Subcutaneous Semaglutide Use for Weight Management: Practice and Attitudes of Physicians in Israel

Dror Dicker MD[1,6], Orly Tamir PhD MSc MHA[2], Gabriella Lieberman-Segal MD[3,4,6], Roy Eldor MD PhD[5,6], Moran Accos-Carmel RD MAN[2], Tatyana Kolobov PhD[2], and Avraham Karasik MD[3,6]

[1]Department of Medicine D and Obesity Clinic, Rabin Medical Center (HaSharon Campus), Petah Tikva, Israel
[2]Segal Israeli Center for Diabetes Research and Policy, [3]Institute of Endocrinology, and [4]Israel Center for Weight Management, Sheba Medical Center, Tel Hashomer, Israel
[5]Department of Endocrinology, Metabolism, and Hypertension, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel
[6]Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

ABSTRACT **Background:** In 2019, 1 mg subcutaneous semaglutide was registered for the treatment of diabetes in Israel. Recognition of its effect on weight has led to its use as a treatment for obesity.

Objectives: To explore physicians' pre-therapy considerations, therapy practices, and attitudes regarding subcutaneous semaglutide for weight loss.

Methods: A 22-item questionnaire was disseminated to physicians who prescribed semaglutide 1-mg for weight loss using an authorized off-label path.

Results: In total, 127 physicians completed the questionnaire. As for pretreatment requirements, in the absence of diabetes, 30% requested a minimal body mass index of 30 kg/m^2. Additional requirements were documented lifestyle-change effort (67%) and prior weight loss medication use (13%). Half of the physicians regarded calorie restriction, and 23% considered physical activity as necessary for weight loss while on therapy. As for dose, most physicians (78%) started with a 0.25-mg weekly injection, 57% doubled the dose monthly, and all others recommended doubling when side effects subsided. Regarding weight loss goal, 43% of the physicians set a personal goal with each patient while 26% limited the goal to 10% of initial weight. Fewer than 50% of physicians discussed treatment duration with their patients, and 52% of patients discontinued therapy in the first 3 months. The main reasons for discontinuation were price, lack of effect, and fear of long-term side effects.

Conclusions: The diverse approaches regarding off-label use of semaglutide for weight reduction highlight the necessity to guide physicians and standardize treatment regimen.

IMAJ 2023; 25: 664–668

KEY WORDS: obesity, off-label, semaglutide, treatment guidelines, weight management

Semaglutide, a glucagon-like peptide 1 receptor analogue (GLP-1RA), has been approved by the U.S. Food and Drug Administration (FDA) as a treatment for type 2 diabetes mellitus (T2DM) and obesity [1-3]. Initially, in 2017 once weekly subcutaneous semaglutide at a dose up to 1 mg (Ozempic®, Novo Nordisk, Denmark) was approved as an adjunct to diet and exercise to improve glycemic control in adults with T2DM and reduce the risk of major cardiovascular events [1]. This indication has been recently expanded to allow a dose increase of up to 2 mg when needed [2]. In June 2021, based on the STEP development program, subcutaneous semaglutide at a dose of up to 2.4 mg (Wegovy®, Novo Nordisk, Denmark) was approved as an adjunct to a reduced calorie diet and increased physical activity for chronic weight management in adult patients with an initial body mass index (BMI) of 30 kg/m^2 or greater (obesity) or 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related co-morbid condition (e.g., hypertension, T2DM, or dyslipidemia) [3].

Since Wegovy is not currently approved for use in Israel, off-label use of Ozempic for weight management, which is allowed subject to authorization granted by the Israeli Ministry of Health, became widespread. This possibility led to a shortage of the medication at the end of April 2022 and the sanctioning of its use by the Ministry of Health. Moreover, without a clear indication and dosing information, physicians prescribed off-label semaglutide at a dose up to 1 mg (Ozempic) for weight management based on personal experience. To better understand this practice and the experience gained from it, we conducted a survey among Israeli endocrinologists, internal medicine physicians, and family physicians who practice obesity medicine.

PATIENTS AND METHODS

A cross-sectional survey was conducted in Israel during the month of April 2022. A 22-item questionnaire was circulated among physicians who prescribed off-label semaglutide (Ozempic) for obesity. The physicians included specialists in endocrinology, internal medicine, and family medicine who practiced obesity medicine. All were members of the Israeli Society for

the Study of Obesity, the National Council for Diabetes, the Israel Endocrine Society, or Forum of Family Practitioners (a total of approximately 1000 physicians). The survey inventory was designed specifically for this study and included questions regarding pre-therapy considerations, therapy practices and recommendations, strategies to promote patient adherence, and adverse events [The English text of the questionnaire is available in the online version only]. The questionnaire was created using Google Forms and disseminated via email and WhatsApp links. Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 25 (SPSS, IBM Corp, Armonk, NY, USA). The study was approved by the institutional review board of the Sheba Medical Center (approval number SMC-9158-22).

