ORIGINAL ARTICLE



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Survey among adult users of semaglutide for weight loss in Denmark: User characteristics, treatment expectations and experienced effects

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Abstract

Aims: Since the launch of semaglutide for weight loss (Wegovy[®], SEMA-WL) in late 2022, there has been a huge increase in new users of SEMA-WL. We explored characteristics, treatment expectations and experienced effectiveness and side effects among Danish adults using SEMA-WL.

Materials and Methods: A questionnaire-based survey was conducted from September to December 2023 across 29 Danish community pharmacies. During a 10-day period, pharmacies invited consecutive individuals aged ≥18 years redeeming a prescription on SEMA-WL to complete an electronic questionnaire.

Results: A total of 1013 individuals were invited to study participation of which 55% (n=559) accepted. Users of SEMA-WL were primarily female (78%, n=434) and middle-aged adults (36–65 years; 76%, n=423), with a median body mass index of 36 (interquartile range [IQR] 32–40) at treatment initiation. Two in three users had personally asked their general practitioner to initiate treatment (70%, n=393). Four in ten users had not discussed expected treatment duration with their general practitioner (42%, n=237), almost half (46%, n=258) expected treatment for a limited time period, while only 11% (n=64) expected lifelong treatment. Self-reported median weight loss was 5.3% (IQR 3.2–8.5) for users treated for <3 months, 10% (IQR 8.2–14) for 3–5 months of treatment and 17% (IQR 13–21) for those treated for >5 months. More than half of users (59%, n=330) had experienced side effects, most commonly nausea (35%, n=193) and constipation (29%, n=160).

Conclusions: This study provides valuable insights into the characteristics, treatment expectations and effects experienced by Danish adult users of SEMA-WL.

KEYWORDS

attitudes, effectiveness, semaglutide, weight control, weight management

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1 | INTRODUCTION

Overweight and obesity are considered one of the greatest global health challenges. The World Health Organization estimates that adult obesity has more than doubled since 1990, with 2.5 billion adults and 890 million adults being overweight and obese, respectively, in 2022. Overweight and particularly obesity are linked to several comorbidities, such as type 2 diabetes, cancer and cardiovascular diseases, negatively affecting public health and healthcare costs. ²

In late 2022, Wegovy® (semaglutide) was launched for weight loss and control (from now on referred to as SEMA-WL) in people with either overweight (body mass index [BMI] ≥27) and at least one weight-related comorbidity or with severe overweight (BMI ≥30) alone. Treatment with SEMA-WL for weight management has proven highly effective with continuous treatment.^{3,4} The STEP 5 randomised trial investigated the efficacy of two years of treatment with onceweekly SEMA-WL 2.4 mg versus placebo in adults with overweight and weight-related comorbidities (excluding diabetes) or with obesity and showed significant differences, with a mean weight loss of 15.2% for SEMA-WL compared with 2.6% for placebo.³ Additionally, the STEP 1 trial showed that participants treated with the same dose of SEMA-WL for a 68-week period had regained two-thirds of their body weight one year after discontinuing treatment.⁴

Since the launch of SEMA-WL, there has been a steady increase in new users. In Denmark, the number of new users of SEMA-WL has exceeded that of existing medical alternatives. Users of SEMA-WL constitute a new and sizeable patient group in everyday clinical care on which there is currently limited information. Understanding this patient group is crucial to ensure safe and rational use of SEMA-WL, including knowledge of users' characteristics, expectations and experienced effectiveness and side effects. In particular, such knowledge is pertinent for healthcare providers who prescribe, monitor and provide treatment guidance as well as for health authorities who regulate treatment with SEMA-WL.

With this study, we aimed to explore characteristics, treatment expectations and experienced effectiveness and side effects among Danish adults using SEMA-WL.

2 | MATERIALS AND METHODS

We conducted a questionnaire-based survey to explore characteristics, treatment expectations and experienced effectiveness and side effects among adult customers redeeming a prescription on SEMA-WL at 29 community pharmacies across Denmark from September to December 2023.

