Pharmacoepidemiology and Drug Safety

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BRIEF REPORT

Documentation of Compounded GLP-1 Receptor Agonists in a Large Primary Care Dataset

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ABSTRACT

Purpose: Large telehealth companies and smaller aesthetic medicine providers used compounded semaglutide and tirzepatide to meet consumer demand for these drugs during their shortages. In this study, we estimate the documentation rate of compounded formulations of these drugs in the US primary care and characterize differences between users of compounded and brand-name formulations of these drugs.

Methods: We conducted a retrospective cohort study using data from the American Family Cohort, a nationwide US database of electronic health records from primary care practices, spanning January 1, 2021, to December 31, 2024. Patients with documented semaglutide and/or tirzepatide use were included. Brand-name drug prescriptions were identified from structured data; compounded formulation use was identified from clinical notes. Outcomes included the proportion of patients using compounded formulations and their characteristics.

Results: Among 153 044 included patients (64.0% female, mean age 55.0 years), 8.2% used compounded formulations, which made up an increasing share of semaglutide and tirzepatide use over time. Users of compounded formulations had longer mean therapy durations (compounded only: 10.0 months vs. brand-name only: 7.8 months) and were more likely to be female, non-Hispanic White, nondiabetic, and to live in areas of lower socioeconomic deprivation compared to patients who used only brand-name drugs.

Conclusions: Between January 2021 and December 2024, documentation of compounded semaglutide and tirzepatide use in US primary care settings appeared lower than surveys reporting that approximately 23% of patients using these medications received them from compounders. This suggests that many patients may access these medications outside of coordinated care.

Plain Language Summary: During drug shortages from 2022 to 2024, many patients turned to compounded formulations of popular weight-loss medications semaglutide (Ozempic/Wegovy) and tirzepatide (Mounjaro/Zepbound) made by specialty pharmacies. We analyzed medical records from over 153 000 patients across the United States who used these medications to understand how often primary care doctors knew their patients were using compounded formulations. We found that only 8.3% of patients had documented use of compounded formulations in their medical records, far lower than previous surveys suggesting 23% of users get these medications from nontraditional sources like telehealth companies or aesthetic clinics. Patients using compounded formulations were more likely to be white, female, nondiabetic, and live in wealthier areas compared to those using brand-name versions. They also used the medications for longer periods. This gap between documented use and actual use suggests many patients are getting these medications outside their regular healthcare system, which could create safety concerns since doctors may not know about all the medications their patients are taking or be able to monitor for side effects properly.

Summary

- Little is known about how patients using compounded semaglutide and tirzepatide interacted with sources of comprehensive, primary care.
- Among 153 044 patients in the American Family Cohort who used these drugs, 8.2% used compounded formulations, alone or in combination with brand-name formulations.
- Use of compounded formulations increased over time as a share of all documented use of these drugs.
- Users of compounded formulations were different from users of brand-name versions: they were more likely to be female, non-Hispanic White, nondiabetic, and to live in areas of low socioeconomic deprivation.
- Use of compounded formulations was associated with longer duration of therapy.

1 | Purpose

In 2022, two popular glucagon-like protein-1 receptor agonists (GLP-1 RAs), semaglutide and tirzepatide, were declared by the US Food and Drug Administration (FDA) to be in shortage. Compounding pharmacies satisfied much of the consumer demand that was left unmet [1]. These pharmacies were able to offer consumers lower-priced drugs with a reliable supply by making their compounded formulations out of bulk drugs purchased from third-party laboratories combined with commodity ingredients like saline. Concerns quickly emerged around safety issues from some services offering compounded GLP-1 RAs, including misleading advertising and inadequate patient education [2]. In response to these problems, the American Diabetes Association published a statement recommending against the use of non-FDA-approved compounded GLP-1 RAs [3].

The official shortages for tirzepatide and semaglutide ended in late 2024 and early 2025, respectively, bringing questions about the appropriateness of compounding laws to the fore. Despite the public health importance of compounded GLP-1 RAs over the 3-year shortage, the decentralized nature of their distribution has also left many open questions about how they were used and how often. A survey found that, among the 12% of Americans who report having used GLP-1 RAs, 23% received prescriptions through aesthetic services or telehealth startups [4], almost all of whom offer compounded instead of brand-name GLP-1 RAs.

In this study, we used a large, nationwide primary care database of extracted electronic health records to assess how often compounded GLP-1 RAs are documented and to characterize differences in users of compounded versus brand-name drugs. Our research questions in this descriptive cohort study were twofold. First, are primary care providers aware of their patients' use of compounded GLP-1 RAs? And second, are users of brand-name GLP-1 RAs different from users of compounded formulations?