RESULTS

The survey was completed by 127 physicians (response rate 12.7%). Among the responders, 65 (51%) were primary care physicians, 36 (28%) endocrinologists, and 26 (21%) specialists in internal medicine. In addition, 58% worked in a community clinic, 35% in a hospital setting, and 7% in private practice. Most of the responders (78%) reported having experience treating fewer than 100 patients with off-label semaglutide (Ozempic) for weight management and the rest (22%) reported experience treating more than 100 patients.

PRE-THERAPY CONSIDERATIONS

In the absence of diabetes, the minimal BMI for treatment with off-label semaglutide (Ozempic) for weight management was reported as 27, 30, and 35 kg/m^2 by 17%, 30%, and 53% of physicians, respectively. In patients without any weight-related co-morbid condition (e.g., hypertension or dyslipidemia), the minimal BMI for treatment was reported as 27, 30, and 35 kg/m^2 by 8%, 26%, and 66% of physicians, respectively. Two-thirds of the responders required lifestyle changes as a prerequisite to treatment initiation, 13% required a previous therapy failure with liraglutide 3 mg, whereas 11% prescribed semaglutide as first-line therapy for weight loss with no previous recorded effort for intentional weight loss. Half of the physicians did not discuss or state the duration of therapy with their patients before initiating semaglutide (Ozempic), while 25% emphasized that the therapy was indefinite. Nine percent recommended the duration of therapy to be until the weight goal was achieved and 12% until required lifestyle changes reached a point that would allow weight loss maintenance. The amount of weight to be lost was not discussed by 17% of physicians; 43% set a personal goal for weight loss, 26% recommended a reduction of 5–10% in weight, and 5% aimed at a BMI of lower than 30 kg/m^2, while 9% encouraged patients to lose as much weight as they could. Sixty percent of physicians reported that they would not prescribe off-label semaglutide (Ozempic) for weight management in patients with diagnosed eating disorders. Whereas 47% of the responders regarded a low-calorie diet and nutritional support as essential for achieving weight loss, 66% deemed it essential only for weight loss maintenance. Only 23% of responders regarded physical activity as essential for achieving weight loss, and 48% deemed it essential only for weight loss maintenance. Of all responders, 77% worked in collaboration with nutritionists when prescribing off-label semaglutide (Ozempic) for weight management and 18% involved no other practitioner in care. The main results are presented in Figure 1.

THERAPY PRACTICES

Most physicians (78%) started with a dose of 0.25 mg once a week, although others started with 0.5 mg once a week. Almost all of those starting with 0.5 mg did so in patients who were already taking another GLP-1 RA. A maximal dose of 1 mg, 2 mg, and 2.4 mg was set by 72%, 2%, and 26% of responders. While 57% of phy-

Table 1. Occurrence and duration of side effects

Side effect	Percent of physician reporting						
	Occurrence				Duration		
	Number	Rare	< 10%	> 10%	Number	< 3 weeks	> 3 weeks
Nausea	127	8%	32%	68%	127	65%	21%
Vomiting	127	39%	85%	15%	127	54%	3%
Constipation	127	35%	72%	27%	127	33%	27%
Diarrhea	127	20%	71%	28%	127	53%	21%
Headache	127	57%	91%	9%	127	30%	9%
Malaise	121		79%	21%			
Dysphoria	121		93%	7%			
Weakness / fatigue	121		80%	17%			

