.⁷

Continuous data were analyzed using a *t* test, and categorical data were analyzed using a χ^2 test for the assessment of demographic characteristics among users of LD-L and other GLP-1 RAs who did not have evidence of T2D. Logistic regression was performed to model the predictive value of either treatment on having no T2D diagnosis, controlled for month of initiation (MOI), age, sex, geographical region, and treatment multiplied by MOI interaction. Differences in the proportions of patients with comorbid conditions between both treatment groups were assessed using Fisher's exact test. Differences in the proportions of patients using concomitant weight loss medications between both treatment groups were assessed using Fisher's exact test.

Results

The study identified 126,178 patients in the Humedica dataset and 245,236 patients in the MarketScan dataset with 1 or more prescription orders or claims for LD-L or another GLP-1 RA between 2014 and 2016 (**Table 1**). Of those in the Humedica dataset, 40,322 met the study inclusion criteria of least a 1-year history in the database, aged at least 18 years, without indication of T1D, and did not

TABLE 2. Baseline Demographics of Patients With GLP-1 RA Use Without an Indication of T2D^a

	Humedica Electronic Medical Record Database					MarketScan Claims Database					
	GLP-1 RA ^b		LD-L		P	GLP-1 RA ^b		LD-L		P	
Patients	376		4651			1531		4497			
Mean (SD) age, years	49	13	42	12	<.001	48	12	47	12	<.001	
Mean (SD) BMI, ^c kg/m ²	36.7	8.5	38.3	8.2	.002						
Sex, n (%)						<.001					.008
Female	267	71.0	3752	74.7		1150	75.1	3525	78.4		
Male	109	29.0	897	17.9		381	24.9	971	21.6		
Region, ^d n (%)						<.001					.055
Midwest/North Central	97	25.8	1758	37.8		214	14.0	655	14.6		
Northeast	89	23.7	797	17.1		187	12.3	639	14.2		
South	154	41.0	1676	36.0		919	60.3	2641	58.8		
West	20	5.3	244	5.3		201	13.2	525	11.7		
Unknown	16	4.3	176	3.8		4	0.3	30	0.7		
Use of Weight Loss Medication, ^e n [%]	13	2.3	118	1.97	.880	21	1.37	61	1.37	>.99	
Comorbidities, n (%)											
Hypertension	139	24.4	1785	32.9	<.001	324	21.2	843	18.7	.040	
Dyslipidemia	119	20.9	1102	20.3	.743	243	15.9	598	13.3	.013	
Hypoglycemia	11	1.9	44	0.80	.017	42	2.7	77	1.7	.014	
Obesity	182	32.0	2767	51.0	<.001	131	8.6	507	11.3	.003	
Chronic kidney disease	8	1.4	59	1.1	.526	13	0.8	39	0.9	>.99	
Mean CCI (SD)	0.64	1.62	0.64	1.27		0.33	0.82	0.27	0.69		
Mean DCSI (SD)	0.33	0.78	0.28	0.69		0.19	0.57	0.16	0.53		

^aPer diagnosis code, medication use, or laboratory data.

^bGLP-1 RA not including liraglutide (LD-L or HD-L).

^cBMI not recorded in the MarketScan data.

^dRegional definitions varied between databases.

^eIncludes weight loss products: phentermine, phentermine and topiramate extended-release, orlistat, lorcaserin, and naltrexone/bupropion extended-release.

BMI indicates body mass index; CCI, Charlson Comorbidity Index; DCSI, Diabetes Complication Severity Index; GLP-1 RA, glucagon-like peptide-1 receptor agonist; LD-L, low-dose liraglutide.

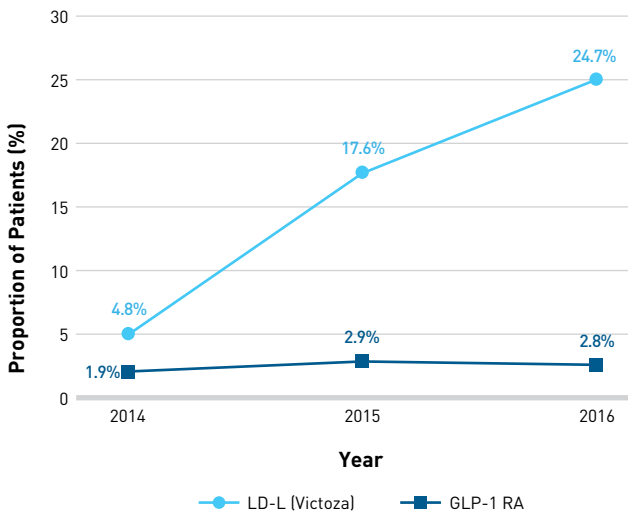
between groups in the proportions of MarketScan patients without a T2D indication were also notable, although not quite as wide as those observed in the Humedica population (Figure 4). Before the launch of HD-L, the proportion of patients without T2D was numerically higher in the LD-L cohort by 0.7% to 5.6%. After launch, the difference increased with a maximum absolute difference of 10.5% .

