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Off-Label Use of Semaglutide in the United States: Increasing Prevalence, Variability in Prescribing Provider Specialty, and Patient Characteristics

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Background

- Ozempic® (semaglutide) is a glucagon-like peptide-1 receptor agonist (GLP-1 RA) initially approved by the Food and Drug Administration (FDA) in 2017 as maintenance treatment for adults with Type 2 Diabetes (T2D). It has demonstrated efficacy in improving glycemic control and promoting weight loss in patients with T2D.[1]
- In 2021, the FDA approved Wegovy®, a higher dosage formulation of semaglutide specifically indicated for chronic weight management in obese or overweight adults with certain comorbidities.[2] Although both products contain the same active ingredient, semaglutide, they are not designed to be used interchangeably, as they have different dosages, titration schedules, and delivery devices.
- There was a significant increase in the demand for Wegovy® following approval, resulting in global supply shortages and has subsequently led to some providers prescribing Ozempic® as off-label treatment for wight loss.[3]
- While the increase in public interest in GLP-1 RAs and their shortages have garnered significant media attention,[4] the extent to which Ozempic® is being used off-label and the associated consequences for patients with T2D, and those with obesity, remains an ongoing and evolving issue.

Objective

- To quantify the level of off-label usage of Ozempic® (hereafter referred to as generic semaglutide) in the United States, and to examine patient and provider characteristics associated with off-label usage

Methods

Data Source

- The Inovalon MORE^2 closed claims database spanning calendar years 2018 - 2022 was used for the current study.
- The Inovalon MORE^2 closed claims database is a primary-sourced medical and pharmacy claims database consisting of over 160 health plans and covering all major U.S. payer lines of business including Commercial (31% of market), Medicare Advantage (29% of market), and Managed Medicaid (89% of market).

Sample

- Adult patients aged 18+ years prescribed semaglutide were segmented into calendar year-based cohorts for years 2018 – 2022, which required continuous enrollment with medical and pharmacy benefits for the year of interest.
- Semaglutide patients were identified by the presence of ≥ 1 pharmacy claim with a corresponding National Drug Code for the medication during the calendar year.
- Patients were then categorized into cohorts based on the presence of on-label vs. off-label use of the medication:
  - On-label cohort: ≥ 1 claim with a diagnosis of T2D (ICD-10-CM: E11*) anytime during the calendar year
  - Off-label cohort: absence of any claims with an ICD-10-CM diagnosis code of T2D anytime during the calendar year

Analysis

- The prevalence of patients presenting on-label vs. off-label use of semaglutide was assessed each calendar year between 2018 – 2022, and a trend analysis using a two tailed t-statistic derived from the R^2 of the linear trend was conducted to assess a significant change over time.[5]
- Demographics and clinical characteristics were assessed between the on- and off-label use cohorts in calendar-year 2022, while the distribution of provider specialties appearing on the initial semaglutide prescription claim was also assessed among the 2022 calendar year cohorts.
- Independent t-tests and chi-squares were used to assess differences in patient characteristics and provider specialties between on- and off-label use cohorts in 2022.

Off-label usage of Semaglutide **increased 256%** from 2018-2022 ($p < 0.05$). By 2022, **over one in five patients** (22.1%) were prescribed this treatment **off-label.**

