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ORIGINAL ARTICLE

Clinical Trials and Investigations

Changes in weight and glycemic control following obesity treatment with semaglutide or tirzepatide by discontinuation status

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Abstract

Objective: The objective of this study was to characterize changes in body weight and glycated hemoglobin (in those with prediabetes at baseline) through 12 months by obesity pharmacotherapy discontinuation status.

Methods: This retrospective cohort study used electronic health record data from a large health system in Ohio and Florida to identify adults with overweight or obesity without type 2 diabetes who initiated injectable semaglutide or tirzepatide between 2021 and 2023. Treatment discontinuation was defined by a >90-day gap between exhaustion of previous supply and next dispense or end of study follow-up (December 2024) and was classified into early discontinuation (i.e., within 3 months of index date) and late discontinuation (i.e., within 3–12 months).

Results: We identified 7881 patients; 6109 received semaglutide, and 1772 received tirzepatide. A total of 80.8% had low maintenance dosages. Mean (SD) percentage weight reduction at 1 year was 8.7% (9.6%); and it was 3.6% (8.1%) with early discontinuation, 6.8% (9.1%) with late discontinuation, and 11.9% (9.2%) with non-discontinuation ($p < 0.001$). The mean (SD) absolute reduction in percent glycated hemoglobin at 1 year was 0.1 (0.4) with early discontinuation, 0.2 (0.4) with late discontinuation, and 0.4 (0.4) with non-discontinuation ($p < 0.001$).

Conclusions: The average weight reduction in this cohort was lower than that observed in the main phase 3 trials, likely because of higher rates of discontinuation and lower maintenance dosages.

INTRODUCTION

Overweight and obesity are highly prevalent conditions that increase the risk of developing type 2 diabetes (T2D), among other major health complications [1, 2]. In randomized controlled trials, the long-acting glucagon-like peptide-1 receptor agonist (GLP-1RA) semaglutide and glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 dual receptor agonist tirzepatide have demonstrated greater weight reduction in patients with obesity without T2D compared to other obesity medications (OMs) previously approved by the Food and Drug Administration (FDA) [3–5]. The emergence of these new medications has revolutionized obesity care and offers a greater

promise to treat obesity and prevent its downstream health complications.

Outside of randomized clinical trial settings, there is a paucity of long-term data on weight reduction and glycemic control with tirzepatide or semaglutide [6, 7]. In the Semaglutide Treatment Effect in People with Obesity (STEP) 1 trial extension study, patients, on average, regained two-thirds of their lost weight and cardiometabolic improvements reversed following the discontinuation of semaglutide and lifestyle intervention [8]. Similarly, discontinuation of tirzepatide resulted in a substantial regain of lost weight in the SURMOUNT-4 trial, with only 17% of participants maintaining at least 80% of the weight loss achieved [9].

Emerging data suggest that discontinuation with these OMs is common [6, 7, 10, 11], but little is known regarding how discontinuation and its timing affect outcomes in clinical practice. We aimed to characterize the changes in body weight and glycated hemoglobin (HbA1c) in those with prediabetes at baseline through 12 months by obesity pharmacotherapy discontinuation status and identify factors associated with ≥10% weight reduction at 1 year in patients who initiated obesity pharmacotherapy with injectable semaglutide or tirzepatide. Our analyses did not attempt to emulate a target trial but rather to describe these outcomes that were recorded in a regular clinical setting, with an emphasis on characterization by treatment discontinuation status.

Study Importance

What is already known?

- Treatment discontinuation is common among patients receiving tirzepatide or semaglutide for obesity, but little is known regarding its impact on weight reduction and glycemic control in clinical practice.

What does this study add?

- In this cohort study of 7881 patients who received semaglutide or tirzepatide for obesity in a routine clinical setting, treatment discontinuation was associated with attenuated weight reduction and, in patients who had prediabetes at baseline, attenuated glycated hemoglobin reduction at 1 year.
- Factors positively associated with achieving at least 10% weight reduction at 1 year included non-discontinuation of obesity pharmacotherapy or late discontinuation (vs. early), tirzepatide (vs. semaglutide), high dosage of the medication, and female sex.

How might these results change the direction of research or the focus of clinical practice?

- Our findings indicate that treatment discontinuation and use of lower maintenance dosages might reduce the likelihood of achieving clinically meaningful weight reduction in patients who initiate obesity pharmacotherapy with semaglutide or tirzepatide.

METHODS

Study design and setting

Data for this retrospective cohort study were obtained from the Cleveland Clinic electronic health record in Ohio and Florida, including linked Surescripts pharmacy dispensation records [12], from January 1, 2021, to December 31, 2024. The Surescripts prescription data service captures prescriptions paid for through insurance benefits, cash, coupons, or other methods from nearly all major pharmacies and pharmacy benefit managers in the United States [13].

This study was approved by the Cleveland Clinic Institutional Review Board as minimal-risk research using data collected for routine clinical practice, for which the requirement for informed consent was waived. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines were followed.

Study participants

We identified adult patients (aged ≥18 years) who initiated obesity pharmacotherapy with a prescription fill for injectable semaglutide or tirzepatide from January 1, 2021, to December 31, 2023, and had a body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) of at least 30.0 recorded on the date of treatment initiation (index date) or during the latest available primary care visit before the index date or who had BMI of at least 27.0 and one or more weight-related comorbidities (i.e., hypertension, dyslipidemia, obstructive sleep apnea, or cardiovascular disease, including coronary artery disease, atrial fibrillation, heart failure, and stroke). In order to ensure that these were initial fills, we required that they were preceded by at least 6 months of no prescription fills for an FDA-approved OM, including semaglutide, liraglutide, tirzepatide, phentermine-topiramate, naltrexone-bupropion, phentermine, or orlistat. Individuals with T2D at the index date were excluded. The presence of T2D was defined by either an HbA1c level of at least 6.5% (to convert to proportion of total hemoglobin, multiply by 0.01) or the presence of a diagnostic code for T2D (*International Classification of Diseases, Ninth Revision* [ICD-9] code 250.X0 or 250.X2 or *International Statistical Classification of Diseases, Tenth Revision* [ICD-10] code E11.X). Patients who underwent bariatric surgery within 2 years before the initial medication fill and those with incomplete data for prescription fill coverage days were also excluded. We required a baseline weight measurement and at least one follow-up measurement of weight between 30 and 365 days after the index date (Figure 1).