Multivariable logistic regression analyses identified that patients receiving LD-L in the Humedica cohort from 2014 to 2016 were more than 6 times likely to have no indication of T2D relative to patients receiving other GLP-1 RAs (odds ratio [OR], 6.28; 95% CI, 5.60-7.05) (Table 3). The model also identified that the likelihood of not having an indication of T2D rose by 6% for each subsequent month of the index date for patients given LD-L (OR, 1.06; 95% CI, 1.05-1.06), but index month was not a predictor of T2D in patients given other GLP-1 RAs. Females were 2 times more likely to lack a T2D

indication (OR, 2.11; 95% CI, 1.95-2.28) while the odds of not having T2D declined with age (OR, 0.95; 95% CI, 0.95-0.96). Variations by US region were also identified; in general, patients in the Northeast were more likely and patients in the West were less likely to lack a T2D diagnosis than other regions. The trends were similar by year; however, the odds of patients given LD-L having no indication for T2D relative to other GLP-1 RAs rose from approximately 2-fold (OR, 2.37; 95% CI, 1.62-3.46) in 2014 to over 9-fold (OR, 9.30; 95% CI, 8.04-10.74) in 2016.

In the MarketScan dataset, multivariable logistic regression analyses identified that patients taking LD-L were also more likely to have no indication of T2D relative to patients taking other GLP-1 RAs, although the OR was less than that observed in the Humedica dataset (OR, 2.32; 95% CI, 2.16-2.49) (Table 4). The model identified that the likelihood of not having an indication for T2D rose by 4% for each subsequent month of the index date for patients receiving

FIGURE 1. Proportion of Patients in Humedica Electronic Medical Record Dataset Prescribed LD-L or Another GLP-1 RA Without Indication of T2D by Year, 2014-2016



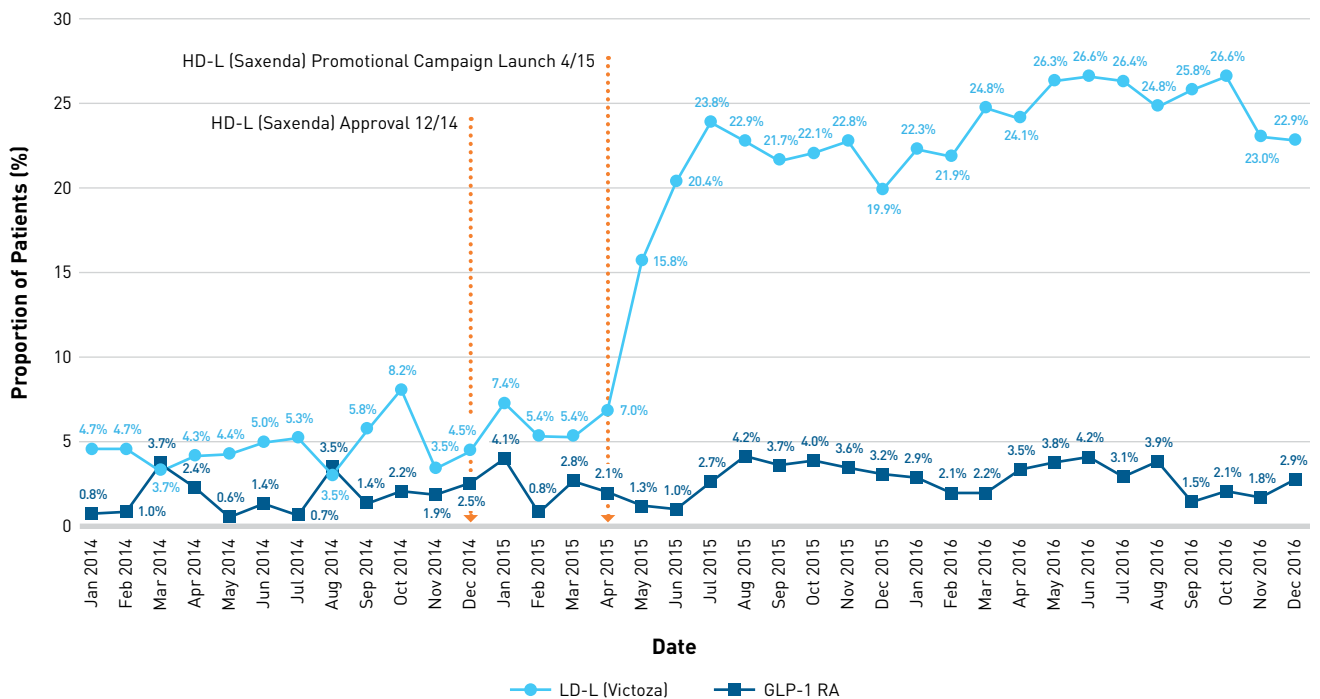
GLP-1 RA indicates glucagon-like peptide-1 receptor agonist; LD-L, low-dose liraglutide; T2D, type 2 diabetes.

