Real-World Treatment Patterns Among Patients with Type 2 Diabetes Mellitus Initiating Treatment with Oral Semaglutide

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ABSTRACT

Introduction: The treatment landscape for type 2 diabetes mellitus (T2DM) is complex and constantly evolving, and real-world evidence of prescribing patterns is limited. The objectives of this study were to characterize lines of therapy (LOTs), calculate the length of time spent on each LOT, and identify the reasons for the LOT end among patients who initiated oral semaglutide for T2DM.

Methods: This retrospective, claims-based study included commercial and Medicare Advantage adults with T2DM. Data from November 1, 2019, and June 30, 2020, were obtained from Optum Research Database. Patients with ≥ 1 claim for oral semaglutide and continuous health plan enrollment for ≥ 12 months prior to (baseline period) and ≥ 6 months following (follow-up period) the date of the first oral semaglutide claim were included. LOT 1 began on the date of the first oral semaglutide claim. The start date of any subsequent LOTs was the date of the first claim for an additional non-insulin anti-diabetic drug class or a reduction in drug class with use of commitment medications. The LOT ended at the first instance of medication class discontinuation, change in regimen or end of follow-up.

Results: Of the 1937 patients who initiated oral semaglutide, 950 (49.0%) remained on their initial regimen over the 6-month follow-up period, 844 (43.6%) had at least one subsequent LOT, and 89 (4.6%) had at least two subsequent LOTs. Among patients with more than one LOT, approximately 20%–25% used oral semaglutide as monotherapy or combination therapy during LOTs 2 and 3. Metformin was frequently used during treatment across all LOTs.

Conclusion: This study provides insight for physicians and payers into the real-world prescribing practices within the first 6 months following oral semaglutide initiation and fills the gap in understanding the frequency of regimen changes in the constantly evolving and complex environment of T2DM care.

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PLAIN LANGUAGE SUMMARY

Type 2 diabetes mellitus is a disease which, over time, can cause higher than normal levels of sugar in the blood (hyperglycemia) which can be harmful if not treated. Treatment for type 2 diabetes mellitus can be complex, and how doctors prescribe medications is always changing. For some people with type 2 diabetes mellitus who are overweight or obese, it is recommended for patients to use certain medications that can help with weight management such as semaglutide and metformin. This study aims to fill gaps in current treatment knowledge about type 2 diabetes mellitus patients and their treatment of oral semaglutide. Researchers in this study explored how patients treated with oral semaglutide differentiated among line of therapies, how long patients stuck to them and why they stopped. The study found that those patients who started with oral semaglutide, almost half of those patients stuck to their initial treatment plan for the entire 6 months. When it came to the top ten treatment plans, about 20% of patients used oral semaglutide alone and about 25% of patients used oral semaglutide plus an additional treatment option. Metformin was frequently used during treatment across all line of therapies. There is little information on the real-life setting of treatment after the start of therapy for type 2 diabetes mellitus. The results from this study show what happens when patients start using oral semaglutide and helps healthcare providers understand how often treatment plans can change in type 2 diabetes mellitus care.

Keywords: Oral semaglutide; Type 2 diabetes mellitus; Treatment patterns; Line of therapy; Treatment regimen

Key Summary Points

The treatment landscape for type 2 diabetes mellitus (T2DM) is complex and constantly evolving, and real-world evidence of prescribing patterns is limited

The aim of this study was to characterize lines of therapy, calculate the length of time spent on each line of therapy and identify the line of therapy terminating event among patients who initiated oral semaglutide for T2DM

Among patients who initiated oral semaglutide, 49% remained on their initial regimen until the end of the 6-month follow-up period

Among the top ten treatment regimens, oral semaglutide was used as monotherapy or combination therapy by 19.7% and 24.8% of patients with a second or third line of therapy, respectively

This study provides insight for physicians and payers into the real-world prescribing practices following initiation with oral semaglutide and fills the gap in understanding the frequency of regimen changes in the constantly evolving and complex environment of T2DM care

INTRODUCTION

Diabetes mellitus affects one in ten Americans, with 90–95% of patients with diabetes diagnosed with type 2 diabetes mellitus (T2DM) [1]. T2DM rarely occurs on its own and is typically associated with a host of comorbid conditions. Comorbidities among patients with T2DM are associated with a lower quality of life [2–5], increased healthcare utilization [6, 7] and worse treatment outcomes [8–10]. Among patients with comorbid T2DM and overweight/obesity, even a small weight loss can result in improved glycemia and a reduction in cardiovascular risk factors, while a larger weight loss may result in sustained remission of T2DM for at least 2 years and long-term reductions in cardiovascular and mortality risk [11].