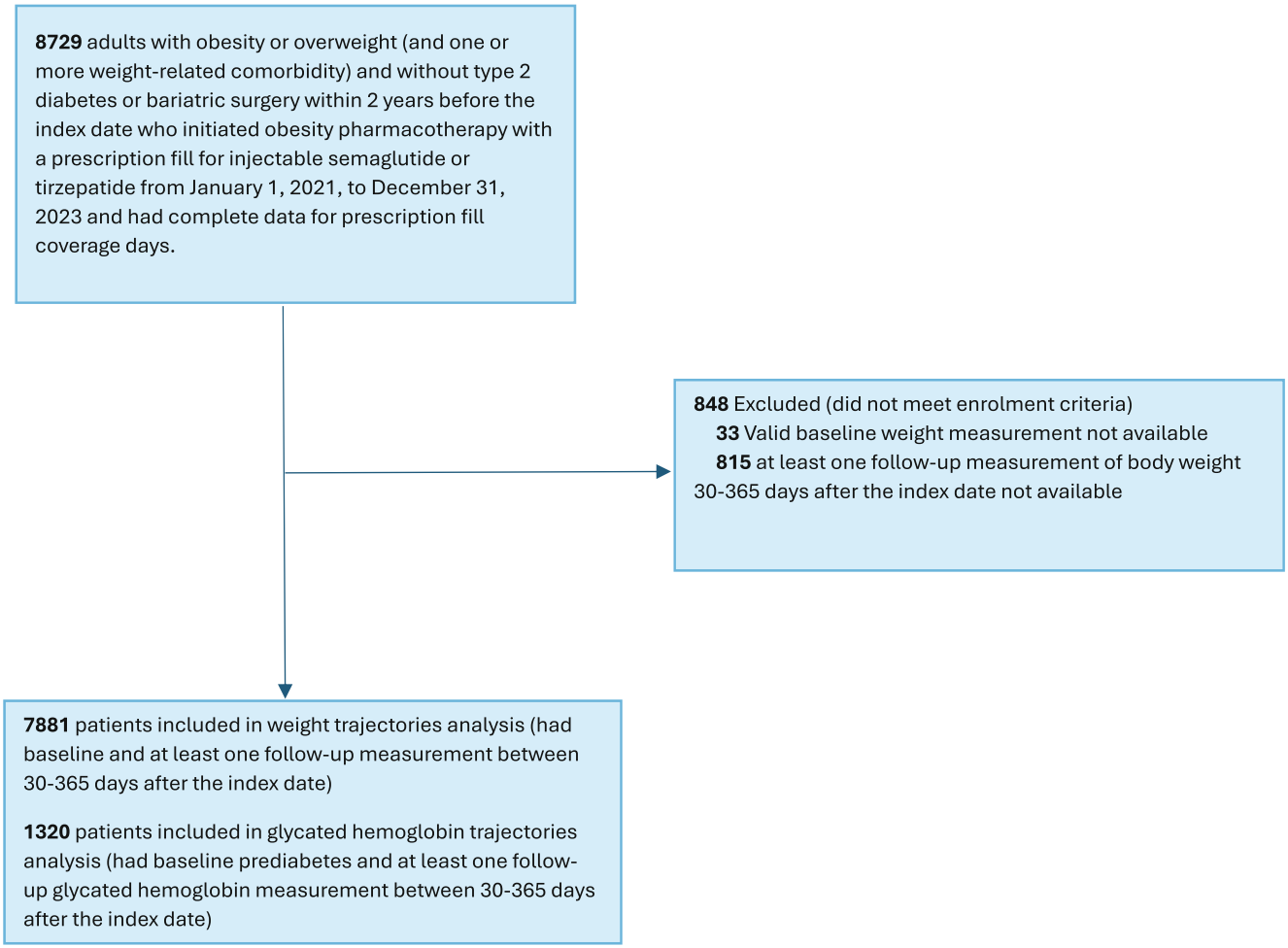

FIGURE 1 Identification of eligible patients for inclusion. [Color figure can be viewed at wileyonlinelibrary.com]

This study captured injectable semaglutide and tirzepatide under the brand names approved by the FDA for obesity (i.e., Wegovy and Zepbound), as well as off-label use of those approved for T2D (i.e., Ozempic and Mounjaro) [14], including all starting and maintenance dosages. Receipt of another OM approved by the FDA (including liraglutide, phentermine-topiramate, naltrexone-bupropion, orlistat, and phentermine) and other agents commonly used for obesity (including metformin, topiramate, bupropion, pramlintide, zonisamide, oral semaglutide, and dulaglutide) during the study follow-up was also captured.

Study variables

The primary outcome measures in this study were trajectories of 1) percentage body weight reduction and 2) in patients with prediabetes at baseline, absolute reduction in HbA1c (percent) from baseline through 12 months. In order to contribute to the analysis for each primary outcome, the patient was required to have baseline data and at least one follow-up measurement from 30 to 365 days from the index date. Follow-up data for primary outcome measures were captured in 1-month increments.