LD-L (OR, 1.04; 95% CI, 1.04-1.05) and it was twice as much per month than that observed for patients receiving other GLP-1 RAs (OR, 1.02; 95% CI, 1.02-1.03). Females were 2.5 times more likely to lack a T2D indication (OR, 2.58; 95% CI, 2.42-2.75) and the odds of not having T2D declined with age (OR, 0.94; 95% CI, 0.93-0.94). Variations by US region were also identified; in general, patients in the West were more likely and patients in the North Central region were less likely to not be diagnosed with T2D than other regions. As with the Humedica cohort, the association between other covariates and lack of T2D diagnoses were similar across time. However, the likelihood of patients given LD-L having no indication for T2D relative to patients given other GLP-1 RAs rose from just under 2 times (OR, 1.83; 95% CI, 1.61-2.07) in 2014 to more than 3 times higher (OR, 3.24; 95% CI, 2.92-3.58) in 2016.

Discussion

The prevalence of obesity in the United States continues to increase in both males and females, and for all age groups, including children aged 2 to 19 years. According to data captured by the National Health and Nutrition Examination Survey, in the 2015-2016 survey cohort, nearly 40% of all US adults aged 20 years and older were estimated to have a BMI of at least 30 kg/m².⁸ This figure represents

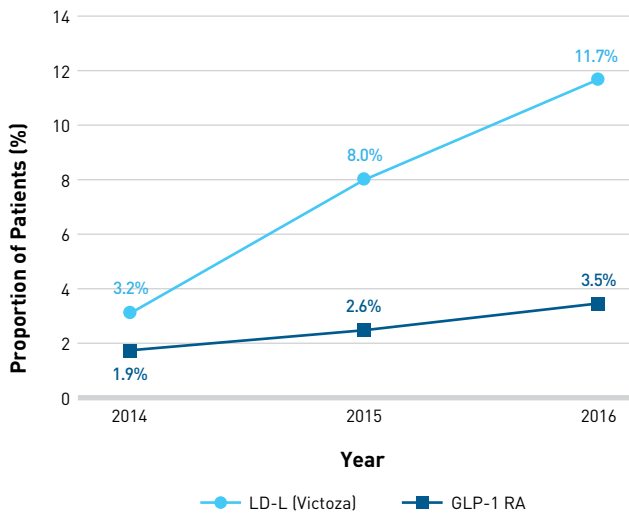
FIGURE 2. Proportion of Patients in the Humedica Electronic Medical Record Database Prescribed LD-L or Another GLP-1 RA Without Indication of T2D By Month, January 2014-December 2016



GLP-1 RA indicates glucagon-like peptide-1 receptor agonist; HD-L, high-dose liraglutide; LD-L, low-dose liraglutide; T2D, type 2 diabetes.