Physicians treating patients with T2DM face competing clinical concerns [12] and complex treatment situations that require prescription of additional medications and dosing adjustments for patients to obtain optimal levels of HbA1c,

blood pressure and LDL cholesterol [13]. While metformin has historically been the treatment of choice in first-line therapy, guidelines now recommend a patient-centered approach with any mono- or combination therapy that allows patients to maintain treatment goals [14]. Nearly all FDA-approved obesity medications have been shown to improve glycemia in people with type 2 diabetes and delay progression to type 2 diabetes in at-risk individuals [15]. In people with T2DM and overweight or obesity, the preferred pharmacotherapy should be a glucagon-like peptide 1 receptor agonist (GLP-1 RA) or dual glucose-dependent insulinotropic polypeptide and GLP-1 RA with greater weight loss efficacy, especially considering their added weight-independent benefits (e.g., glycemic and cardiometabolic) [16].

With the increasing availability of more effective treatments, individuals with diabetes and overweight or obesity should be informed of the potential benefits of both modest and more substantial weight loss and guided in the range of available treatment options [16]. In patients with T2DM, comorbid conditions such as obesity may decrease the benefit of treatment [9, 10] and negatively influence patients' emotional wellbeing and ability to self-manage their T2DM [17]. Semaglutide, a GLP1-RA, was initially granted market authorization for the treatment of type 2 diabetes as an adjunct to diet and exercise. In 2021 and 2022, regulatory agencies in the USA and Europe licensed semaglutide for the treatment of individuals who are obese or overweight and who have at least one weight-related comorbidity [18]. Manufacturer-sponsored randomized controlled trials have shown a loss of almost 12% of body weight over a 68-week period. Once the medication was stopped patients regained most of their pretreatment weight [19].

Given the medical complexity of patients with T2DM and their risk for additional health complications, there is a need to understand patterns of non-insulin antidiabetic medication (NIAD) prescribing to improve treatment outcomes in these patients. As there is limited information on the real-world treatment trajectory taken after initiation of treatment for T2DM, the aim of this study was to characterize lines of therapy (LOTs) and the top medications used in each LOT, calculate the length of time spent on each LOT and identify the reasons for the end of each LOT among patients with T2DM who initiated treatment with oral semaglutide.

METHODS

Data Source and Study Design

This was a retrospective database study based on methodology and similar practices of previously conducted work [20]. Commercial and Medicare Advantage health plan members in the Optum Research Database were identified from November 1, 2018, through December 31, 2020 (study period). Diagnoses of T2DM and comorbid conditions were identified in medical claims, and prescription medications were identified using National Drug Codes. These data used in this study have been de-identified in accordance with Health and Human Services Privacy Rule's requirements for de-identification codified at 45 C.F.R § 164.514(b) and thus were not subject to an IRB review.