Figure 1. Pre-therapy considerations

BMI = body mass index

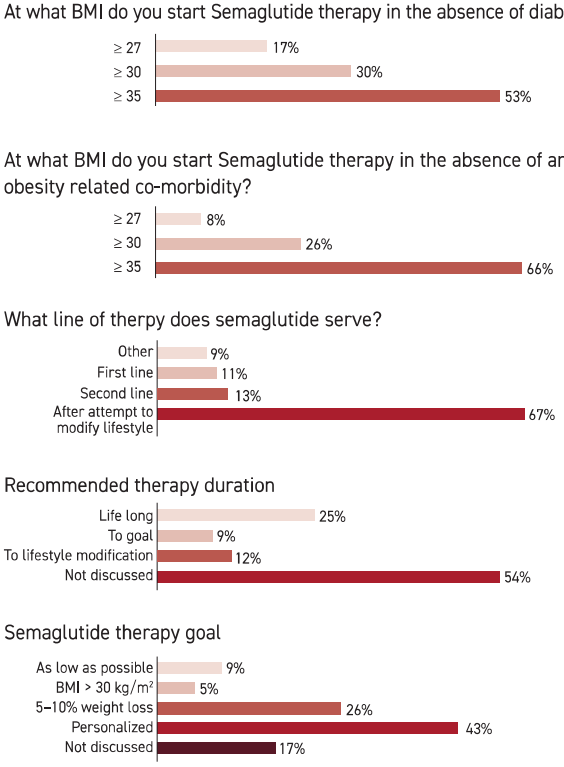
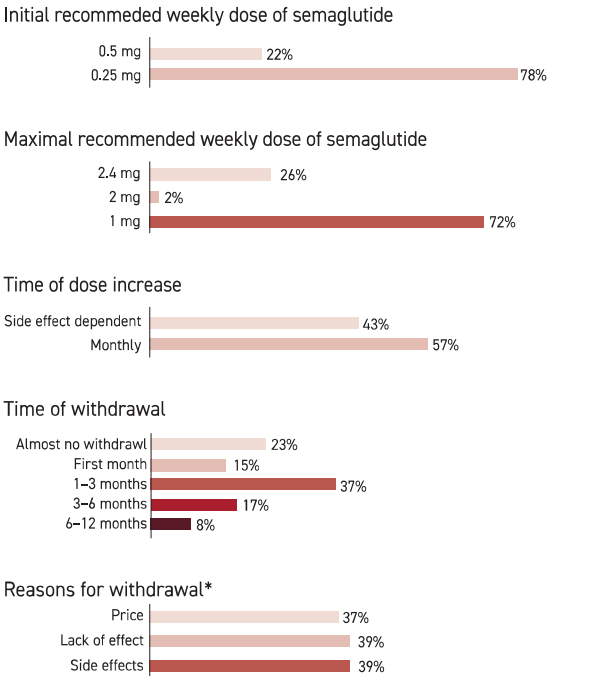


Figure 2. Therapy practices



*Top 3 reasons. All the rest were mentioned by < 20% of responders

sicians doubled the dose after 4 weeks, others increased the dose after side effects disappeared. Half (51%) recommend reduction of dose on appearance or persistence of disturbing side effects and one-third (33%) left the decision to the patient's discretion. Most patients discontinue therapy during the first 3 months, according to 52% of the physicians. The main reasons for discontinuation as interpreted by the physicians were: price of the medication (37%), lack of effect (39%), and adverse effects (39%). The main results are presented in Figure 2.

SIDE EFFECTS

The most common side effects were gastrointestinal, with nausea being the leading complaint. Most of the reported side effects subsided within 3 weeks. Other commonly observed side effects were headache, malaise, weakness/fatigue, and dysphoria [Table 1].

DISCUSSION

We examined the way physicians in Israel acted when prescribing off-label use of subcutaneous semaglutide 1 mg for weight management. This practice quickly became widespread, even though there are currently other weight loss medications available and registered in Israel for this purpose (e.g., liraglutide 3 mg, orlistat, and phentermine). This off-label use led to several problems, including a shortage of the medication affecting patients treated for the labeled indication (e.g., T2DM); confusion with regard to patient selection, treatment initiation, dose escalation, maintenance, and multidisciplinary follow-up; and a limited ability to increase the dose beyond 1-mg and a lack of clear criteria and guidance on how and in whom to recommend higher dosage. Our survey included information on the choices and behaviors of physicians who prescribed off-label Ozempic for weight management, which can serve as a basis for a guidance plan.

While the label for both semaglutide and liraglutide for obesity are clear and similar (indicated as an adjunct to a reduced calorie diet and increased physical activity for chronic weight management in adult patients with an initial BMI ≥ 30 kg/m^2 or BMI ≥ 27 kg/m^2 in the presence of at least one weight-related co-morbid condition), when prescribing off-label semaglutide for weight management, common clinical practice is different. Most physicians chose a BMI ≥ 35 kg/m^2 as a threshold for initiating therapy regardless of weight-relat-

ed co-morbid conditions. However, 8% of physicians recommended this therapy even in patients with a BMI as low as 27 kg/m^2 without weight-related co-morbid conditions. Similarly, most physicians required a previous attempt at lifestyle modification to initiate therapy and not as an adjunct to therapy. Others defined prescribing off-label semaglutide for weight management as a second line therapy despite no mention of this approach in the FDA-approved label.