2.1 | Setting and participants

Danish community pharmacies were recruited through the Danish Network for Research and Development in Pharmacy Practice,⁶ which is a research network currently including 98 community pharmacies across Denmark. Each pharmacy received an e-mail invitation directly from the network, while an open invitation was also posted on the network's Facebook page. Pharmacies interested in participating were encouraged to contact the project group via e-mail or phone. Pharmacies were recruited from August to September 2023.

Participating pharmacies were offered an individual online video meeting with the project leader (MSS) prior to data collection to discuss the project in details and clarify expectations. Pharmacies were asked to assign a project manager among their staff to handle practical matters related to data collection, including communication with the project group. The project manager received a set of documents and guidelines, including an instruction on how to extract daily sales statistics from their computer system and a document for data records. Additionally, the project manager got access to an online video to share with colleagues in order to introducing them to the data collection process—from identifying study participants to submitting the electronic questionnaire.

2.2 | Questionnaire development

The initial draft of the questionnaire was developed based on existing literature⁷⁻⁹ and through discussion in the project group, including both clinicians and researchers with expertise and experience within rational pharmacotherapy, endocrinology, weight management and research in the Danish community pharmacy setting. The questionnaire underwent three rounds of pilot testing and adjustment at a large community pharmacy in Odense. All pilot tests were conducted with paper versions of the questionnaire. The first pilot test was conducted by the project leader (MSS), who recruited a total of nine customers redeeming a prescription on SEMA-WL at the counter and brought them into a secluded room where the questionnaire was reviewed. First, the costumers answered the guestionnaire as MSS read them aloud and marked their responses. Subsequently, they were asked a few follow-up questions regarding whether they found the questions understandable, the length appropriate and if they would be willing to answer the questions at the counter. The secluded setting was selected due to concerns about the costumers' willingness to answer body-related personal questions, such as the individual's weight. However, this initial pilot test revealed that participants were generally willing to provide such information. The second pilot test was also performed by MSS, but this time at the pharmacy counter. Feedback from this pilot test, including four participants, led to further adjustments of the questionnaire. The third pilot test was also conducted at the counter, but this time by both MSS and pharmacy staff. Based on this third pilot, including feedback from two participants, the questionnaire was adjusted into a final version. An English version of the final questionnaire is available in Appendix 1. The final version of the questionnaire was set up in the online database collection tool REDCap. 10

2.3 | Data collection and analysis

Pharmacy staff handling customer transactions at the counter, including pharmacists, pharmaconomists and students, invited consecutive customers to participate. Customers were eligible for study participation if they were aged ≥18 years and redeemed a prescription on SEMA-WL, either for themselves or their close ones. Pharmacy staff read each question aloud to the customer and entered the customer's responses into REDCap. The data collection period at each pharmacy was set at two weeks, equivalent to ten business days (excluding weekends), and took place throughout the pharmacy's entire opening hours.

At the end of each data collection week, the pharmacy project manager sent a summary of their sales statistics for SEMA-WL packages during that week. Based on these data, along with the questionnaire responses, each pharmacy received a weekly individual report on participant responses and the percentage of sold packages identifiable in the questionnaire responses. This approach aimed to not only motivate pharmacy staff for participant recruitment but also to identify the percentage of customers invited to participate (out of the total number of packages sold during the 10-day period) and thus to validate the participant recruitment.

Based on initial sales statistics and discussion with pharmacy staff, we expected each pharmacy to invite a mean of five costumers to study participation per day. We aimed for 20 participating pharmacies, which, with a 10-day data collection period, would result in a minimum of 1000 customers invited to participate in the study.

Data were analysed using descriptive statistics.

2.4 | Ethics

The study was registered with the repository of the Region of Southern Denmark (approval 23/32304). The Regional Committees on Health Research Ethics waived registration due to the study design (case number 20232000-89). Patient inclusion was based on informed and verbal consent obtained at the counter of the pharmacies. Participants were provided with a written patient information, detailing their rights as study participants.