Study Population

Patients with at least one claim for oral semaglutide between November 1, 2019, and June 30, 2020, were included in the study population (Fig. 1). The index date was the date of the first oral semaglutide claim. Patients were required to have continuous enrollment in the health plan for ≥ 12 months prior to and including the index date (baseline period) and ≥ 6 months following the index date (follow-up period). Patients were also required to have a diagnosis of T2DM during the baseline or follow-up periods and be ≥ 18 years of age as of the index year. Patients with missing data were excluded as were patients with evidence of pregnancy.
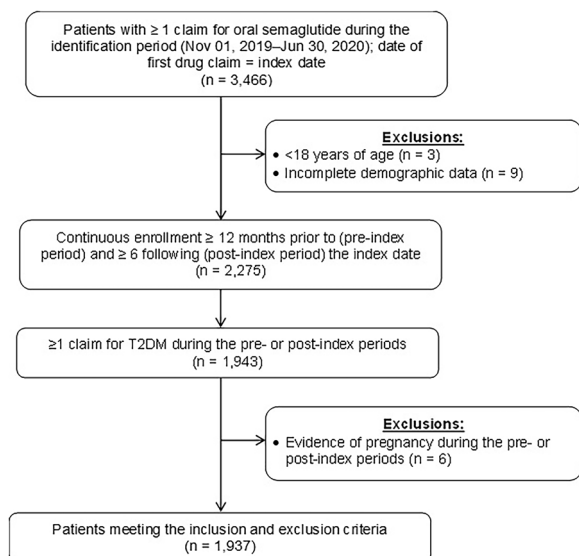
Fig. 1 Patient sample selection

Baseline Patient Characteristics

Patient characteristics captured from the administrative claims data during the 12-month baseline period included age, gender, insurance type, geographic region, Charlson comorbidity index [21, 22] and commonly diagnosed comorbid conditions operationalized by the Agency for Healthcare Research and Quality [23].

Outcomes

The top ten NIAD regimens by LOT were identified during the first 90 days of the follow-up period. LOT was determined based on an algorithm at the medication class level. The start of LOT 1 was the day of the first oral semaglutide claim. To accommodate concomitant therapies that do not initiate on the same day, the LOT included all agents received within a 90-day period following the day of the first fill. The start of any subsequent LOTs was the day of the first claim for an additional or new NIAD class or the end of the previous LOT in patients that reduced therapy as part of a regimen change. The LOT ended at the first instance of a medication class discontinuation with use concomitant medications (i.e., run out of a prescription fill

prior to a ≥ 60-day gap in medication class), a change in regimen (i.e., addition or switch of a medication class) or the end of follow-up. The length of the LOT was the number of days from the start to the end of the LOT. Persistence with oral semaglutide was defined as the time from the index date to the runout of days' supply prior to a ≥ 60-day gap in oral semaglutide among patients with at least 90 days of continuous treatment.

Analysis

Study variables were analyzed descriptively. Numbers and percentages were provided for dichotomous and categorical variables. Means and standard deviations were provided for continuous variables. Analyses were conducted using SAS software version 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

Baseline Patient Characteristics

A total of 1937 patients met inclusion/exclusion criteria and were included in the study population (Fig. 1). Patients had a mean (SD) age of 58.7 (11.7) years, 51.8% were male, and the majority had commercial insurance (66.5%) and lived in the South (61.4%) (Table 1). The mean (SD) Charlson comorbidity score was 1.2 (1.5). Common comorbid conditions included lipid metabolism disorders (82.7%), hypertension (81.0%), T2DM with complications (75.0%) and other nutritional, endocrine or metabolic disorders including overweight/obesity (67.1%).

Top ten regimens by LOT

By definition, all patients ($n = 1937$) had a least one LOT, 844 patients (43.6%) had at least one subsequent LOT, and 89 patients (4.6%) had at least two subsequent LOTs (data not shown) during the study period. Patients had a mean (SD) of 1.5 (0.6) different regimens over the 6-month follow-up period. Metformin was a commonly prescribed concomitant medication, occurring

Table 1 Patient demographic and clinical characteristics

	Total (n = 1937)
Age, mean (SD)	58.7 (11.7)
Age group, n (%)	
18–39 years	106 (5.5)
40–64 years	1237 (63.9)
65–74 years	424 (21.9)
75 + years	170 (8.8)
Male gender, n (%)	1004 (51.8)
Insurance type, n (%)	
Commercial	1288 (66.5)
Medicare	649 (33.5)
Region, n (%)	
Northeast	118 (6.1)
Midwest	410 (21.2)
South	1190 (61.4)
West	219 (11.3)
Quan-Charlson comorbidity index score, mean (SD)	1.2 (1.5)
Comorbid conditions of interest, n (%)	
Diabetes mellitus without complications	1633 (84.3)
Lipid metabolism disorder	1601 (82.7)
Hypertension	1569 (81.0)
Diabetes mellitus with complications	1453 (75.0)
Other nutritional, endocrine or metabolic disorder	1299 (67.1)
Chronic kidney disease	416 (21.5)
Atherosclerotic cardiovascular disease	328 (16.9)

in at least 45.4% of patients in LOT 1, at least 41.2% in LOT 2 and at least 36.0% in LOT 3.