Secondary outcome measures included the following: 1) categorical weight loss of 10% or greater at 1 year, given that sustained weight loss of 10% or more in patients with obesity has a major beneficial impact on obesity-related comorbidities [15]; and 2) in patients with prediabetes at baseline, glycemic status at year 1 (prediabetes, defined by HbA1c between 5.7% and 6.4%; diabetes, i.e., HbA1c ≥ 6.5%; and normoglycemia, i.e., HbA1c ≤ 5.6%). Descriptions of how baseline and 1-year measurements of study outcomes were calculated are presented in Table S1. The end of the follow-up period for outcome ascertainment was December 31, 2024.

Medications were classified by their active agent (i.e., semaglutide vs. tirzepatide). For individuals who switched to a different OM (defined by a different agent in the first vs. last fill within the first year), the active agent was classified based on the index medication. We also created a dichotomous variable for medication maintenance dosage with semaglutide 1.7, 2.0, or 2.4 mg and tirzepatide 10.0, 12.5, or 15.0 mg classified as high, and all other dosages classified as low. The maintenance dosage was determined by the prescription with the largest number of covered days filled within the first year.

Discontinuation of obesity pharmacotherapy at 1 year was defined as a gap of greater than 90 days between exhaustion of

previous supply and next dispense or between exhaustion of last supply and end of study follow-up [16]. Patients who switched between injectable forms of semaglutide, tirzepatide, or a different OM (including semaglutide, tirzepatide, liraglutide, phentermine-topiramate, naltrexone-bupropion, orlistat, phentermine, metformin, topiramate, bupropion, pramlintide, zonisamide, and dulaglutide) but had a gap of less than 90 days were not considered to have discontinued obesity pharmacotherapy. We grouped patients who discontinued pharmacotherapy into those who discontinued early (within 3 months of the index date) and late (within 3–12 months).

Sociodemographic variables, including patients' age, sex, race and ethnicity, primary payer type, and Area Deprivation Index (ADI) quartile based on census block group neighborhood-level data [17], were recorded from the primary care visit closest to the index date. Data on sex and race and ethnicity were based on patient self-report using fixed categories. Race was categorized into Asian, Black, White, and other groups (including American Indian or Alaska Native, multiracial, Native Hawaiian or other Pacific Islander, and other). Ethnicity was grouped into Hispanic and non-Hispanic categories. Data on race and ethnicity were included because they could be associated with both exposure and study outcomes. ADI percentiles were based on a nationwide ranking from 1 to 100, in which ADI with a ranking of 1 indicates the lowest level of disadvantage [17]. Age-adjusted Charlson Comorbidity Index was also captured from the electronic health record [18].

Statistical analysis

Mean and SD was used to summarize normally distributed data, and median and IQR was used for data that were not normally distributed. Pearson χ^2 tests, Fisher exact tests, Wilcoxon rank sum tests, and Kruskal-Wallis rank sum tests were used for standard group comparisons [19]. In order to construct the weight trajectory graphs, we summarized the mean percent change from baseline in 1-month increments by group across all patients who had a weight measurement in a given month; these data are presented unadjusted. A similar approach was used for HbA1c trajectory analyses.

A multivariable logistic regression model was used to examine the association of ≥10% weight loss at 1 year with the following independent variables: obesity therapy discontinuation status at 1 year, medication, dosage, age, sex, race and ethnicity, primary payer type, ADI quartile, baseline BMI, and age-adjusted Charlson Comorbidity Index. In the multivariable model, individuals with unknown race and ethnicity, primary payer type, or ADI quartile were included as a separate category. All statistical testing was two-tailed with $\alpha = 0.05$ used to determine statistical significance. All analyses were conducted in R version 4.4.0 (R Project for Statistical Computing).

In order to assess the robustness of the identified associations between treatment discontinuation, medication, and changes in body weight, we conducted sensitivity analyses by excluding 1) patients who had a different OM in the first versus last fill within the first year, as well as 2) those with a prescription fill for an FDA-approved OM up to 12 months prior to the index fill of semaglutide or tirzepatide from the weight trajectory analyses and the multivariable logistic regression models.

RESULTS

This study included 7881 patients who filled an initial prescription for injectable semaglutide (6109) or tirzepatide (1772) from January 1, 2021, to December 31, 2023. Mean age was 51.3 (SD 13.4) years, mean baseline weight was 112.2 (SD 25.7) kg, and mean baseline BMI was 39.7 (SD 7.8). A total of 5923 patients (75.2%) were female, and 1958 (24.8%) were male. In terms of race and ethnicity, 51 patients (0.6%) were Asian, 1217 (15.4%) were Black, 6150 (78.0%) were White, and 297 (3.8%) were of other race; 477 (6.1%) were of Hispanic ethnicity. Most patients were privately insured (5810 [73.7%]), and 1909 (24.2%) resided in an area in the most disadvantaged ADI quartile. Most patients (6370 [80.8%]) had a low maintenance dosage, including 81.4% of those taking semaglutide and 78.9% of those taking tirzepatide (Table 1).

During the first year, 21.6% (1318) of patients who initiated treatment with semaglutide and 16.4% (291) of those with tirzepatide discontinued obesity pharmacotherapy early, whereas 31.4% (1917) with semaglutide and 34.1% (605) with tirzepatide discontinued later; 47.0% (2874) and 49.4% (876) of patients on semaglutide and tirzepatide, respectively, did not discontinue (Table 1). Figure 2 presents the cumulative incidence of obesity pharmacotherapy discontinuation by index medication. Of the total of 1609 patients who discontinued obesity pharmacotherapy early, 230 (14.3%) later had another fill for either semaglutide or tirzepatide through the end of the first year. Of the 2522 patients who discontinued late, the corresponding number was 218 (8.6%).

Reduction in body weight

Figure 3 presents the mean percent change in weight by index medication and treatment discontinuation status from initiation of medication use during follow-up. The median patient had weight measurements recorded in 4 separate months (IQR, 2–6) during the first year; that number was 5 (IQR, 3–6) among patients who did not discontinue obesity pharmacotherapy, 4 (IQR, 2–6) among those who discontinued late, and 3 (IQR, 2–6) among those who discontinued early.