3 | RESULTS

A total of 1013 individuals redeeming a prescription on SEMA-WL were invited to participate in the study, of which 587 (58%) accepted. Of these, 28 individuals were excluded because they picked up the prescription on behalf of a relative, resulting in a total of 559 (55%) SEMA-WL users who completed the questionnaire.

3.1 | User characteristics

More than three-quarters of SEMA-WL users were aged 36–65 years (76%, n = 423) and female (78%, n = 434) (Table 1). The median BMI

at the time when users had initially started SEMA-WL treatment was 36 (IQR 32-40), based on self-reported weight and height at treatment initiation. Further, 93% (n = 482) had a BMI of ≥ 30 at treatment initiation, while 6.9% (n = 36) had a BMI <30 (data not shown). Very few (1%, n = 5) had a BMI of <27 at treatment initiation. Half of users reported having comorbidities linked to overweight (47%, n = 262), most commonly hypertension (27%, n = 149), muscle/joint pain (23%, n=126) and hypercholesterolemia (10%, n=55) (Table 1). Additionally, 6% (n = 35) mentioned having reduced quality of life due to overweight. Half of users reported having no overweight-related comorbidities (52%, n = 289). The majority of users had previously tried other weight-reducing interventions prior to treatment initiation with SEMA-WL (90%, n = 505), most often changes in dietary and physical exercise habits (87%, n = 485 and 70%, n = 392, respectively). Further, 27% (n = 150) had previously tried other weight-reducing medications, most often combinations of ephedrine and caffeine (10%, n = 54) and medications containing liraglutide (7%, n = 41).

3.2 | Treatment expectations

Users had heard about treatment with SEMA-WL from several sources, most often friends and family (35%, n=193), a physician (32%, n=178), social media (24%, n=134) and the news (23%, n=130) (Table 2). Two in three users had personally asked their general practitioner to initiate treatment with SEMA-WL (70%, n=392). Further, almost half of users had not discussed treatment duration with their general practitioner (42%, n=237); 46% (n=258) expected treatment for a limited time period, while only 11% (n=64) expected lifelong treatment. For those who expected treatment for a limited time period, this would be determined by a specific weight loss (59%, n=152).

3.3 | Experienced effectiveness, side effects and drug administration

Experienced weight loss increased with increasing treatment length for the overall study population (Figure 1). Specifically, self-reported weight loss corresponded to a median weight loss of 5.3% (IQR 3.2–8.5) for users treated with SEMA-WL for <3 months (24%, n=115), 10% (IQR 8.2–14) for 3–5 months of treatment (17%, n=82) and 17% (IQR 13–21) for those treated for >5 months (58%, n=276). Self-reported weight loss was similar for men and women after <3 and 3–5 months of treatment, respectively; however, women tend to lose slightly more weight after >5 months of treatment, with a median weight loss of 18% (IQR 14–22) for women (79%, n=219) compared with 14% (IQR 11–16) for men (21%, n=57) (Appendix 2).

Almost all users had been informed about one or more potential side effects to treatment with SEMA-WL (99%, n=521), most often nausea (72%, n=402), constipation (55%, n=305), diarrhoea (47%, n=261), headache (43%, n=238), decreased appetite (40%, n=226) and abdominal pain (40%, n=225) (Figure 2A). More than half of users had experienced one or more side effects (59%, n=330), most

TABLE 1 Characteristics of Danish adult users of semaglutide for weight loss and control (Wegovy®, SEMA-WL).