In LOT 1, the top ten regimens observed were used by 85.2% of study patients (Fig. 2a). Among the top ten regimens, oral semaglutide monotherapy was the most prescribed regimen (30.4%), followed by oral semaglutide plus metformin (23.0%). Only 9.4% of all patients had combination therapy that did not include metformin in the top ten regimens. Of the 1650 patients included in the top 10 regimens, 589 patients (35.7%) had a monotherapy regimen, 604 patients (36.6%) had a dual therapy regimen, 408 patients (24.7%) had a triple therapy regimen, and 49 patients (3.0%) had four or more medication classes in their regimen.

Among patients with a second LOT (n=844), 58.3% of patients used one of the top ten regimens observed, most commonly metformin monotherapy (16.7%), oral semaglutide plus metformin (8.5%) and oral semaglutide monotherapy (8.1%) (Fig. 2b). A total of 60.8% of all patients with a second LOT used combination therapy (data not shown) and 19.7% had a regimen containing oral semaglutide (2b). Of the 492 patients included in the top 10 regimens, 285 patients (57.9%) had a monotherapy regimen, 181 patients (36.8%) had a dual therapy regimen, and 26 patients (5.3%) had a triple therapy regimen.

Among patients with a third LOT (n=89), 62.9% of patients used one of the top ten regimens (Fig. 2c). A total of 53.9% of all patients with a third LOT used combination therapy (data not shown), and 24.8% had a regimen containing oral semaglutide (Fig. 2c). Of the 56 patients included in the top 10 regimens, 32 (57.1%) had a monotherapy regimen, 17 (30.4%) had a dual therapy regimen, and 7 (12.5%) had a triple therapy regimen.

Length of Treatment by LOT in Top Ten Most Common LOTs

In LOT 1, patients remained on their initial prescription of oral semaglutide monotherapy for a mean of 106.3 days. Patients who utilized oral semaglutide in combination with metformin and an SGLT-2i had the longest mean LOT length (153.8 days) (Table 2).

Among patients with a second LOT, those who used metformin plus sulfonylurea, metformin plus an SGLT-2i and SGLT-2i monotherapy remained on their medication the longest, with a mean LOT length of 110.5, 104.6 and 104.7 days, respectively (Table 2). Patients who used oral semaglutide plus metformin and GLP-1 RA monotherapy had the shortest LOT lengths (68.9 and 61.2 days, respectively).

Among patients with a third LOT, those who used metformin plus GLP-1 RA, metformin plus SGLT-2i and sulfonylurea monotherapy had the longest LOT lengths (66.5, 64.3 and 61.8 days, respectively) (Table 2). Patients who used oral semaglutide plus metformin had the shortest LOT length (23.4 days).

Persistence and Reason for LOT End

A total of 1207 patients (62.3%) were persistent on oral semaglutide through the end of the 6-month follow-up period.

Almost half of patients (49.0%) continued on their first LOT until the end of the 6-month follow-up period (Fig. 3). After censoring (i.e., end of the follow-up period), the most common event terminating LOT 1 was a medication class switch (33.9%).

Among patients with a LOT 2 ($n = 844$), 88.0% continued their second LOT until the end of the follow-up period (Fig. 3). After censoring, a medication class switch by 8.2% of patients was the most common reason for the end of the LOT.

Among patients with a LOT 3 ($n = 89$), almost all patients (98.9%) continued their third LOT until the end of follow-up (Fig. 3).