2 | Methods

2.1 | Data Source

Our data source was the American Family Cohort (AFC), a nationwide collection of electronic health records from primary care practices maintained by the American Board of Family Medicine in collaboration with Stanford University [5]. It contains records of over 5000 providers' encounters with nearly 8 million unique patients in 1331 clinics. The analytic dataset was finalized on March 12, 2025, though reporting lags mean that data was missing from some practices in the final months of 2024.

2.2 | Participants and Exposures

Included patients received either semaglutide or tirzepatide between January 1, 2021 and December 31, 2024. While semaglutide initially entered the US market in 2017, the publication in 2021 of several high-profile clinical weight loss trials substantially increased demand [6]. Tirzepatide entered the US market in 2022, but already had published evidence of its weight loss impacts when it began sales [7].

Brand-name drug prescriptions were available in structured data, but we had to consult clinical notes for mentions of compounded GLP-1 RAs. We iteratively developed a keyword-based search strategy aimed at achieving high positive predictive value. Our final, case-insensitive search strategy was as follows, where "%" indicates wildcard characters: [("%semaglutide%," "%ozempic%," "%wegovy%," "%tirzepatide%," "%mounjaro%," OR "%zepbound%") AND ("%compound%") AND NOT ("% compound %" OR "% compounds %")] OR ("%semaglutide/%" OR "%tirzepatide/%"). Specifically, we excluded the stand-alone terms "compound" and "compounds" because they tended to appear in reference to supplements and in patient education around drug interactions (e.g., "avoid herbal supplements containing compounds like..."). We also found that many providers referred to compounded GLP-1 RAs containing added ingredients using a forward slash without explicit mention of the compounded nature of these drugs (e.g., "semaglutide/B12 injection").

We estimated the positive predictive value of this method by reporting the number of false positives in a manual review of 500 random notes captured by the search strategy.

2.3 | Variables

We captured certain patient- and area-level variables to better characterize the populations using brand-name and/or compounded GLP-1 RAs. Specifically, we included gender, race/ethnicity, age, documented diagnosis of type 2 diabetes, whether the patient's home address is in a state in which Medicaid covers GLP-1 RAs for weight loss [8], and Reproducible Area Deprivation Index [9] of their home address. When available, we also included two population measures of hemoglobin A1c at initial prescription: mean A1c and percent of individuals with an A1c over 6.5%, which is the threshold for a diagnosis of type 2 diabetes.

2.4 | Statistical Methods

We separately evaluated intergroup differences across two stratified populations. First, we assessed differences between brand-name-only users, compounded-only users, and switchers. Second, we assessed differences between subgroups of switchers: those who initially used brand-name drugs, those who initially used compounded formulations, and those who had simultaneous documentation of both sources. We used ANOVA to assess the significance of differences in continuous values and chi-square tests for differences in categorical values.

3 | Results

We identified 153 044 patients who received a prescription for an included GLP-1 RA (Figure S1). Of these, 127 024 used semaglutide and 53 142 used tirzepatide (27 122 used both). Overall, 140 471 (91.8%) used only brand-name drugs, while 6512 (4.3%) used only compounded formulations. Compounded semaglutide was much more common than compounded tirzepatide, both across all GLP-1 RA users, where it outnumbered compounded tirzepatide by approximately 27:1, and within users of each of these drugs (8.1% of exclusive semaglutide users were prescribed compounded formulations versus 2.8% of exclusive tirzepatide users). Usage rates for compounded formulations increased over time as a share of overall GLP-1 RA use (Figure 1). Among the 6061 (3.9%) who had documented use of both drug sources, switching was common, with most (3732, 61.6%) starting a brand-name drug before switching to compounded formulations. Up to 2.5% of patients with documented use of an included medication in a given month switched between drug sources.

We observed significant differences between patients who used brand-name only versus those who used compounded formulations only (Table 1). Compounded-only patients were less likely to have a type 2 diabetes diagnosis—13.8% versus 50.5% for brand-name-only patients—just as they were more likely to be female and non-Hispanic White. Users of compounded formulations were more likely to live in states with Medicaid coverage of GLP-1 RAs for obesity—92.2% of compounded-only users lived in these states, versus 84.1% of brand-name-only users—and lived in areas with significantly lower deprivation (Area Deprivation Index [ADI] of 20.2 for compounded-only users versus 30.2 for brand-name-only users). Notably, brand-name-only patients seemed to use the medications for a shorter duration than those who used compounded formulations alone or switched between drug sources. While individuals who used only brand-name drugs had 7.8 (standard deviation [SD]: 10.5) months between their first and last documentation of medication use, compounded-only users had 10.0 (SD: 12.9) months.