Among those with available 1-year weight measurements ($n = 6477$), the mean (SD) percentage weight reduction at 1 year was 8.7% (9.6%; 95% confidence interval [CI]: 8.5%–9.0%). Mean (SD) weight reduction was 3.6% (8.1%; 95% CI: 3.2%–4.1%) and 6.8% (9.1%; 95% CI: 6.3%–7.2%) for those who discontinued obesity pharmacotherapy early and late, respectively. Those who did not discontinue treatment lost a mean (SD) 11.9% (9.2%; 95% CI: 11.6%–12.2%) of weight ($p < 0.001$). In terms of the index medication, mean (SD) weight reduction at 1 year was 7.7% (9.0%; 95% CI: 7.4%–7.9%)

TABLE 1 Characteristics of patients who initiated treatment with injectable semaglutide or tirzepatide for obesity during 2021 to 2023 ($N = 7881$)

	Overall, no. (%) ($N = 7881$)	Semaglutide, no. (%) ($n = 6109$)	Tirzepatide, no. (%) ($n = 1772$)	*p* value[a]
Age, mean (SD), y	51.3 (13.4)	51.8 (13.4)	49.5 (12.9)	<0.001
Sex				0.3
Male	1958 (24.8%)	1534 (25.1%)	424 (23.9%)	
Female	5923 (75.2%)	4575 (74.9%)	1348 (76.1%)	
Race				0.2
Asian	51 (0.6%)	37 (0.6%)	14 (0.8%)	
Black	1217 (15.4%)	973 (15.9%)	244 (13.8%)	
Other[b]	297 (3.8%)	228 (3.7%)	69 (3.9%)	
White	6150 (78.0%)	4749 (77.7%)	1401 (79.1%)	
Not reported	166 (2.1%)	122 (2.0%)	44 (2.5%)	
Ethnicity				>0.9
Hispanic	477 (6.1%)	366 (6.0%)	111 (6.3%)	
Non-Hispanic	7180 (91.1%)	5569 (91.2%)	1611 (90.9%)	
Not reported	224 (2.8%)	174 (2.8%)	50 (2.8%)	
Primary payer				<0.001
Private	5810 (73.7%)	4478 (73.3%)	1332 (75.2%)	
Traditional Medicare	193 (2.4%)	172 (2.8%)	21 (1.2%)	
Medicare Advantage	966 (12.3%)	786 (12.9%)	180 (10.2%)	
Medicaid	724 (9.2%)	524 (8.6%)	200 (11.3%)	
Self-pay/other	174 (2.2%)	137 (2.2%)	37 (2.1%)	
Unknown	14 (0.2%)	12 (0.2%)	2 (0.1%)	
ADI quartile[c]				0.02
1–25	1027 (13.0%)	767 (12.6%)	260 (14.7%)	
26–50	2241 (28.4%)	1708 (28.0%)	533 (30.1%)	
51–75	2595 (32.9%)	2036 (33.3%)	559 (31.5%)	
76–100	1909 (24.2%)	1514 (24.8%)	395 (22.3%)	
Unknown	109 (1.4%)	84 (1.4%)	25 (1.4%)	
Baseline weight, mean (SD), kg	112.2 (25.7)	112.4 (25.8)	111.5 (25.3)	0.1
Baseline BMI, mean (SD), kg/m^2	39.7 (7.8)	39.8 (7.8)	39.4 (7.7)	0.04
Baseline glycated hemoglobin, mean (SD), %	5.5 (0.4)	5.6 (0.4)	5.5 (0.4)	<0.001
Unknown	3320 (42.1)	2527 (41.4)	793 (44.8)	
Charlson Comorbidity Index, median (IQR)	2.0 (1.0–4.0)	2.0 (1.0–4.0)	2.0 (1.0–4.0)	<0.001
Obesity pharmacotherapy discontinuation status[d]				<0.001
Early discontinuation	1609 (20.4%)	1318 (21.6%)	291 (16.4%)	
Late discontinuation	2522 (32.0%)	1917 (31.4%)	605 (34.1%)	
Never	3750 (47.6%)	2874 (47.0%)	876 (49.4%)	
Medication dosage[e]				0.02
High	1511 (19.2%)	1137 (18.6%)	374 (21.1%)	
Low	6370 (80.8%)	4972 (81.4%)	1398 (78.9%)	
Number of antiobesity agents trialed,[f] median (IQR)	2.0 (1.0–2.0)	2.0 (1.0–2.0)	1.0 (1.0–2.0)	0.2
Year of treatment initiation				<0.001
2021	496 (6.3%)	496 (8.1%)	0 (0.0%)	

(Continues)

TABLE 1 (Continued)

	Overall, no. (%) (*N* = 7881)	Semaglutide, no. (%) (*n* = 6109)	Tirzepatide, no. (%) (*n* = 1772)	*p* value[a]
2022	2620 (33.2%)	1798 (29.4%)	822 (46.4%)	
2023	4765 (60.5%)	3815 (62.4%)	950 (53.6%)	

Abbreviation: ADI, Area Deprivation Index.

[a]Based on Pearson χ^2 test, Fisher exact test, or Wilcoxon rank sum test.

[b]Other race included American Indian or Alaska Native, multiracial, Pacific Islander, and other.

[c]ADI quartiles were structured by ranking ADI from low to high nationally, in which ADI with a ranking of 1 indicates the lowest level of disadvantage.

[d]Discontinuation of obesity pharmacotherapy at 1 year was defined as a greater than 90-day gap between exhaustion of previous supply and next dispense or between exhaustion of last supply and end of study follow-up. Patients who switched between injectable forms of semaglutide, tirzepatide, or other antiobesity agents but had a gap of less than 90 days were not considered to have discontinued their obesity pharmacotherapy. We grouped patients who discontinued obesity pharmacotherapy into those who discontinued early (i.e., within 3 months of index date) and late (i.e., within 3–12 months of index date).