DISCUSSION

The aim of this study was to describe prescribing patterns and LOTs among patients with T2DM in a real-world clinical setting 6 months following an initial pharmacy fill for oral semaglutide. During the short 6-month follow-up period, half of initiating patients were stable on their prescribed regimen (i.e., no additional LOTs) while the other half were navigating therapy changes (i.e., additional LOTs). Patients who initiated a regimen containing oral semaglutide had a mean (SD) of 1.5 (0.6) different regimens over the 6-month follow-up period, with 49.0% of patients remaining on their initial regimen until the end of follow-up. Among patients with a second or third LOT, 19.7% and 24.8%, respectively, had oral semaglutide as a component in one of the top ten regimens. More than 80% of patients with T2DM had comorbid lipid metabolism disorders and hypertension.

In a survey of physicians, the most frequently cited considerations when choosing which antihyperglycemic agent to prescribe were the patients' health status and comorbid conditions (89%), the extent of hemoglobin A1c elevation (74%) and the patients' weight (66%) [24]. Physicians reported using clinical assessments and perceptions of patients' adherence, motivation and concerns about treatment in their decision-making, revealing a more complicated decision-making process than adhering to suggested treatment guidelines. In this study, almost half of patients remained on their initial LOT over the 6-month follow-up period. Of those that were prescribed more than one LOT, 43.6% had ≥ 2 LOTs and only 4.6% had ≥ 3 LOTs. It is possible that discussion and care for comorbid conditions and other concerns may have overshadowed T2DM management and discussions of medication change during physician visits. Care prioritization and goal setting by both patient and physician is a balancing act during each encounter in a manner that considers patient resources, expectations and willingness to intensify therapy [25, 26]. In a study by Parchman et al., each additional patient concern discussed during a physician visit was associated with a 49% reduction in the likelihood of a change in medication among patients with a hemoglobin A1c > 7% [12]. More proactive strategies to tackle the persistent risk factor burden in patients with T2DM should be considered [27]. Though the follow-up period in the current study was over a short time span, longer durations of follow-up time are needed to fully understand prescribing patterns.

Achieving and maintaining long-term glycemic control is often challenging, and many

a

b

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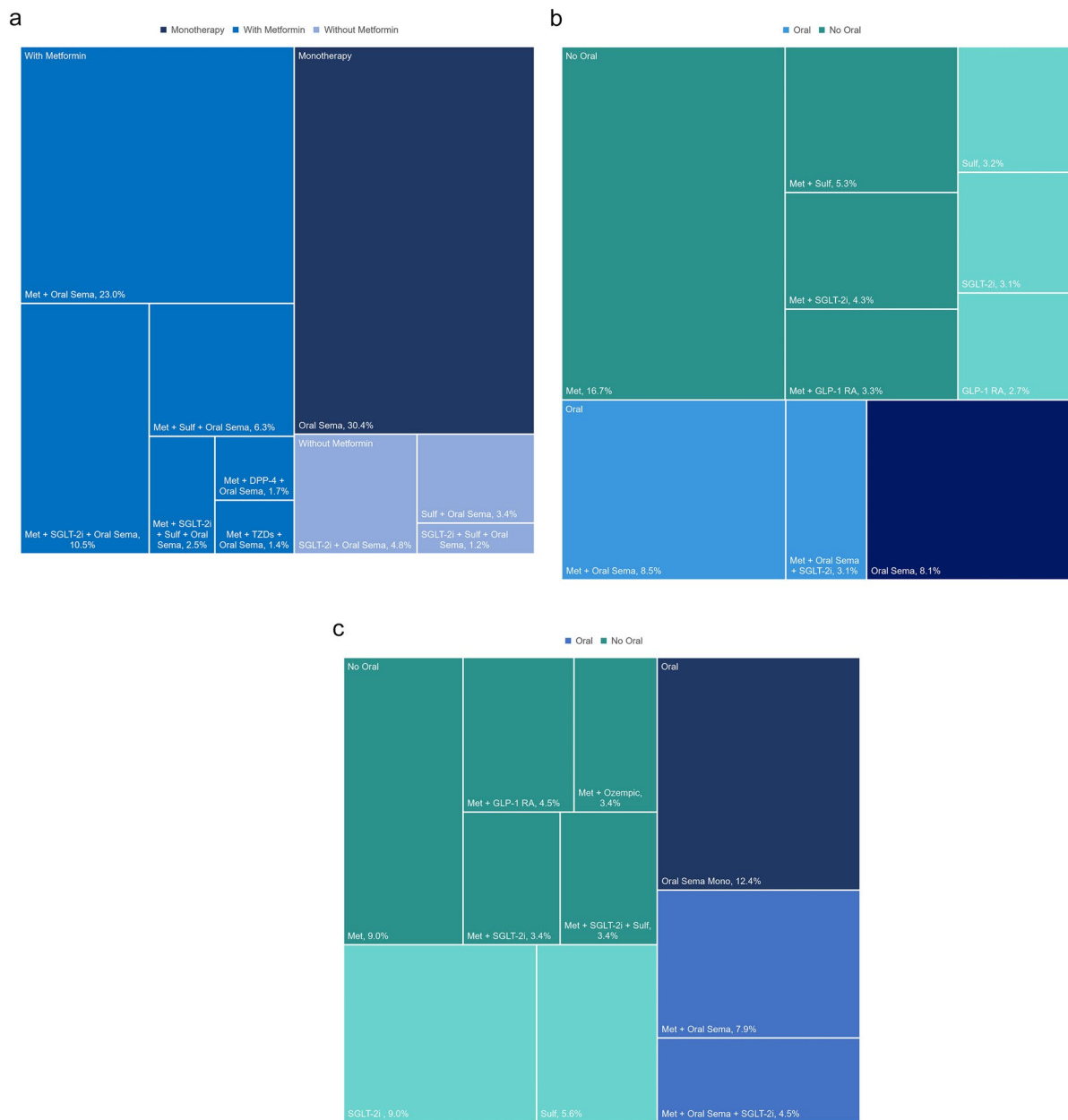
Fig. 2 Top ten regimens by LOT. **a** LOT 1. **b** LOT 2. **c** LOT 3. *DPP-4* dipeptidyl peptidase 4 inhibitor; *GLP-1 RA* glucagon-like peptide 1; *injectable sema* injectable semaglutide; *met* metformin; *oral sema* oral semaglutide; *SGLT-2i* sodium glucose cotransporter 2 inhibitor; *sulf* sulfonylurea; *TZD* thiazolidinedione