In the SCALE and STEP program studies, a rapid increase in weight was observed on cessation of liraglutide or semaglutide, even after a long duration of therapy [4,5], which highlights the importance of chronic treatment with these medications. Nonetheless, more than half of the physicians who responded to the survey did not discuss the duration of the therapy with patients and some believed that the treatment should be terminated once the weight loss goal was obtained or on achievement of lifestyle modification. This approach is contradictory to the label and to clinical research data and may result in loss of the therapeutic effect achieved. Interestingly, 43% of physicians felt that the amount of weight that needed to be lost with treatment should be personalized, which is somewhat different than the paradigm used in the past few years, advocating a 5–10% weight loss to achieve a metabolically significant change. This finding may represent a paradigm change based on high variability in the reaction to weight lowering medications, with many people exceeding the weight loss expectations with semaglutide [6].

While initiating treatment, most physicians adhered to the FDA-approved label of subcutaneous semaglutide 1 mg (Ozempic) with regard to the initial dose, maximal dose, and dose increase. However, 43% of physicians based their escalation technique on the side effects experienced by the patient. This regime, based on real-life experience and different from what was evaluated in the clinical trials, probably better serves the patient, and is gradually being recommended by experts in obesity medicine.

Semaglutide is a potent drug for weight reduction. A phase-2 study [7] showed that doses as low as 0.1–0.2 mg per day, which is somewhat equivalent to the 1 mg per week dose and the prevalent choice of our responders, were at least as potent as liraglutide 3.0 mg a day, leading to an average weight loss of 8.6–11.6% vs. 7.8% with liraglutide. A weight loss of 5% and 10% was observed in 67–75% and 37–56% of participants receiving 0.1–0.2 mg per day of semaglutide, respectively. Due to the high efficacy of semaglutide for weight reduction, even at low doses, it is somewhat surprising that 52% of physicians in our survey reported that patients withdrew from treatment within the first 3 months, with lack of effect and intolerable side effects being the top two reasons. Our understanding is that this situation is one of the consequences of the off-label regime, with patients facing shortages of the medication and consequently receiving it in a lower than recommended dose and exposure, leading them to a sense of failure that may serve to discourage them trying semaglutide 2.4 mg (Wegovy) when it will become available.

In our survey, we also studied perceptions of physicians regarding a multidisciplinary approach in the treatment of weight reduction and maintenance. One-third of the responders considered it mandatory for other practitioners (i.e., nutritionists and nurses) and the physician to participate in the process of achieving and maintaining weight loss, while no clear mention of this approach appears on the label. This finding may represent the understanding of Israeli physicians that a team approach, enhancing the availability of team members to the patients in dealing with emerging side effects, and providing nutritional guidance is inherent to a successful weight-loss and weight maintenance program. Moreover, with potent drugs causing significant appetite suppression, this approach may ensure that all the nutritional needs of the patients are met.

Last, the side effects reported in our survey were generally similar to those reported in other GLP-1RA studies [8,9] and consisted mainly of gastrointestinal related events. However, physicians responding to our survey also reported a high occurrence of malaise and dysphoria, which have not been commonly reported in clinical trial of semaglutide 1 mg for T2DM or semaglutide 2.4 mg for obesity.

Our study had several limitations. First, the survey was conducted at a time when the shortage of the drug first became apparent. This finding may have led to a change in practice during the data collection period. This limitation can be addressed by performing follow-up survey assessments at multiple time points to evaluate shifts in the studied practice and attitudes. Second, the study used a self-report approach. Data such as actual BMI at therapy initiation were not validated.

This study provides a unique opportunity to observe clinical practices that arose from necessity rather than choice. Moreover, our findings highlighted the complexity of obesity treatment in a world of increasing demand for a quick solution for weight loss and misunderstanding of the chronic nature of obesity as a disease. Physicians prescribing off-label semaglutide 1 mg for the treatment of obesity developed and expressed different modes of using this new potent drug, underscoring the need to better characterize and implement the optimal treatment regime.

CONCLUSIONS

Diverse modes of therapy with off-label use of semaglutide for weight management are practiced by physicians in Israel. This observation addresses the issues raised in the survey and defines clearer guidelines with regard to dosing, the chronic nature of this therapy, and the importance of combining ongoing lifestyle support and a team approach to ensure maximal persistence and an optimal effect on weight loss and maintenance of this potent drug in the real world.