[e]Medication maintenance dosages of semaglutide 1.7, 2.0, or 2.4 mg and tirzepatide 10.0, 12.5, or 15.0 mg were classified as high, and all other dosages as low.

[f]Including semaglutide, tirzepatide, liraglutide, phentermine-topiramate, naltrexone-bupropion, orlistat, phentermine, metformin, topiramate, bupropion, pramlintide, zonisamide, and dulaglutide.

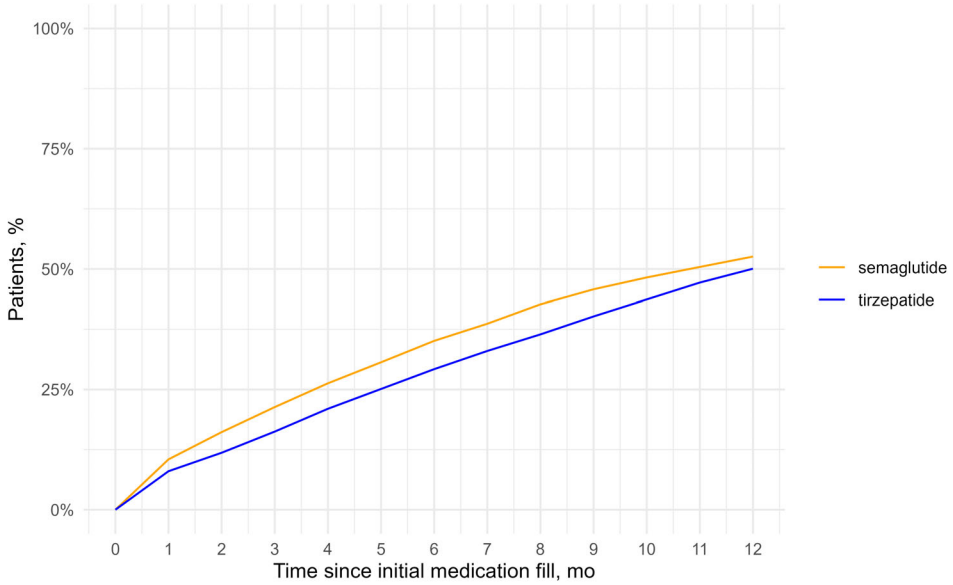

FIGURE 2 Cumulative incidence of obesity pharmacotherapy discontinuation by index medication. A total of 7881 patients contributed to this analysis. Discontinuation of obesity pharmacotherapy was defined as a greater than 90-day gap between exhaustion of previous supply and next dispense or between exhaustion of last supply and end of study follow-up. Patients who switched between injectable forms of semaglutide, tirzepatide, or other obesity medications but had a gap of less than 90 days were not considered to have discontinued obesity pharmacotherapy. [Color figure can be viewed at wileyonlinelibrary.com]

with semaglutide and 12.4% (10.5%; 95% CI: 11.9%–12.9%) with tirzepatide. Mean percentage weight reduction at 1 year by medication and obesity pharmacotherapy discontinuation status is presented in Table S2. Among patients who did not discontinue obesity pharmacotherapy at year 1 (*n* = 3293 with available data at 1 year), the mean (SD) percentage reduction in weight was 10.9% (8.7%; 95% CI: 10.5%–11.2%) with semaglutide and 15.3% (10.0%; 95% CI: 14.6–16.0) with tirzepatide. Those who did not discontinue and were on a high maintenance dosage of an OM (*n* = 967 with available weight at 1 year) lost a mean (SD) 14.7% (9.2%; 95% CI: 14.1%–15.3%) of weight at 1 year, including 13.7% (8.3%; 95% CI: 13.1%–14.3%) with semaglutide and 18.0% (10.8%; 95% CI: 16.6%–19.5%) with tirzepatide. The cumulative distribution of categorical weight reduction at 1 year by obesity pharmacotherapy discontinuation status and medication is shown in Tables S3 and S4 and Figures S1 and S2.

In the multivariable model, the odds of achieving ≥10% weight loss at 1 year were higher in patients who did not discontinue pharmacotherapy (vs. early discontinuation, adjusted odds ratio [AOR], 4.68; 95% CI: 3.97–5.55) or who discontinued late (vs. early, AOR, 1.74; 95% CI: 1.45–2.08), received tirzepatide (vs. semaglutide,