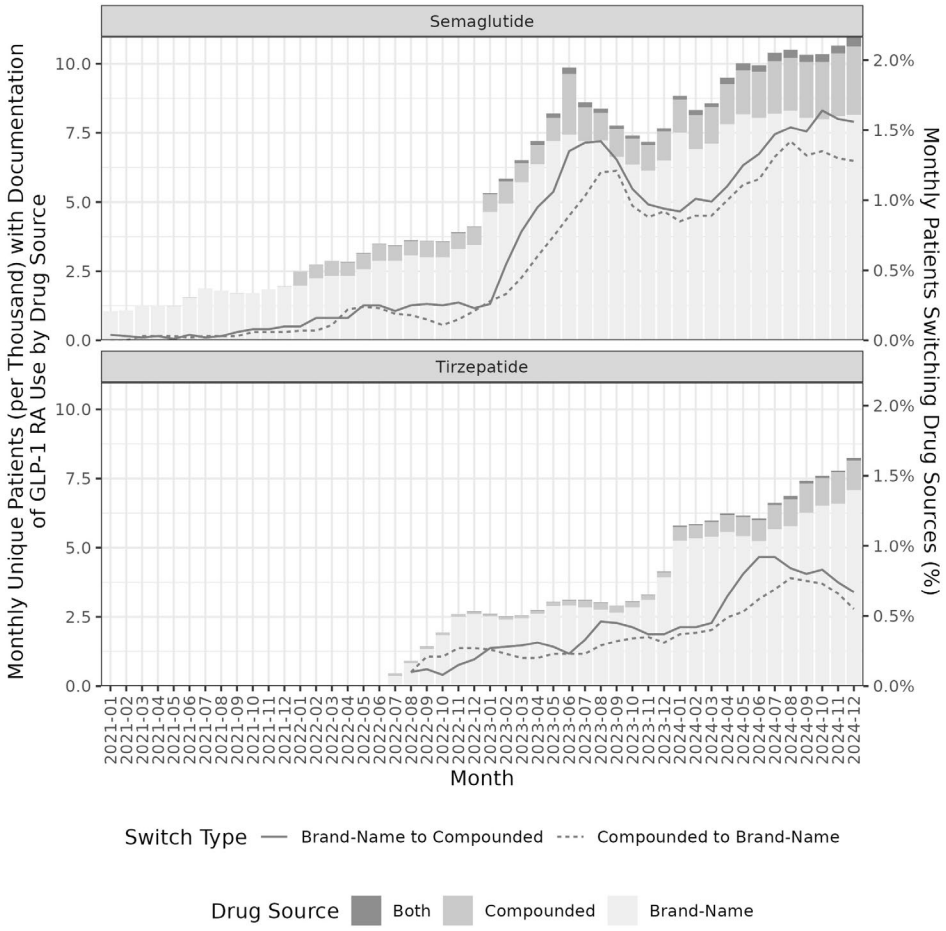

FIGURE 1 | Monthly documentation of semaglutide and tirzepatide by drug source per thousand patients.

TABLE 1 | Characteristics of patients with documented semaglutide and/or tirzepatide use.

				Both compounded and brand name[a]			
	All *n* = 153 044	**Brand-name only *n* = 140 471**	**Compounded only *n* = 6512**	**All *n* = 6061**	**Brand-name first *n* = 3732**	**Compounded first *n* = 1722**	**Simultaneous *n* = 607**
Female, *N* (%)	98 009 (64.0%)	88 674 (63.1%)**	4759 (73.1%)**	4576 (75.4%)	2822 (75.6%)	1297 (75.3%)	457 (75.3%)
Non-Hispanic White, *N* (%)	98 182 (64.2%)	89 691 (63.9%)**	4424 (67.9%)**	4067 (67.1%)	2546 (68.2%)*	1101 (63.9%)*	420 (69.2%)*
Age, mean (SD)	55.0 (13.7)	55.2 (13.5)**	53.4 (18.1)**	51.4 (13.1)	51.3 (13.0)*	51.9 (13.3)*	50.2 (13.5)*
Type 2 diabetes diagnosis, *N* (%)	73 108 (47.8%)	70 927 (50.5%)**	880 (13.5%)**	1301 (21.5%)	821 (22.0%)**	430 (25.0%)**	50 (8.2%)**
Lives in state with Medicaid GLP-1 coverage for obesity, *N* (%)	129 420 (84.6%)	118 100 (84.1%)**	6004 (92.2%)**	5291 (87.3%)	3266 (87.5%)	1494 (86.8%)	531 (87.5%)
Area deprivation index, mean (SD)	29.6 (25.4)	30.2 (25.8)**	20.2 (13.8)**	26.9 (21.6)	29.0 (22.4)**	22.2 (18.6)**	28.2 (22.2)**
Months between first and last documentation, mean (SD)	8.08 (10.7)	7.81 (10.5)**	9.96 (12.9)**	12.4 (11.0)	13.8 (10.5)**	13.3 (11.5)**	1.27 (3.5)**
A1c ≥ 6.5, *N* (%)	29 447 (42.5%) [83 794 (54.8%) missing]	28 443 (44.6%)** [76 739 (54.6%) missing]	426 (14.7%)** [3605 (55.4%) missing]	578 (22.1%) [3450 (56.9%) missing]	374 (22.2%)** [2049 (54.9%) missing]	192 (26.4%)** [994 (57.7%) missing]	12 (2.0%)** [407 (67.1%) missing]
A1c, mean (SD)	7.01 (1.81)	7.09 (1.83)**	5.96 (1.16)**	6.25 (1.45)	6.21 (1.39)**	6.44 (1.62)**	5.89 (1.18)**

