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Janine V. Kyrillos

Neil S. Skolnik

Bhasha Mukhopadhyay

Nicholas Pennings

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SUPPLEMENT: SEMAGLUTIDE FOR WEIGHT MANAGEMENT – AN INTRODUCTION FOR PRIMARY CARE

Integrating semaglutide into obesity management – a primary care perspective

Janine V. Kyrillos [a], Neil S. Skolnik [b], Bhasha Mukhopadhyay [a] and Nicholas Pennings [c]

[a]Jefferson Comprehensive Weight Management, Thomas Jefferson University, Philadelphia, PA, USA; [b]Abington Family Medicine, Abington Jefferson Health, Abington, PA, USA; [c]Family Medicine, Campbell University School of Osteopathic Medicine, Campbell University, Lillington, NC, USA

ABSTRACT

This final article in the supplement aims to summarize a clinical approach for weight management geared toward primary care practitioners, offering practical advice about how to integrate weight management into day-to-day practice. To achieve long-term successful weight loss, a comprehensive multimodal approach is recommended, focusing on both lifestyle modification and appropriate use of therapy. Once-weekly subcutaneous semaglutide 2.4 mg is a novel treatment that can be used as an adjunct to lifestyle modification for the management of overweight and obesity. Key considerations are presented to support its optimal administration in conjunction with lifestyle modification, with a focus on assessing suitability and the importance of dose escalation and monitoring.

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1. Introduction

The prevalence of obesity in the United States is over 40% [1], yet it is often not identified as a medical problem that needs to be addressed. While multiple medical organizations recognize obesity as a chronic disease, including the American Medical Association and World Health Organization [2], and evidence-based treatment options are available [3–6], multiple barriers to effective obesity care exist. Physicians and other healthcare stakeholders may not recognize obesity as a disease that requires ongoing management [7]. In addition, education and training for physicians on caring for patients with obesity is often inadequate, and primary care physicians do not discuss obesity with their patients or formally diagnose obesity as often as they could [7–10]. Additional considerations include limited time [7,8], lack of availability of multidisciplinary teams to support with lifestyle and behavioral changes, and challenges related to reimbursement [8,10]. Findings from a large study of over 300,000 patients at the Cleveland Clinic highlight the existence of barriers to care; three-quarters of patients seeing primary care physicians had overweight or obesity, but less than half of those patients received a formal diagnosis [7]. In addition, despite the high frequency of encounters, less than 2% of patients eligible for anti-obesity medications receive treatment [11].

Overweight and obesity can have negative effects on health-related quality of life and increase the risk of developing comorbidities. Weight loss of at least 5–10% is recommended for improving weight-related cardiometabolic complications and risk factors [5,6]. Many people with overweight or obesity can benefit from treatment within a primary care setting to help them lose weight and maintain weight loss. Given the consequences of obesity, as well as the barriers and challenges that people face when trying to lose weight, it is important to actively diagnose patients, include the diagnosis of obesity or overweight on the problem list, and address it as a routine medical condition that is part of ongoing medical care, just like any other chronic disease.

The previous articles in this supplement have summarized the accumulating evidence supporting the treatment benefits of once-weekly subcutaneous semaglutide 2.4 mg in weight management. In the first article, Dr Amaro, Dr Sugimoto, and Dr Wharton described in detail the efficacy and safety of once-weekly semaglutide 2.4 mg. Clinically significant and sustained mean reductions in body weight of 14–16% in participants without type 2 diabetes (T2D) and 9.6% in people with T2D were observed in the phase 3 Semaglutide Treatment Effect in People with obesity (STEP) 1–5 trials, with no unexpected safety issues. In the second article in this supplement, Dr Amaro, Dr Skolnik, and Dr Sugimoto explored the effects of once-weekly semaglutide 2.4 mg on cardiometabolic risk factors. Improvements in blood pressure, lipids, glycated hemoglobin, and C-reactive protein, a marker of inflammation, were observed across the STEP 1–5 trials, demonstrating that the beneficial effects of once-weekly semaglutide 2.4 mg extend beyond weight loss alone. In the third article of this supplement, Dr O'Neil and Dr Rubino described how overweight or obesity can affect quality of life and the potential improvements in quality of life that can be gained with once-weekly semaglutide 2.4 mg. Benefits favoring once-weekly semaglutide 2.4 mg have been observed in physical functioning, physical and mental quality of life, and urinary incontinence, which can improve many aspects of daily life for people with overweight or obesity. This fourth and final article in the supplement is intended for a US-based audience with a main focus toward primary care physicians and aims to provide an overview of key considerations for the practical integration of once-weekly semaglutide 2.4 mg into the treatment of obesity in primary care.