COMPARISON OF LOW-DOSE LIRAGLUTIDE USE VERSUS OTHER GLP-1 RECEPTOR AGONISTS

FIGURE 3. Proportion of Patients in MarketScan Claims Dataset Using LD-L or Another GLP-1 RA Without Indication of T2D by Year, 2014-2016

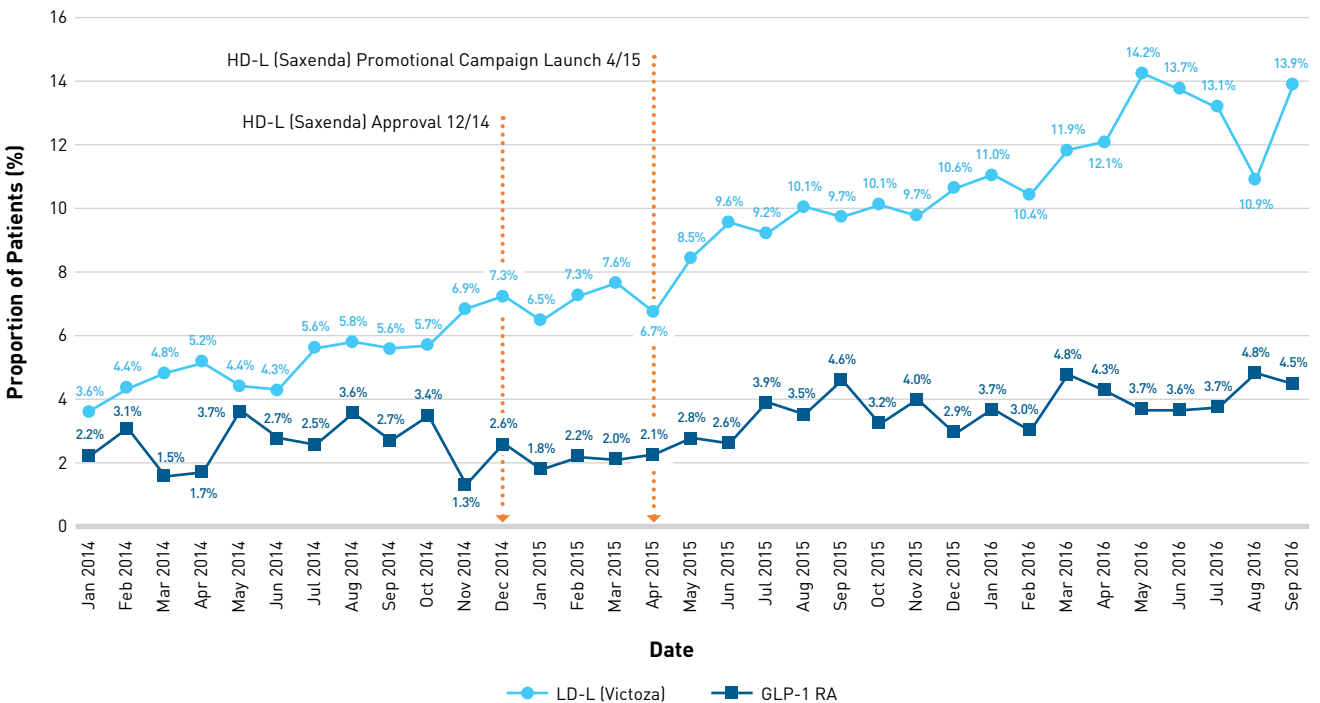


GLP-1 RA indicates glucagon-like peptide-1 receptor agonist; LD-L, low-dose liraglutide; T2D, type 2 diabetes.

a relative increase of nearly 30% since the 1999-2000 cohort, when the obesity prevalence was approximately 30.5%. Guidelines developed by the American Association of Clinical Endocrinologists/American College of Endocrinology and the American College of Cardiology/American Heart Association/The Obesity Society recommend lifestyle interventions, including physical activity, dietary caloric reductions, and behavioral modification, as initial therapy for obese patients.^{9,10} The treatment goal is to prevent obesity-related complications such as diabetes and cardiovascular disease (CVD). Pharmacotherapy is recommended as an additive intervention to lifestyle modifications, because clinical trials have demonstrated that weight loss is greater with the combination compared with either component alone. Phentermine/topiramate extended-release, HD-L, or orlistat are recommended for a 10% weight loss when used with lifestyle interventions to mitigate the risk of developing T2D. Initial treatment combining lifestyle modifications and pharmacotherapy may be warranted in obese patients with documented complications, such as diabetes, dyslipidemia, and CVD. Bariatric surgery is reserved for individuals with severe obesity (BMI ≥ 40 kg/m², ≥ 35 kg/m² with complications).