	Study population (n = 559)	Men (n = 125)	Women (n = 434
Age			
18-25 years	19 (3%)	n <5	15 (4%)
26-35 years	68 (12%)	17 (14%)	51 (12%)
36-45 years	115 (21%)	19 (15%)	96 (22%)
46-55 years	168 (30%)	36 (29%)	132 (30%)
56-65 years	140 (25%)	34 (27%)	106 (24%)
66-75 years	45 (8%)	15 (12%)	30 (7%)
>76 years	n <5	0	n <5
Self-reported BMI (kg/m²) at treatment initiation with SEMA-WL, median (IQR) ^a	36 (32-40)	37 (33-40)	36 (32-41)
Self-reported comorbidities linked to overweight ^b			
No	289 (52%)	58 (46%)	231 (53%)
Yes	262 (47%)	65 (52%)	197 (45%)
Hypertension	149 (27%)	44 (35%)	105 (24%)
Muscle and joint pain	126 (23%)	23 (18%)	103 (24%)
Hypercholesterolemia	55 (10%)	9 (7%)	46 (11%)
Sleep apnoea	20 (4%)	11 (9%)	9 (2%)
• Diabetes	5 (1%)	n <5	n <5
Cardiovascular disease	12 (2%)	n <5	8 (2%)
• Cancer	n <5	0	n <5
Mental problems	13 (2%)	n <5	12 (3%)
Unfulfilled pregnancy wish	n <5	0	n <5
Decreased quality of life	35 (6%)	5 (4%)	30 (7%)
Previous weight-reducing interventions before treatment initiation with SEMA-WI	L		
No	54 (10%)	18 (14%)	36 (8%)
Yes	505 (90%)	107 (86%)	389 (90%)
Changes in dietary habits	485 (87%)	102 (82%)	383 (88%)
Changes in physical exercise habits	392 (70%)	90 (72%)	302 (70%)
Surgical treatment (bariatric surgery)	25 (4%)	0	25 (6%)
Previous experience with weight-reducing medication before treatment initiation v	with SEMA-WL		
No	409 (73%)	106 (85%)	303 (70%)
Yes	150 (27%)	19 (15%)	131 (30%)
Orlistat® (orlistat)	11 (2%)	n <5	9 (2%)
Regenon® (amfepramone)	14 (3%)	0	14 (3%)
Mysimba [®] (bupropion/naltrexone)	n <5	n <5	n <5
Saxenda [®] , Victoza [®] , Xultophy [®] (liraglutide)	41 (7%)	6 (5%)	35 (8%)
Ephedrine/caffeine combinations	54 (10%)	5 (4%)	49 (11%)

Abbreviations: BMI, body mass index; IQR, interquartile range; SEMA-WL, semaglutide for weight loss and control (Wegovy®).

commonly nausea (35%, n = 193), constipation (29%, n = 160) and decreased appetite (17%, n = 95) (Figure 2B).

Finally, the majority of users reported being comfortable with administering SEMA-WL via self-injection (91%, n=510), while only 6% (n=32) felt uncomfortable about it (data not shown). Despite this, 42% (n=235) reported that they would prefer a daily tablet over a weekly injection if this should ever be an option. While 40% (n=222) reported that they would prefer a weekly injection over a

daily tablet, the remaining 18% (n=102) had no preferences towards either of it.

4 | DISCUSSION

Based on our national survey of 559 adult users of SEMA-WL recruited from Danish community pharmacies, we found three in four

^a7.3% of users did not respond to this question. BMI calculated based on self-reported weight and height at treatment initiation.

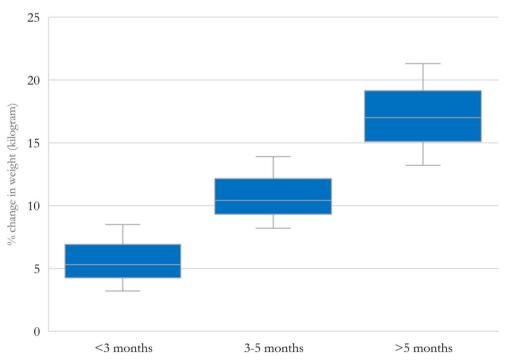
^b1% of users did not respond to this question.

Considerations related to treatment initiation with semaglutide for weight loss and control (Wegovy®, SEMA-WL) among users.