Correspondence

Dr. A. Karasik

Institute of Endocrinology, Sheba Medical Center, Tel Hashomer 5262100, Israel

Email: karasik@tauex.tau.ac.il

References

1. Novo Nordisk. Company Announcements: Ozempic® (semaglutide) approved in the US. 5 December 2017. [Available from https://www.novonordisk.com/content/nncorp/global/en/news-and-media/news-and-ir-materials/news-details.html?id=712]. [Accessed 8 April 2023].
2. Novo Nordisk. Press release: Novo Nordisk receives FDA approval of higher-dose Ozempic® 2 mg providing increased glycemic control for adults with type 2 diabetes. [Available from https://www.novonordisk-us.com/media/news-archive/news-details.html?id=108097]. [Accessed 8 April 2023].
3. US Food and Drug Administration. FDA news release. FDA Approves New Drug Treatment for Chronic Weight management, First Since 2014. Updated 4 June 2021. [Available from https://www.fda.gov/news-events/press-announcements/fda-approves-new-drug-treatment-chronic-weight-management-first-2014]. [Accessed 6 June 2022]
4. le Roux CW, Astrup A, Fujioka K, et al; SCALE Obesity Prediabetes NN8022-1839 Study Group. 3 years of liraglutide versus placebo for type 2 diabetes risk reduction and weight management in individuals with prediabetes: a randomized, double-blind trial. *Lancet* 2017; 389 (10077): 1399-409.
5. Davies M, Færch L, Jeppesen OK, et al. STEP 2 Study Group. Semaglutide 2·4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): a randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial. *Lancet* 2021; 397: 971-84.
6. Bray GA, Ryan DH. Evidence-based weight loss interventions: Individualized treatment options to maximize patient outcomes. *Diabetes Obes Metab* 2021 23 (Suppl 1): 50-62.
7. O'Neil PM, Birkenfeld AL, McGowan B, et al. Efficacy and safety of semaglutide compared with liraglutide and placebo for weight loss in patients with obesity: a randomised, double-blind, placebo and active controlled, dose-ranging, phase 2 trial. *Lancet* 2018; 392: 637-49.
8. Bettge K, Kahle M, Abd El Aziz, et al. Occurrence of nausea, vomiting and diarrhoea reported as adverse events in clinical trials studying glucagon-like peptide-1 receptor agonists: a systematic analysis of published clinical trials. *Diabetes Obes Metab* 2017; 19: 336-47.
9. Horowitz M, Aroda VR, Han J, et al. Upper and/or lower gastrointestinal adverse events with glucagon-like peptide-1 receptor agonists: incidence and consequences. *Diabetes Obes Metab* 2017; 19: 672-81.

There is always more goodness in the world than there appears to be, because goodness is of its very nature modest and retiring.

Evelyn Beatrice Hall (1868–1956), wrote under the pseudonym S[tephen] G. Tallentyre, was an English writer best known for her biography of Voltaire

Capsule

Regulatory T cells of distinction

Blocking the suppressive activity of CD4+ regulatory T cells (T_{regs}) to reinvigorate the immune system against tumors comes with substantial risks of adverse effects because of their critical role in immune tolerance. **Shan** et al. identified a subpopulation of T_{regs} enriched in the tumor microenvironment specifically by comparing CD4+ T cells from healthy individuals with those from patients with head and neck squamous cell carcinomas. Characterized by gene expression programs and suppressor function under the control of the transcription factor BATF, these distinct T_{regs} were associated with poorer outcomes across a variety of cancers. It may thus be possible to inhibit tumor-infiltrating T_{regs} by targeting the distinct gene-regulatory networks that control their suppressor function without impairing immune homeostasis in general.

Sci Immunol 2023; 8 (87): eadf6717

Eitan Israeli

Capsule

Alternative splicing for invadopodia

Different transcripts can be produced from the same gene through alternative splicing. **Li** et al. found that colorectal cancer cells formed metastasis associated structures called invadopodia, which are caused by alternative splicing. Signaling from the tumor stroma induced the expression of a long noncoding RNA in colorectal cancer cells. The long noncoding RNA altered the way that a splicing factor acted on a target pre-messenger RNA, resulting in more of the longer transcript and less of the shorter tumor-suppressive transcript. This switch enabled invadopodia formation and invasion in colorectal cancer cells.

Sci Signal 2023; 16 (803): eadh4210

Eitan Israeli