Despite the significant clinical and economic burdens of obesity on society, challenges to the coverage of lifestyle and

FIGURE 4. Proportion of Patients in the MarketScan Claims Database Using LD-L or Another GLP-1 RA Without Indication of T2D by Month, January 2014-December 2016



GLP-1 RA indicates glucagon-like peptide-1 receptor agonist; HD-L, high-dose liraglutide; LD-L, low-dose liraglutide; T2D, type 2 diabetes.

TABLE 3. Likelihood of Not Having T2D: Patients Initiated on LD-L Versus Other GLP-1 RAs in the Humedica Database, 2014-2016 and by Index Date Year

Variable	2014-2016		2014		2015		2016	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
LD-L (ref: other GLP-1 RA) ^a	6.28	(5.60, 7.05)	2.37	(1.62, 3.46)	5.93	(4.90, 7.18)	9.30	(8.04, 10.74)
LD-L, month of initiation	1.06	(1.05, 1.06)	1.03	(0.99, 1.07)	1.12	(1.10, 1.14)	1.00	(0.99, 1.02)
Other GLP-1 RA, month of initiation	1.01	(0.99, 1.02)	1.04	(0.93, 1.15)	1.06	(1.00, 1.12)	0.98	(0.94, 1.02)
Female (ref: male)	2.11	(1.95, 2.28)	2.34	(1.78, 3.07)	2.02	(1.78, 2.29)	2.11	(1.91, 2.34)
Age (per 1 year)	0.95	(0.95, 0.96)	0.96	(0.95, 0.97)	0.95	(0.95, 0.96)	0.96	(0.95, 0.96)
Midwest vs Northeast	0.49	(0.45, 0.54)	0.71	(0.46, 1.11)	0.57	(0.48, 0.68)	0.44	(0.39, 0.50)
Midwest vs Other/Unknown	0.72	(0.60, 0.87)	0.61	(0.32, 1.18)	0.78	(0.57, 1.06)	0.72	(0.56, 0.91)
Midwest vs South	0.82	(0.77, 0.89)	0.89	(0.67, 1.18)	0.77	(0.68, 0.87)	0.88	(0.79, 0.97)
Midwest vs West	1.13	(0.98, 1.30)	0.31	(0.23, 0.43)	1.17	(0.91, 1.50)	1.76	(1.40, 2.21)
Northeast vs Other/Unknown	1.47	(1.21, 1.78)	0.86	(0.14, 1.79)	1.36	(0.98, 1.88)	1.62	(1.26, 2.09)
Northeast vs South	1.68	(1.52, 1.85)	1.25	(0.82, 1.93)	1.34	(1.14, 1.58)	1.99	(1.75, 2.26)
Northeast vs West	2.30	(1.96, 2.69)	0.44	(0.28, 0.70)	2.05	(1.56, 2.67)	4.00	(3.14, 5.08)
Other/Unknown vs South	1.14	(0.95, 1.37)	1.46	(0.76, 2.78)	0.99	(0.73, 1.33)	1.23	(0.96, 1.57)
Other/Unknown vs West	1.57	(1.26, 1.95)	0.51	(0.26, 0.99)	1.50	(1.04, 2.18)	2.46	(1.79, 3.39)
West vs South	0.73	(0.63, 0.84)	2.86	(2.11, 3.86)	0.66	(0.51, 0.84)	0.50	(0.40, 0.63)

^aTreatment at month 21.92, 6.68, 19.15, and 30.45 for 2014-2016, 2014, 2015, and 2016, respectively.

GLP-1 RA indicates glucagon-like peptide-1 receptor agonist; LD-L, low-dose liraglutide; OR, odds ratio; T2D, type 2 diabetes.

TABLE 4. Likelihood of Not Having T2D: Patients Initiated on LD-L Versus Other GLP-1 RAs in the MarketScan Database, 2014-2016 and by Index Date Year