	Study population (n = 559)	Men (n = 125)	Women (n = 434)
Who suggested treatment with SEMA-WL			
The patient	392 (70%)	91 (73%)	301 (69%)
The general practitioner	129 (23%)	23 (18%)	106 (24%)
Others (e.g., weight loss clinic)	38 (7%)	11 (9%)	27 (6%)
Where did the user hear about treatment with SEMA-WL			
The general practitioner	178 (32%)	44 (35%)	134 (31%)
Friends and family	193 (35%)	39 (31%)	154 (36%)
The news	130 (23%)	34 (27%)	96 (22%)
Social media	134 (24%)	27 (22%)	107 (25%)
Official healthcare websites (e.g., sundhed.dk, minmedicin.dk)	27 (5%)	8 (6%)	19 (4%)
Other sources ^a	42 (8%)	10 (8%)	32 (7%)
Expected duration of treatment with SEMA-WL based on discussion	n with physician		
Not discussed	237 (42%)	41 (33%)	196 (45%)
Treatment for a limited period	258 (46%)	66 (53%)	192 (44%)
Lifelong treatment	64 (11%)	18 (14%)	46 (11%)
Focus for limited treatment period with SEMA-WL	n = 258	n = 66	n = 192
Time (e.g., a certain limited time period)	84 (33%)	17 (26%)	67 (35%)
Determined weight loss (specific body weight)	152 (59%)	46 (70%)	106 (55%)
Other reasons ^b	42 (16%)	6 (9%)	36 (19%)

Abbreviation: SEMA-WL, semaglutide for weight loss and control (Wegovy®).

FIGURE 1 Self-reported weight loss[†] among users of semaglutide for weight loss and control (Wegovy®, SEMA-WL) for < 3 months (n = 115), 3-5 months(n = 82) and >5 months (n = 276), respectively. [†]Weight loss calculated based on selfreported weight at treatment initiation and time of data collection, respectively.

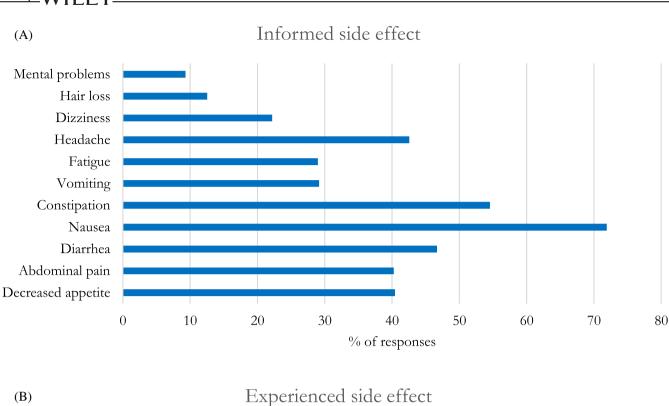


Treatment duration at time of data collection

users to be female and middle-aged. Two in three users had personally suggested treatment initiation with SEMA-WL to their general practitioner. Four in ten users had not discussed expected treatment duration with their general practitioner, almost half expected treatment for a limited time period, while only one in ten expected lifelong treatment. Selfreported weight loss corresponded to a median weight loss of 5.3% (IQR

^aOther sources mainly included hospitals, specialist physicians, the internet and work.

^bOther reasons included a variety of factors such as economics, personal desire to undergo treatment and lifestyle changes.



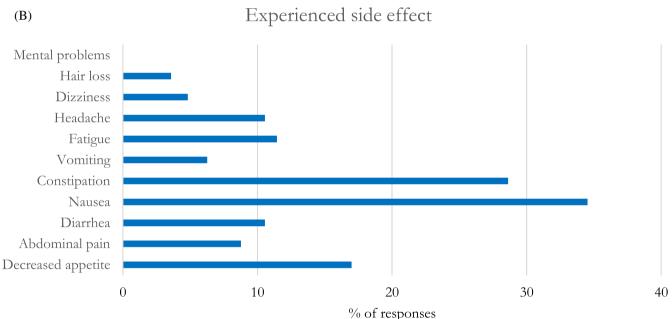


FIGURE 2 Self-reported informed (A) and experienced (B) side effects among users of semaglutide for weight loss and control (Wegovy®, SEMA-WL).