[a]Significance testing was done in two separate groups: "brand-name only" versus "compounded only," and "brand-name first" versus "compounded first" versus "simultaneous."
*$p < 0.05$.
**$p < 0.001$.

Among switchers, differences were less pronounced. There were significantly fewer non-Hispanic White patients among those who started with compounded formulations (63.9%) versus brand-name drugs (68.2%). Those who initiated with compounded formulations were also more likely to have a diagnosis of type 2 diabetes (25.0% vs. 22.0% for those starting with brand-name drugs). Similarly to the comparison of brand-name-only to compounded-only users, switchers who started with brand-name drugs lived in areas with higher deprivation levels (ADI of 29.0) compared to those who started with compounded formulations (22.2).

Our manual review of notes captured by our search strategy identified five false positives out of 500 sampled notes, indicating a positive predictive value of 99.0% (95% confidence interval: 97.7%–99.6%).

4 | Conclusion

During the approximately 2 years in which the popular GLP-1 RAs semaglutide and tirzepatide were in shortage, telehealth businesses and aesthetic medicine providers sold compounded formulations of these drugs. Patient demand spiked because of the affordability and accessibility of these formulations. In this study, we present novel data on the documentation of compounded GLP-1 RAs in a large, nationwide cohort of primary care practices. We find that 8.2% of patients who used one of the two most popular GLP-1 RAs have documented use of compounded formulations of these drugs. Relatively high rates of switching between drug sources may highlight widespread access difficulties stemming from supply and affordability issues. Furthermore, we observe significant differences in users of compounded formulations versus those who only use brand-name versions.

The need to search for documentation of compounded drugs in clinical notes highlights the inaccessibility of this data and the fragmented nature of the clinical ecosystem providing these drugs. Without interoperability between compounded drug providers' records and clinical electronic health records, we cannot perform pharmacovigilance to ensure the safety and efficacy of compounded formulations, and clinicians may be unable to coordinate their patients' medication use in alignment with evidence-based care. Notably, our finding that 8.3% of GLP-1 RA users have clinical documentation of compounded drugs is far short of the previously published estimate that 23% of users get prescriptions from someone other than their primary care provider or specialist. These higher estimates likely reflect patients obtaining compounded formulations outside of traditional care; for example, through aesthetic or weight-loss service providers.

Our study has several limitations. First, our keyword search strategy for the identification of compounded GLP-1 RA use prioritized high positive predictive value, likely at the expense of sensitivity: this makes our estimate a conservative lower bound of true prevalence. Second, documentation may not reflect actual use. Since our records are not linked to pharmacy claims, we cannot confirm that patients filled any prescriptions. Third, without prescription end dates or refill data, we relied on documentation gaps to determine end dates for usage since we could not identify when prescriptions had been refilled. Finally, our data came entirely from primary care practices. As such, it is unclear how these conclusions might generalize to other specialties with a potentially high prevalence of GLP-1 RA users such as endocrinology.

In this novel national analysis of primary care documentation data, we used a high positive predictive value method for identifying compounded drug documentation from clinical notes within primary care, discovering compounded GLP-1 RA use in a meaningful minority of patients, at rates far lower than prior survey-based estimates. The discrepancy suggests significant patient receipt of these medications outside of coordinated or traditional primary care, and underscores the pressing need for clearer clinical guidance, regulatory oversight, and interoperable data systems that can bridge gaps between whole-person primary care and newer channels of access to compounded formulations.

Ethics Statement

This research was exempted from human subjects protection by the Stanford University Institutional Review Board.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Complete data are available from the AFC for approved research projects. See up-to-date access requirements at https://www.AmericanFamilyCohort.org.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Figure S1:** Patient usage of select GLP-1 receptor agonists by drug source.