Variable	2014-2016		2014		2015		2016	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
LD-L (ref: other GLP-1 RA) ^a	2.32	(2.16, 2.49)	1.83	(1.61, 2.07)	2.84	(2.56, 3.15)	3.24	(2.92, 3.58)
LD-L, month of initiation	1.04	(1.04, 1.05)	1.04	(1.03, 1.06)	1.04	(1.02, 1.06)	1.01	(0.99, 1.04)
Other GLP-1 RA, month of initiation	1.02	(1.02, 1.03)	1.01	(0.98, 1.04)	1.04	(1.01, 1.06)	1.00	(0.97, 1.04)
Female (ref: male)	2.58	(2.42, 2.75)	2.36	(2.14, 2.60)	2.72	(2.42, 3.06)	2.74	(2.44, 3.08)
Age (per 1 year)	0.94	(0.93, 0.94)	0.93	(0.93, 0.94)	0.94	(0.93, 0.94)	0.94	(0.93, 0.94)
North Central vs Northeast	0.84	(0.76, 0.93)	0.91	(0.78, 1.07)	0.86	(0.72, 1.02)	0.73	(0.60, 0.89)
North Central vs South	0.73	(0.68, 0.79)	0.73	(0.65, 0.83)	0.88	(0.77, 1.01)	0.60	(0.51, 0.70)
North Central vs Unknown ^b	2.33	(1.64, 3.30)	2.37	(1.65, 3.43)	0.57	(0.13, 2.49)	--	--
North Central vs West	0.71	(0.64, 0.79)	0.66	(0.56, 0.77)	0.85	(0.70, 1.03)	0.67	(0.55, 0.83)
Northeast vs South	0.87	(0.80, 0.94)	0.80	(0.70, 0.91)	1.02	(0.89, 1.18)	0.82	(0.71, 0.95)
Northeast vs Unknown ^b	2.77	(1.96, 3.93)	2.60	(1.80, 3.76)	0.66	(0.15, 2.89)	--	--
Northeast vs West	0.85	(0.76, 0.94)	0.72	(0.61, 0.85)	0.99	(0.82, 1.20)	0.92	(0.75, 1.13)
Unknown vs South ^b	0.31	(0.22, 0.44)	0.31	(0.22, 0.44)	1.56	(0.36, 6.83)	--	--
West vs South	1.02	(0.94, 1.11)	1.13	(0.98, 1.27)	1.04	(0.88, 1.21)	0.90	(0.75, 1.05)
Unknown vs West ^b	0.31	(0.22, 0.43)	0.28	(0.19, 0.40)	1.50	(0.34, 6.63)	--	--

^aTreatment at month 21.90, 3.87, 18.12, and 29.05 for 2014-2016, 2014, 2015, and 2016, respectively.

^bToo few patients with unknown geographic location to provide a meaningful estimate.

GLP-1 RA indicates glucagon-like peptide-1 receptor agonist; LD-L, low-dose liraglutide; OR, odds ratio; T2D, type 2 diabetes.

pharmacologic interventions persist.¹¹ These include the discordance between the magnitude of weight loss desired by patients and providers and that expected from combination approaches, the belief that obesity is the result of individual decisions and is the responsibility of the patient to manage rather than the health-care system, and the paucity of properly trained professionals to adequately support obesity treatment programs. Recent withdrawals of anti-obesity drugs from the US market due to safety signals, the relatively modest expected reductions in body weight (approximately 5%-10%), and the perception that obesity is a life-long condition requiring long-term treatment are specific reasons for payer resistance to coverage of such treatments.^{12,13} These obstacles to reimbursement were likely in place when HD-L was approved for the treatment of obesity in late 2014. Payers were fully managing the GLP-1 RA class at this time due to its presence in the US market for the treatment of T2D (since 2005 when exenatide twice daily [Byetta] was approved and 2010 when LD-L [Victoza] was approved). Due to the favorable reimbursement environment for LD-L, many payers cover it as the preferred GLP-1 RA in T2D for patients who remain uncontrolled on oral antihyperglycemic agents. As such, LD-L has been a leader in the GLP-1 RA market. The lack of coverage for obesity treatments, including HD-L, creates the potential for payers unknowingly reimbursing GLP-1 RAs in general and LD-L in particular for patients who lack the T2D indication but in whom weight loss is desired. Our data support this theory; patients without T2D accounted for 2.6% and 2.7% of the GLP-1 RA cohort and 5.3% and 17.5% of the LD-L cohort in the MarketScan and Humedica datasets, respectively.