3.2-8.5) for users treated with SEMA-WL for <3 months, 10% (IQR 8.2-14) for 3-5 months of treatment and 17% (IQR 13-21) for those treated for >5 months. More than half of users had experienced side effects to SEMA-WL, most often nausea and constipation.

4.1 | Strengths and limitations

The main strength of our study is the large number of participants, recruited from community pharmacies from all five Danish regions

and including both urban and rural areas. Our study also has several limitations that need to be considered. First, we had a response rate of 55%, which is lower compared with previous Danish community pharmacy-based surveys (range 77%–90%)^{11–13} and thus a risk of selection bias. Several factors might explain this. Questions and discussions about lifestyle, weight and use of medication for weight management are likely sensitive to some users, as they may be associated societal stigma and discrimination.¹⁴ Further, users that accepted study participation might be those who feel safe about and/or tolerate their treatment with SEMA-WL, that is, those who experience

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weight loss with minimal side effects, as their longer use of SEMA-WL increases the likelihood of being invited to study participation. This also means that the experienced weight losses and side effects reported in our study might not reflect the effectiveness and severity of side effects experienced by the entire population of initiators of SEMA-WL. Second, our use of an interview-based questionnaire introduces the possibility of social desirability bias, that is, with users responding what is perceived socially acceptable. ¹⁵ However, because our study population likely constitutes a selected group of users that are seemingly willing to discuss personal matters about weight management, we believe this to have limited impact on our findings. Third, while our questionnaire included questions about previous weight loss interventions (changes in dietary and physical exercise habits, use of weight-reducing medications), it did not assess whether any of these interventions were still used concurrently with use of SEMA-WL. Use of any of such interventions might have impacted the reported weight losses and thus potentially confound our data interpretation. Fourth, not all consecutive users were invited to participate in the study. Based on sales statistics from the participating pharmacies, 51% of individuals redeeming a prescription on SEMA-WL were invited to study participation. The share of SEMA-WL customers that were invited by staff varied extensively across pharmacies (range 10%-98%), with pharmacies with poor participant recruitment all mentioning busyness, in particular in outer opening hours, as the main reason. Pharmacies with poor participant recruitment included pharmacies from both urban and rural areas. Finally, our three pilot tests of the questionnaire were restricted to only one pharmacy in one of the larger cities in Denmark. However, given our inclusion of participants from pharmacies in both urban and rural areas across Denmark, we believe this to have limited impact on our findings.

4.2 | Comparison with existing literature

Our finding of the majority of users of SEMA-WL being middle-aged and female aligns with the user characteristics reported in a recent population-based cohort study of Danish adult users of SEMA-WL¹⁶ as well as in the STEP trials,^{3,17–19} which investigated the efficacy of SEMA-WL in people without diabetes. However, the proportion of users with overweight-related comorbidities appears to be lower in our study compared with both the Danish cohort study (e.g., hypertension 27% vs. 30%)¹⁶ and the STEP trials (hypertension range 36%–37%).^{3,17–19} This might be partly explained by this risk of social desirability as well as self-reporting bias in our study.

The median weight loss of 15% among users treated with SEMA-WL for >5 months in our study is similar to the weight losses reported in both the STEP 1 and 5 trials, 3.17 which investigated the efficacy of 68 and 104 weeks of treatment with SEMA-WL respectively. At the time of our data collection, SEMA-WL had been available for 9–13 months in Denmark, corresponding to 39–56 weeks. Despite this being less than the durations of the STEP trials, 3.17 our findings could potentially indicate that the long-term users of SEMA-WL (>5 months) were about to reach the plateau in weight loss, which was demonstrated after approximately