current agents have treatment-limiting side effects [28]. With 10 currently available medication classes to treat T2DM and almost 30 different agents that can be used as monotherapy or combination therapy [29], it is not surprising that regimens, particularly those in LOT 2 and 3, differed considerably among patients. Charbonnel et al. found T2DM patients at baseline (Start of LOT 2) and 36 months' follow-up, almost 43% changed treatment at least once during follow-up, usually involving the addition of an oral glucose-lowering drug, the initiation of an

Table 2 Mean (SD) length (days) of antihyperglycemic regimen by LOT among patients initiating oral semaglutide

	LOT 1 (n = 1937)	LOT 2 (n = 844)	LOT 3 (n = 89)
Oral semaglutide monotherapy	106.3 (65.0)	86.2 (37.2)	38.1 (24.2)
Metformin + oral semaglutide	141.5 (55.2)	68.9 (29.5)	23.4 (24.0)
Metformin + SGLT-2i + oral semaglutide	153.8 (51.5)	91.9 (34.9)	33.8 (8.9)
Metformin + sulfonylurea + oral semaglutide	140.1 (54.0)	–	–
SLGT-2i + oral semaglutide	111.7 (63.3)	–	–
Sulfonylurea + oral semaglutide	119.6 (62.7)	–	–
Metformin + SGLT-2i + sulfonylurea + oral semaglutide	145.8 (58.2)	–	–
Metformin + DPP-4 + oral semaglutide	124.8 (67.3)	–	–
Metformin + thiazolidinedione + oral semaglutide	139.2 (57.5)	–	–
SGLT-2i + sulfonylurea + oral semaglutide	116.3 (47.4)	–	–
Metformin monotherapy	–	92.3 (39.4)	35.1 (35.9)
Metformin + sulfonylurea	–	110.5 (38.2)	–
Metformin + SGLT-2i	–	104.6 (38.7)	64.3 (18.9)
Metformin + GLP-1 RA	–	101.5 (41.0)	66.5 (42.7)
Sulfonylurea monotherapy	–	88.0 (44.7)	61.8 (41.1)
SGLT-2i monotherapy	–	104.7 (36.3)	52.8 (44.3)
GLP-1 RA monotherapy	–	61.2 (42.1)	–
Metformin + injected semaglutide	–	–	54.3 (34.3)
Metformin + SLGT-2i + sulfonylurea	–	–	81.3 (18.5)