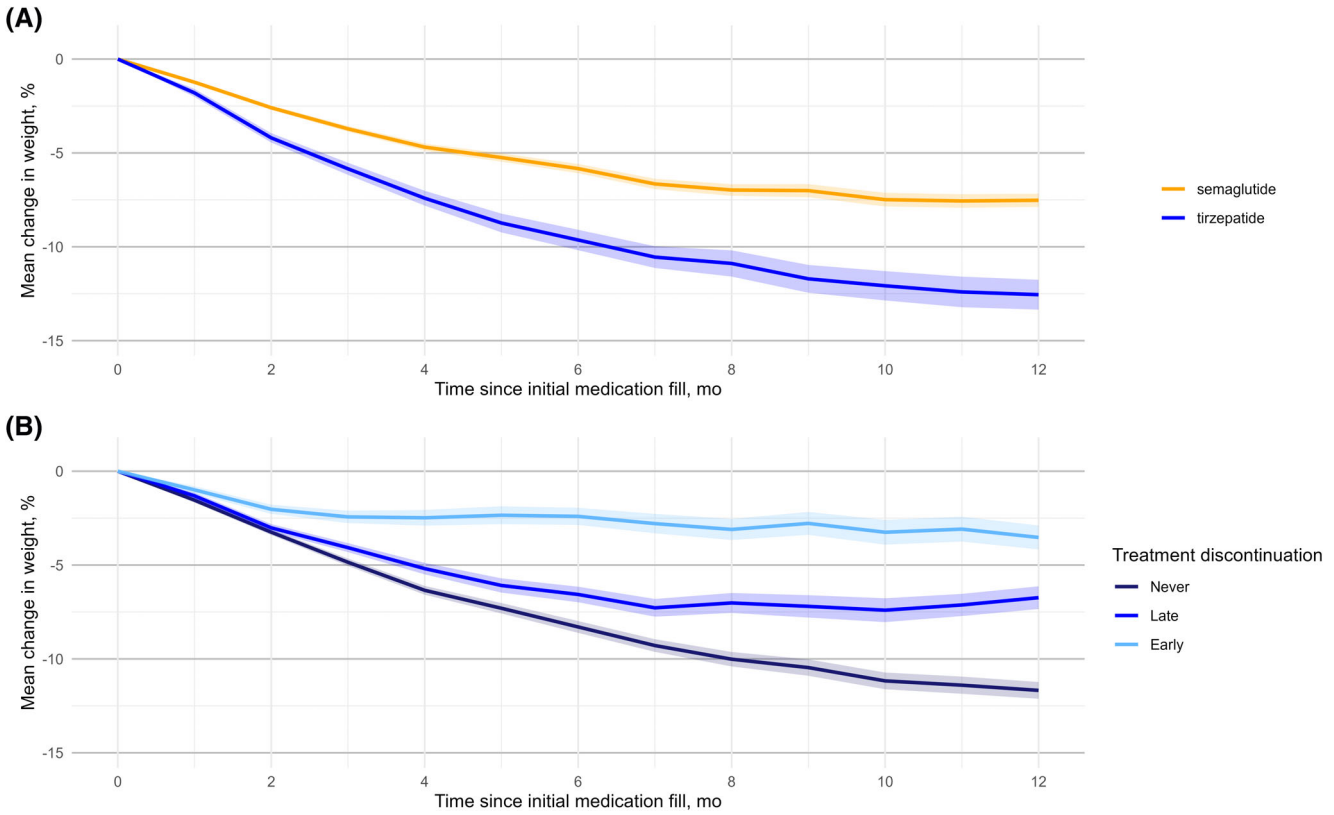

FIGURE 3 Mean percentage weight reduction by (A) index medication and (B) obesity pharmacotherapy discontinuation status from initiation of the medication. A total of 7881 patients contributed to this analysis. Available weight measurements were captured from baseline through 12 months in 1-month increments. Discontinuation of obesity pharmacotherapy at 1 year was defined as a greater than 90-day gap between exhaustion of previous supply and next dispense or between exhaustion of last supply and end of study follow-up. Patients who switched between injectable forms of semaglutide, tirzepatide, or other obesity medications but had a gap of less than 90 days were not considered to have discontinued obesity pharmacotherapy. Shaded areas indicate 95% CI. [Color figure can be viewed at wileyonlinelibrary.com]

AOR, 2.46; 95% CI: 2.16–2.80), had a high dosage of the medication (vs. low, AOR, 2.39; 95% CI: 2.08–2.75), and were female (vs. male, AOR, 1.86; 95% CI: 1.62–2.13; Table 2).

These findings were supported by the sensitivity analyses that excluded 1) patients who had a different OM in the first versus last fill within the first year and 2) those with a prescription fill for an FDA-approved OM up to 12 months prior to the index fill of semaglutide or tirzepatide (Tables S5–S7 and Figures S3 and S4).

Change in glycemic status among those with prediabetes

Figure 4 presents the mean absolute change in HbA1c in patients with prediabetes at baseline by treatment discontinuation status and medication during follow-up.

Among those with baseline prediabetes and 1-year HbA1c measurements ($n = 895$), the mean (SD) absolute reduction in HbA1c at 1 year was 0.3 (0.4; 95% CI: 0.3–0.3); it was 0.1 (0.4; 95% CI: 0.0–0.2) in those who discontinued obesity pharmacotherapy early, 0.2 (0.4; 95% CI: 0.1–0.2) in those who discontinued late, and 0.4 (0.4; 95% CI: 0.4–0.5) in those who did not discontinue ($p < 0.001$). In terms of the index medication, mean (SD) HbA1c reduction at 1 year was 0.3 (0.4; 95% CI: 0.3–0.3) with semaglutide and 0.4 (0.4; 95% CI: 0.3–0.4) with tirzepatide. Of those 895 patients, 53.9% (482) converted to normoglycemia at 1 year, including 33.1% (56) of those who discontinued early, 41.0% (102) of those who discontinued late, and 67.9% (324) of those who did not discontinue treatment; only 3.4% (30) progressed to T2D, including 6.5% (11) who discontinued early, 4.4% (11) who discontinued late, and 1.7% (8) who never discontinued ($p < 0.001$).

DISCUSSION

In this large cohort of patients who initiated obesity pharmacotherapy with injectable semaglutide or tirzepatide, patients lost an average of 8.7% of body weight at 1 year. Weight reduction and change in HbA1c varied significantly by treatment discontinuation status. In the multivariable analysis, patients who did not discontinue obesity pharmacotherapy or discontinued late (vs. early), received tirzepatide (vs. semaglutide), had a high dosage of the medication (vs. low), and were female (vs. male) had significantly higher odds of achieving 10% or greater weight reduction at 1 year.