60 weeks of treatment in the STEP 5 trial,³ also considering that users in our study and the STEP trials had similar BMIs at treatment initiation with SEMA-WL (mean 37 vs. mean 38¹⁷ vs. mean 39³). Interestingly, a recent cohort study of 110 748 Danish adults who filled prescriptions on SEMA-WL from December 2022 to December 2023 found that few followed the dose titrations schemes tested in premarket clinical trials (target dose of 2.4 mg); rather, 33%-48% continued with a dose of 1 mg from the fourth prescription onward. 16 We did not register dosages of SEMA-WL used by our study participants and it is thus unclear whether the weight losses were achieved with lower-than-recommended dosages or the target dose of 2.4 mg. A recent Danish qualitative study of weight loss management with SEMA-WL in general practice found that some users of SEMA-WL declined to increase their dose due to economic constraints, while others would have discussions with their general practitioner about continuing at a lower dose in case of side effects, and/or changing the dose when the weight loss effect of treatment did not live up to the users' expectations.²⁰ Given our national participant recruitment, this could potentially also apply to some of the users of SEMA-WL in our study. Regardless, future research should look into whether users of SEMA-WL achieve weight losses with lower-than-recommended dosages or the target dose of 2.4 mg to better understand the effectiveness and side effects of SEMA-WL as it is used in the real-world setting.

Our finding that two in three users had personally suggested treatment initiation with SEMA-WL to their general practitioner aligns with findings from a recent qualitative study where some Danish general practitioners felt a patient-demand to prescribe SEMA-WL. Opecifically, some general practitioners described the introduction of SEMA-WL as having completely changed the discussion about weight and weight management in general practice; where it would previously rely on general practitioners to bring up such discussion it was now often brought up by well-informed and -prepared patients. The user-initiated prescription of SEMA-WL found in our study and the pressure from patients demanding (continuous) prescribing of SEMA-WL experienced by some Danish general practitioners 20,21 are further supported by recent register-based findings of close to 90% of all SEMA-WL prescriptions in Denmark being issued in general practice. 16

We found that almost all users of SEMA-WL had been informed about one or more potential side effects to treatment with SEMA-WL, which aligns with findings from observations of consultations in Danish general practice, where general practitioners and nurses spoke openly with their patients about side effects to SEMA-WL, including unknown long-term side effects.²⁰ Users of SEMA-WL in our study most often mentioned being aware of nausea and constipation as potential side effects, which were also the side effects most frequently experienced (35% and 29%, respectively). This generally aligns with findings from the STEP trials, where nausea (range 44%–53%) and constipation (range 23%–31%) were also some of the most frequently reported adverse events among study participants.^{3,17}

In conclusion, this study provides valuable insights into the characteristics, expectations, effectiveness and side effects experienced by adult users of SEMA-WL in Denmark. Users to some extent resembled those of trial participants in terms of characteristics as well as



experienced effectiveness and side effects. Further, for two in three users, treatment was initiated based on a personal request to the general practitioner, often with no discussion about expected treatment duration. This knowledge is pertinent for healthcare providers who prescribe, monitor and provide treatment guidance as well as for health authorities who regulate treatment with SEMA-WL.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest. Anton Pottegård reports participation in research projects funded by Alcon, Almirall, Astellas, AstraZeneca, Boehringer-Ingelheim, Novo Nordisk, Servier and LEO Pharma (all regulator-mandated phase IV-studies), and an unrestricted research grant from Novo Nordisk, all with funds paid to the institution where he was employed (no personal fees) and with no relation to the work reported in this article. Reimar W. Thomsen reports that he has given presentations and lectures on medical research (both with and without financial compensation) for various companies, including Astra-Zeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Novo Nordisk and Sanofi. He reports no other personal conflicts of interest; however, the Department of Clinical Epidemiology, Aarhus University and Aarhus University Hospital receives funding for other studies from companies in the form of research grants to (and administered by) Aarhus University. None of these studies have any relation to the current study.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.16222.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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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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