DPP-4 dipeptidyl peptidase 4 inhibitor; *GLP-1 RA* glucagon-like peptide 1; *LOT* line of therapy; *SGLT-2i* sodium glucose cotransporter-2 inhibitor

injectable drug or a switch between treatment classes [30]. In LOT 1, most patients (85.2%) were prescribed one of the top ten most common regimens, which suggests that despite complexity of care, there are patterns of use that cover the majority of patients initiating oral semaglutide. In LOT 2 and 3, approximately 60% of patients had a regimen that included
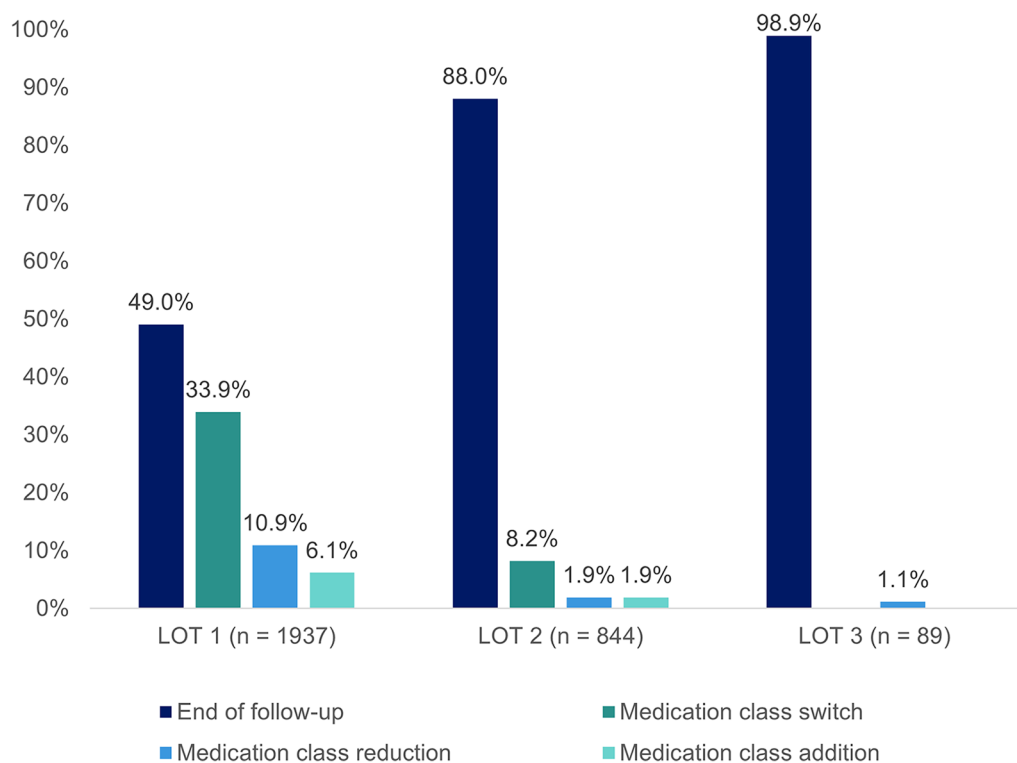
Fig. 3 Reason for the end of the LOT. *LOT* line of therapy

at least one of the ten most commonly pre-scribed classes. Metformin was commonly used as monotherapy and concomitantly with other regimens across the reported LOTs. Metformin has historically been the most frequently pre-scribed NIAD because of its effectiveness, afford-ability and tolerability among patients with T2DM [31]. Metformin alone and in combina-tion with other therapies has been the recom-mended first-line treatment for T2DM patients for decades, remaining so among patients with-out cardiovascular and renal disease [32]. In the current study, LOT 1 showed patients remained on their initial prescription of oral semaglutide monotherapy for 106.3 days on average. Patients who utilized oral semaglutide in combination with metformin and an SGLT-2i had the long-est mean LOT length of 153.8 days. Abrahami et al. examined trends of second-line therapies of T2DM patients initiating first-line metformin in the US and the UK. Throughout the study period between 2013–2019, sulfonylurea and dipeptidyl peptidase-4 inhibitors were the most