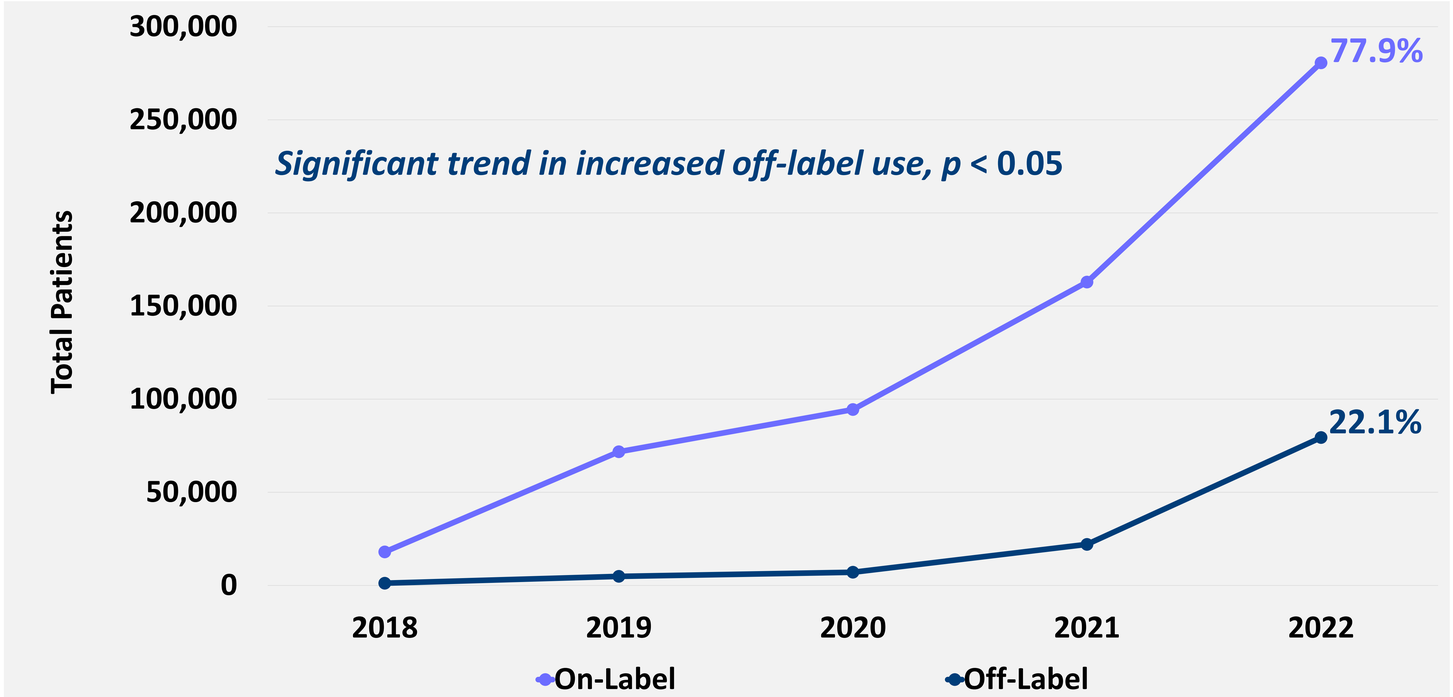

Figure 1. Patient Characteristics

Gender

Off-label patients were more likely to be female: 80.7% vs. 60.1%; $p < 0.05$

Insurance

Off-label patients were more likely to be commercially insured: 69.6% vs. 51.5%; $p < 0.05$

Age

Off-label patients were younger: 45.7 vs. 54.3 years; $p < 0.05$

Obesity

Off-label patients were more likely to have an obesity diagnosis: 64.9% vs. 56.0%; $p < 0.05$

Results

- Between 31.3 and 37.2 million patients qualified for each calendar year sample within the MORE^2 closed claims database **(Table 1)**.
- From 2018 to 2022, the number of patients treated with semaglutide increased from 19,171 to 359,999, which corresponds to a proportional increase of 1,840% (see primary figure).
- Off-label usage of semaglutide increased 256% from 2018-2022 ($p < 0.001$), with 6.2% of patients receiving the treatment off-label in 2018 compared to 22.1% by 2022 (see primary figure).
- In calendar year 2022, there were statistically significant differences in demographic and clinical characteristics between patients receiving semaglutide off-label compared to patients receiving in-label **(Figure 1)**.
- Among patients with physician specialty data, family medicine was among the most common provider type appearing on the initial semaglutide claim for both on-label and off-label cohorts **(Table 2).** Additionally, the off-label cohort was approximately half as likely to receive their medication from an endocrinologist (19.8% vs. 37.9%), were 4-fold more likely to receive it from an obesity medicine specialist (3.3% vs. 0.8%), and 6-fold more likely to receive it from a gastroenterologist (1.2% vs. 0.2%). A diverse mixture of provider specialties unrelated to endocrinology or obesity medicine were observed in larger proportions among the off-label vs. on-label cohorts, including sports medicine (1.0% vs. 0.5%), women's health (0.7% vs. 0.2%), and psychiatry/mental health (0.9% vs. 0.3%).

Table 1. Calendar Year Sample Sizes

	2018		2019		2020		2021		2022	
	N	%	N	%	N	%	N	%	N	%
Yearly Sample	35,427,208	100%	34,936,887	100%	31,271,651	100%	35,048,635	100%	37,243,785	100%
Semaglutide Sample	19,171	0.1%	76,629	0.2%	101,526	0.3%	184,900	0.5%	359,999	1.0%
On-Label	17,982	93.8%	71,763	93.6%	94,445	93.0%	162,874	88.1%	280,599	77.9%
Off-Label	1,189	6.2%	4,867	6.4%	7,081	7.0%	22,026	11.9%	79,402	22.1%

Table 2. Provider Specialties by Label Status Cohorts

Provider Specialty	Off-Label Cohort *Percent*	On-Label Cohort *Percent*
Family	43.9%	37.1%
Endocrinology, Diabetes & Metabolism	19.8%	37.9%
Medical	7.4%	6.4%
Adult Health	3.4%	3.2%
Obesity Medicine	3.3%	0.8%
Cardiovascular Disease	2.7%	1.6%
Primary Care	2.4%	1.6%
Gastroenterology	1.2%	0.2%
Gerontology	1.1%	0.7%
Geriatric Medicine	1.0%	1.4%
Sports Medicine	1.0%	0.5%
Acute Care	0.8%	0.6%
Women's Health	0.7%	0.2%
Nephrology	0.6%	1.1%
Adult Medicine	0.6%	0.7%
Psychiatry	0.5%	0.1%
Pediatric Endocrinology	0.5%	0.4%
Interventional Cardiology	0.5%	0.4%
Surgical	0.5%	0.2%
Psychiatric/Mental Health	0.4%	0.2%

Conclusions

- Results of the present analyses demonstrated that over one in five patients prescribed semaglutide were receiving the medication off-label by 2022.
- Patients receiving it off-label were characteristically different than patients receiving it on-label, as this group was composed of a greater proportion of younger females with commercial insurance presenting an obesity diagnosis.
- The global shortage of GLP-1 RAs is largely attributable to increased off-label use.[6-7] This has spurred the production of counterfeit medications, in addition to patients seeking these treatments at compounding pharmacies. In response, the FDA has issued a warning letter concerning post-market drug safety following reports of adverse events caused by unsafe versions of semaglutide.[8]
- Recent evidence also suggests that GLP-1 RAs taken for weight loss are associated with a higher risk for serious gastrointestinal events such as gastroparesis, pancreatitis, and bowel obstructions compared to other weight loss medications.[9] Although these serious adverse events are rare, the increasing utilization of GLP-1 RAs will still translate into a substantial number of patients at risk of experiencing these events.
- Taken together, payers and providers alike must ensure appropriate guardrails are in place to curtail off-label use, thereby increasing availability of semaglutide for T2D patients in need of additional glycemic control.

References

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