As clinicians and policy makers pay closer attention to the issue of treatment discontinuation of these highly effective medications, relatively little real-world data are available on the relationship between discontinuation and long-term weight outcomes [10, 20, 21]. In this study, 20.4% of patients discontinued their obesity pharmacotherapy early, and 32.0% discontinued late, which is considerably higher than the rates of discontinuation at ~1 year in the main phase 3 trials (including 17.1% for semaglutide 2.4 mg injection [STEP 1] and 14.3%–16.4% for tirzepatide 5–15 mg [SURMOUNT-1] [3, 4]). These discontinuation rates are also lower than previously reported rates based on claims data (64.8% at 1 year), albeit for a different combination of OMs [11]. High out-of-pocket costs, insurance coverage-related issues, adverse effects, and medication supply shortages could explain the higher discontinuation rates in this study compared to clinical trial settings, warranting future studies on determinants of novel OM discontinuation [10, 11, 22].

The average weight reduction in this cohort was lower than that observed in the main phase 3 trials of semaglutide 2.4 mg (STEP 1) and tirzepatide 5 to 15 mg (SURMOUNT-1), in which 14.9% and 15.0% and 20.9% weight reduction, respectively, was demonstrated in patients with overweight or obesity (without T2D) plus a lifestyle intervention [3, 4]. This is likely because of higher rates of discontinuation and lower maintenance dosages of these OMs in our cohort; patients who did not discontinue obesity pharmacotherapy and received a high maintenance dosage had comparable weight reduction, including 13.7% with semaglutide and 18.0% with tirzepatide. Our findings concerning the real-world use patterns of these medications and associated clinical outcomes could inform the decisions of health care providers and their patients on the role of treatment discontinuation and maintenance dosage in achieving clinically meaningful weight reductions.

Interestingly, although patients who discontinued obesity pharmacotherapy lost significantly less weight compared to those who

TABLE 2 Factors associated with ≥10% weight reduction at 1 year ($n = 6477$)

	AOR (95% CI)[a]	*p* value
Medication		<0.001
Semaglutide	Reference	
Tirzepatide	2.46 (2.16–2.80)	
Medication dosage[b]		<0.001
Low	Reference	
High	2.39 (2.08–2.75)	
Baseline BMI (1-unit increase)	0.99 (0.99–1.00)	0.07
Obesity pharmacotherapy discontinuation status[c]		<0.001
Early discontinuation	Reference	
Late discontinuation	1.74 (1.45–2.08)	
Never	4.68 (3.97–5.55)	
Age (1-y increase)	0.99 (0.99–1.00)	0.005
Sex		<0.001
Male	Reference	
Female	1.86 (1.62–2.13)	
Race		<0.001
Asian	0.78 (0.36–1.60)	
Black	0.67 (0.57–0.79)	
Other[d]	0.77 (0.55–1.09)	
White	Reference	
Not reported	1.22 (0.80–1.86)	
Ethnicity		0.04
Hispanic	0.70 (0.53–0.92)	
Non-Hispanic	Reference	
Not reported	0.94 (0.64–1.36)	
Charlson Comorbidity Index (1-unit increase)	1.01 (0.99–1.04)	0.3
ADI quartile[e]		0.3
1–25	Reference	
26–50	1.01 (0.84–1.21)	
51–75	0.92 (0.76–1.11)	
76–100	0.88 (0.72–1.07)	
Unknown	0.70 (0.40–1.19)	
Primary payer		0.005
Private	Reference	
Traditional Medicare	1.20 (0.84–1.71)	
Medicare Advantage	0.94 (0.78–1.13)	
Medicaid	0.67 (0.54–0.82)	
Self-pay or other	0.96 (0.66–1.40)	
Unknown	1.71 (0.41–6.30)	

Abbreviations: ADI, Area Deprivation Index, AOR, adjusted odds ratio.
[a]Based on a multivariable logistic regression model with the following independent predictors: medication, dosage, obesity therapy discontinuation status at 1 year, age, sex, race and ethnicity, primary payer type, ADI quartile, baseline BMI, and age-adjusted Charlson Comorbidity Index.
[b]Medication maintenance dosage was dichotomized with semaglutide 1.7, 2.0, or 2.4 mg and tirzepatide 10.0, 12.5, or 15.0 mg classified as high, and all other dosages classified as low. The maintenance dosage was determined by the medication fills with the largest number of covered days within the first year.
[c]Discontinuation of obesity pharmacotherapy at 1 year was defined as a greater than 90-day gap between exhaustion of previous supply and next dispense or between exhaustion of last supply and end of study follow-up. Patients who switched between injectable forms of semaglutide, tirzepatide, or other obesity medications but had a gap of less than 90 days were not considered to have discontinued obesity pharmacotherapy. We grouped patients who discontinued obesity pharmacotherapy into those who discontinued early (i.e., within 3 months of index date) and late (i.e., within 3–12 months).
[d]Other race and ethnicity included American Indian or Alaska Native, multiracial, Pacific Islander, and other.
[e]ADI quartiles were structured by ranking ADI from low to high nationally, in which a ranking of 1 indicates the lowest level of disadvantage.