frequently initiated second-line medications in the US (43.4% and 18.2%, respectively) and the UK (42.5% and 35.8%, respectively). After 2018, sodium-glucose co-transporter 2 inhibitors and glucagon-like peptide-1 receptor agonists were more commonly used as second-line agents in the US and the UK [33]. In recent years, this pattern has begun to change as products with higher efficacy and a larger list of benefits have become available [16].

Patients in this study were medically complex, and comorbidities were common. More than 80% of patients with T2DM had comorbid lipid metabolism disorders and hypertension, 67% had nutritional or endocrine or other metabolic disorders (including overweight/obesity), 22% had chronic kidney disease, and 17% had cardio-vascular disease. These proportions were similar to those reported in a study by Iglay et al., where 82.1% of patients with T2DM had comorbid hypertension, 78.2% had overweight/obesity, 77.2% had hyperlipidemia, 24.1% had chronic kidney disease, and 21.6% had cardiovascular

disease [34]. Comorbid conditions contribute to worse treatment outcomes and management of T2DM. Comorbid conditions may shift the priority away from diabetes, complicate self-management efforts [35, 36] and serve as a competing demand on patients' self-management resources. In Kerr et al., a higher burden of macrovascular conditions and discordant conditions (i.e., lung disease, cancer, arthritis) was associated with both lower prioritization of diabetes management and lower self-management ability in patients with T2DM [37]. Despite the high rates of comorbid conditions in the current study, most patients had few regimen changes over the 6-month follow-up period.

This study provides real-world evidence of the treatment patterns following initiation with oral semaglutide; however, as healthcare claims data are collected for service payment and not research; there are several limitations inherent in this study. First, medication use was measured from pharmacy claims. Patients may not have taken the medication or consumed it as prescribed, and any medication samples provided to the patient would not be included in the analysis. Second, claims data did not include clinical data such as BMI/weight or contain social determinants of health information. Also, the reasons for a change in LOT (e.g., adverse events, cost, lack of effectiveness) could not be deduced from the data. Lastly, this study was conducted in a large US managed care population whose study period was defined by the first prescription for oral semaglutide and may not be representative of all patients with T2DM.

CONCLUSIONS

Nearly half of all patients who initiated oral semaglutide treatment remained on oral semaglutide therapy for the full 6-month follow-up period. Among those with more than one LOT, 20–25% of patients in the second and third LOT had oral semaglutide as monotherapy or combination therapy. Metformin was frequently used as a concomitant NIAD. This exploratory study provides insight for physicians and payers into the real-world prescribing practices within the first 6 months following oral semaglutide initiation and

fills the gap in understanding the frequency of regimen changes in the constantly evolving and complex environment of T2DM care. This may also provide insights for clinicians in clinical practice as to what is to be expected when prescribing oral semaglutide for their patients such as the possible need of additional therapy as well as persistence. Future studies are needed to adapt current management strategies to treat patients with T2DM who have multiple comorbid conditions more effectively. Additionally, further study is needed to understand treatment stability and its association with patient outcomes.

includes restrictive covenants governing the use of the data.

Declarations

Conflict of Interests. Caroline Swift, Sarah Alvarez, Tyler J. Dunn, Josh Noone, and Mico Guevarra are employees of Novo Nordisk. Monica Frazer was an employee of Optum at the time the study was conducted. Andrew Sargent, Michael Leszko, Noelle N. Gronroos, and Erin Buysman are employees of Optum.

Ethical Approval. The use of de-identified claims data from the Optum Research Database (ORD) for retrospective research studies was reviewed by the WCG IRB and granted an IRB exemption under 45 CFR § 46.104(d)(4). Throughout the process, patient privacy was preserved, and researchers complied strictly with all applicable Health Insurance Portability and Accountability Act data management rules and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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