The current study results also demonstrate a dramatic and significant increase in LD-L use in individuals without a diagnosis of T2D over the study period that is temporally associated with the FDA approval of HD-L and the promotional campaign for it. The rapid upward trajectory post approval was followed by subsequent tapering that was likely due to the maximization of use in the susceptible population. Concurrently, the trendline for the GLP-1 RAs other than LD-L reflected a minimally perceptible change from baseline, generally indicating a small increase in use of the former in patients without T2D. This finding is consistent with previously reported low rates of GLP-1 RA use in patients without T2D by Nelson et al. In that analysis of more than 10,000 patients taking exenatide twice daily from the GE Centricity database, 96% had at least 1 diagnostic code for T2D.¹⁴

Furthermore, the current study revealed significantly increased adjusted odds of LD-L use without T2D by month of use, in younger patients, and in females. These findings were identified in a national electronic medical records system and corroborated by prescription claims data in a large commercial insurance database. However, the odds of LD-L use without T2D present in the MarketScan analysis was lower than in the Humedica EHR analysis likely as the former

was based solely on prescription claims data. Thus, any insurance rejections for lack of documented indication or daily dosage limits would be reflected in the MarketScan data. Humedica also captures prescription orders, but it does not account for those that are subsequently rejected at the pharmacy.

Besides the economic burden to payers and patients for reimbursement of inappropriate LD-L use, other risks deserve consideration. First, the expected weight loss from liraglutide in doses not studied for this purpose is less than that for the approved higher dose. Second, use of the lower dose exposes patients to unnecessary adverse effects, creating an unfavorable risk-benefit ratio. Lastly, no multiple dosing increments of LD-L provide the 3-mg dose approved for obesity. Several injections of liraglutide 1.2 mg or 1.8 mg would be required, which are more than the single dose per day approved for T2D or obesity, and may add to patient discomfort.

Approval of the GLP-1 RA semaglutide (Ozempic) by the FDA in December 2017 offered the most robust weight loss data of any product thus far in this class, with placebo-adjusted changes in weight of up to -5.6 kg for the higher 1-mg dose in clinical trials.¹⁵ As with the other GLP-1 RAs, the potential for use of semaglutide in patients without T2D exists but may be greater due to the pronounced reduction in weight. Monitoring for appropriate use of GLP-1 RAs remains an important activity for payers with this new addition to the US market.

Limitations

Many limitations must be kept in mind when interpreting these data. Administrative claims data are subject to potential coding errors and are not collected for research purposes; undercoding of comorbidities potentially explains the relatively low CCI and DCSI scores. In addition, these datasets are national but not nationally representative, and are limited to individuals with commercial or employer-sponsored health insurance. Thus, findings from this study, including factors such as regional variations, may not be generalizable to the entire US population, including the populations of individuals who are uninsured or those who have insurance coverage through Medicaid, the Department of Defense, or Veterans Administration. Missing values may result in exclusion from the study or analysis. Finally, observational retrospective analyses such as the present study may be subject to residual confounding due to unmeasured variables.

Conclusions

The use of LD-L (Victoza, 1.2 mg and 1.8 mg) in patients without a T2D diagnosis was 8.8-fold greater than other GLP-1 RAs by prescription orders and 2.4-fold greater by prescription claims within 6 months after US FDA approval of HD-L (Saxenda) and remained substantially greater than the use of the other GLP-1 RAs over the 21-month

evaluation period. Increased payer scrutiny of the use of LD-L is warranted as part of a comprehensive evaluation of reimbursement policies for obesity treatments, including formulary management of the anti-obesity medication class, appropriate daily or weekly dose limits for GLP-1 RAs, application of a point-of-sale step edit to require prior or concurrent treatment with another antihyperglycemic agent, or the requirement of a T2D diagnostic code for GLP-1 RA prescriptions. ■

Acknowledgements

Editorial support was provided by Prime, Knutsford, Cheshire, UK, in accordance with Good Publication Practice guidelines (available at <http://annals.org/aim/fullarticle/2424869/good-publication-practice-communicating-company-sponsored-medical-research-gpp3>) and supported by AstraZeneca. However, ultimate responsibility for opinions, conclusions, and data interpretation lies with the authors.

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Funding source: This study was funded by AstraZeneca.

Author disclosures: Mr Eudicone and Dr Wittbrodt report employment with AstraZeneca; the subject matter of this supplement pertains to an AstraZeneca product. Mr Farahbakhshian reports employment with AstraZeneca Pharmaceuticals at the time of the study and ownership of stock in AstraZeneca. Dr McAdam-Marx reports receipt of research grants from AstraZeneca and Sanofi.

Authorship information: Concept and design (JME, SF, ETW); acquisition of data (ETW); analysis and interpretation of data (JME, SF, CM-M, ETW); drafting of the manuscript (SF, CM-M); critical revision of the manuscript for important intellectual content (JME, CM-M, ETW); administrative, technical, or logistic support (ETW); supervision (ETW).

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