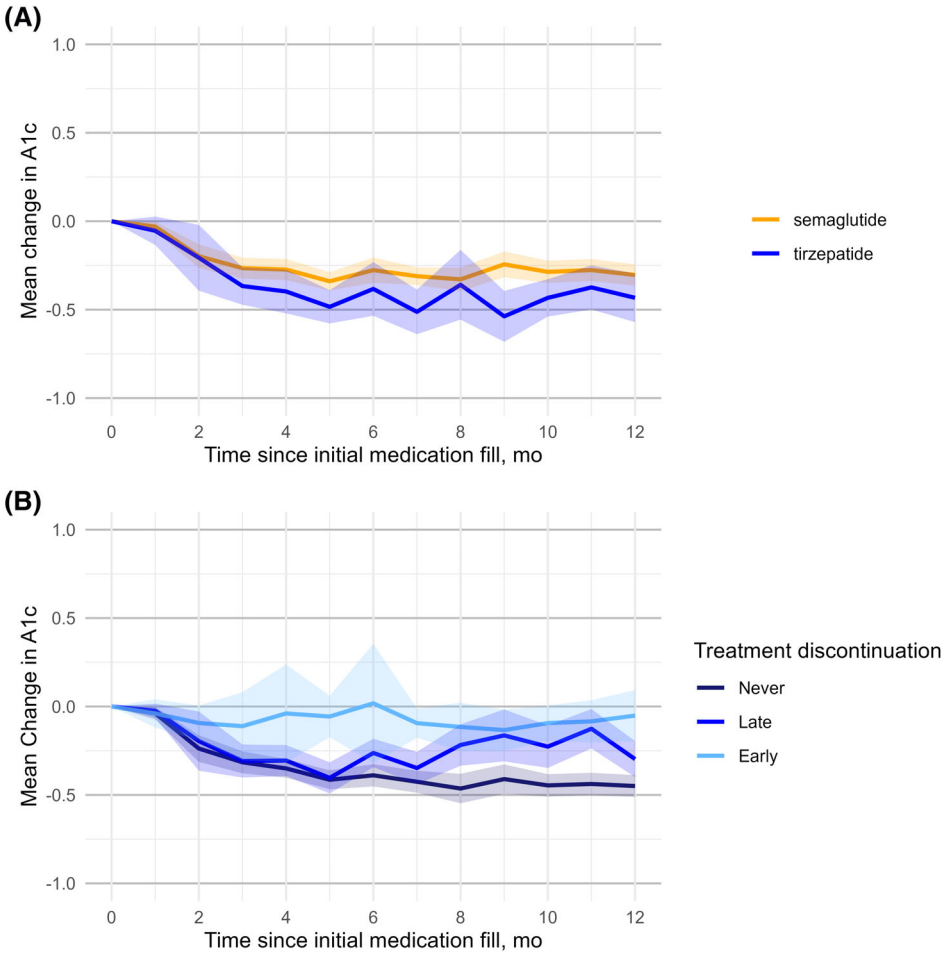

FIGURE 4 Mean absolute change in glycated hemoglobin level (HbA1c) (percent) by (A) index medication and (B) obesity pharmacotherapy discontinuation status from initiation of the medication in patients with prediabetes at baseline. A total of 1320 patients contributed to this analysis. Available HbA1c level (percent) measurements were captured from baseline through 12 months in 1-month increments. Discontinuation of obesity pharmacotherapy at 1 year was defined as a greater than 90-day gap between exhaustion of previous supply and next dispense or between exhaustion of last supply and end of study follow-up. Patients who switched between injectable forms of semaglutide, tirzepatide, or other obesity medications but had a gap of less than 90 days were not considered to have discontinued obesity pharmacotherapy. Shaded areas indicate 95% CI. [Color figure can be viewed at wileyonlinelibrary.com]

persisted, weight trajectories remained surprisingly stable after discontinuation throughout the study follow-up period. This is in contrast to what has been observed after medication discontinuation at the end of randomized trials [9, 23]. Future studies are needed to understand this discrepancy, in particular, what additional weight management efforts patients might pursue in real-world settings.

Finally, 67.9% of patients with prediabetes at baseline who did not discontinue obesity pharmacotherapy, compared to 33.1% who discontinued early, achieved normoglycemia at 1 year. The effectiveness of these medications for prediabetes has been reported earlier [24, 25]. Our findings highlight the importance of continuing treatment.

Strengths of this study include its large and contemporaneous sample, integration of prescription dispensation data from Surescripts with clinical information [12, 13], and inclusion of all patients who received the medication, regardless of whether they discontinued treatment. This study also has some limitations. We included adult patients from Ohio and Florida in a single, large integrated health system. Patient characteristics and health care delivery patterns vary across the United States, which may limit the generalizability of our findings. Shortages of semaglutide and tirzepatide during the study period could have contributed to temporary discontinuation. Some of the observed weight reductions may be associated with other interventions (e.g., lifestyle interventions, nutritional counseling); nevertheless, the studied medications have been approved to be used in addition to diet and exercise. This study did not capture participation in lifestyle interventions and nutritional counseling or patient- and clinician-related factors (such as discontinuation of the medication therapy owing to inadequate weight reduction, adverse effects, or coverage issues), and the impact of these factors could not be examined in this study.

CONCLUSION

In this retrospective cohort study of 7881 patients treated with injectable forms of semaglutide or tirzepatide for obesity in a routine clinical setting, treatment discontinuation and lower maintenance dosages were common. The average weight reduction in this cohort at 1 year was lower than that observed in the main phase 3 trials, likely because of these factors. In patients who had prediabetes at baseline, treatment discontinuation was also associated with attenuated HbA1c reduction at 1 year. Our findings could inform the decisions of health care providers and their patients on the role of treatment discontinuation and maintenance dosage in achieving clinically meaningful weight loss.O

CONFLICT OF INTEREST STATEMENT

W. Scott Butsch reported advisory board fees from Novo Nordisk A/S, Eli Lilly and Company, Boehringer Ingelheim, and Abbott Laboratories, as well as research funding from Eli Lilly and Company, outside the submitted work. Christopher B. Boyer reported consulting fees from Janssen Pharmaceuticals outside the submitted work. Marcio L. Griebeler reported research funding from Novo Nordisk A/S outside the submitted work. Michael B. Rothberg reported receiving consulting fees from the Blue Cross Blue Shield Association outside the submitted work. The other authors declared no conflicts of interest.

DATA AVAILABILITY STATEMENT

The dataset generated during the current study is not publicly available to preserve patient confidentiality. However, the dataset is available from the corresponding author to academic investigators following receipt of a signed data-sharing agreement and after reviewing the study protocol (approved by a local institutional review board or research ethics committee), statistical analysis plan, and publication plan. The Cleveland Clinic Institutional Review Board and the Law Department must approve the request before sharing the deidentified data. The corresponding author will respond to these requests within 2 months of receipt.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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