CONTACT Janine V. Kyrillos janine.kyrillos@jefferson.edu Jefferson Comprehensive Weight Management, Thomas Jefferson University, Philadelphia, PA, USA; Neil S. Skolnik nskolnik@yahoo.com Abington Jefferson Health, Abington, PA, USA

Article overview and relevance to clinical practice

- This supplement has explored the clinical profile of once-weekly semaglutide 2.4 mg for weight management, based on results from the phase 3 STEP clinical trial program.
- This final article in the supplement draws on the results from the STEP trials to provide practical guidance on integrating onceweekly semaglutide 2.4 mg into clinical practice in primary care.
- In this article, we answer key questions relating to weight management in clinical practice, including:
  - What treatment options are available for patients with overweight or obesity, including lifestyle and pharmacotherapy.
  - How to respectfully and effectively counsel patients to maximize benefits of treatment.
  - Which patient populations would be most suitable for treatment with once-weekly semaglutide 2.4 mg, and those who would not be recommended this treatment.
  - Important considerations for follow-up, monitoring, and maintenancetreatment after initiation of once-weekly semaglutide 2.4 mg.

2. Clinical practice guidelines for weight management

Primary care practitioners (PCPs) have a critical role in weight management since they usually represent the initial point of contact, can assess the degree of importance that patients attach to overweight or obesity as a health-related risk factor, and primary care practices are the most common place where people receive medical care for weight and weight-related issues. PCPs can also determine when wider support services are needed [3, 6, 12–14] which, when available, may include obesity medical specialists, dietitians, physical activity specialists, behavioral health specialists, and nurses [3–6]. Irrespective of whether a wider support team is available, PCPs play a key role in obesity management, guiding the intensity of care and regularly advising patients on lifestyle modification and the use of medication [3,6,12–14].

A patient-centric approach is important, as disease progression, presence of weight-related comorbidities, and patient characteristics vary from patient to patient. It follows that interventions should be tailored to the individual patient's needs and goals for optimal effectiveness [3–6,13].

PCPs are usually the first point of contact for people with obesity. Their attitude toward the patient and the language they use often determine the degree to which patients feel comfortable addressing their weight as a medical problem. It is crucial that patients feel welcome in the clinical practice and for providers to build a trusting relationship [3,15]. The 5 As counseling framework for initial discussions with patients is often recommended in guidelines as a means of building patient–provider trust and defining an individualized obesity management plan (Figure 1) [13,15–17]. The Ask 'A' suggests that PCPs ask for a patient's permission to talk about their weight [15,18,19]. Asking permission shows respect and sensitivity toward the patient [13]. If a patient agrees to discuss their weight, motivational interviewing is a non-judgmental, collaborative discussion style that can help identify the patient's motivation to actively engage in their treatment plan, leading to positive behavioral changes [3,6,13,18,20,21].

It is important to recognize that patients often experience weight bias and stigma, both outside and within the medical system. A key barrier in the treatment of obesity is weight-related stigmatization due to implicit and explicit bias toward people with obesity, which is found in families, social circles, the workplace, and healthcare settings [3,22–24]. Such stigmatization can result in feelings of shame and embarrassment and deter people with obesity from seeking or receiving appropriate treatment [22], which could further compound the negative health impact of obesity [3,13]. There are many studies that demonstrate that patients with obesity are less likely to seek preventive care, are more likely to visit emergency departments, and if they feel shamed by their provider, are more likely to continue maladaptive behaviors [25–27]. Obesity is a serious, chronic, and progressive disease caused by complex abnormalities in body weight regulation [28]; shame and blame have no place in the treatment of obesity, or any chronic disease.

Several factors help guide diagnosis and treatment of overweight and obesity. Body mass index (BMI) has remained the most common indicator to diagnose obesity and measure progress, but there are other factors important for diagnosis and treatment. These include a detailed medical history to understand the patient's weight trajectory to this point and previous efforts to treat it; investigating indicators for insulin resistance and metabolic syndrome such as waist circumference, skin tags, and acanthosis nigricans, plus laboratory testing; assessing for other comorbid conditions – psychological, metabolic, and structural – that may be contributing to obesity or may be a consequence of overweight; exploration of current lifestyle patterns; and finally a discussion of the patient's general health, wellbeing, and realistic expectations that may extend beyond simple BMI measurement [5,13,17,29–32]. Once individualized and achievable goals have been defined, an appropriate treatment plan can be developed.

Several national and international clinical practice guidelines for obesity management are available, including those with a particular focus on weight management in primary care [3–6,13,17,18,30]. The guidelines align in recommending that treatment plans adopt a comprehensive approach, with increasing intensity of intervention determined by patients' values, preferences, and degree of weight-related comorbidities [3–6]:

(1) Lifestyle modification encompassing a multifactorial program of nutrition, physical activity, and behavioral therapy. When available and appropriate, there are potential benefits to a multidisciplinary team (including an obesity medical specialist, dietitian, specialist in physical activity, and behavioral health specialist), in addition to the patient's PCP.
(2) Pharmacotherapy as an adjunct to lifestyle intervention for those with a BMI of ≥30 kg/m^2, or a BMI of ≥27 kg/m^2 with weight-related complications.

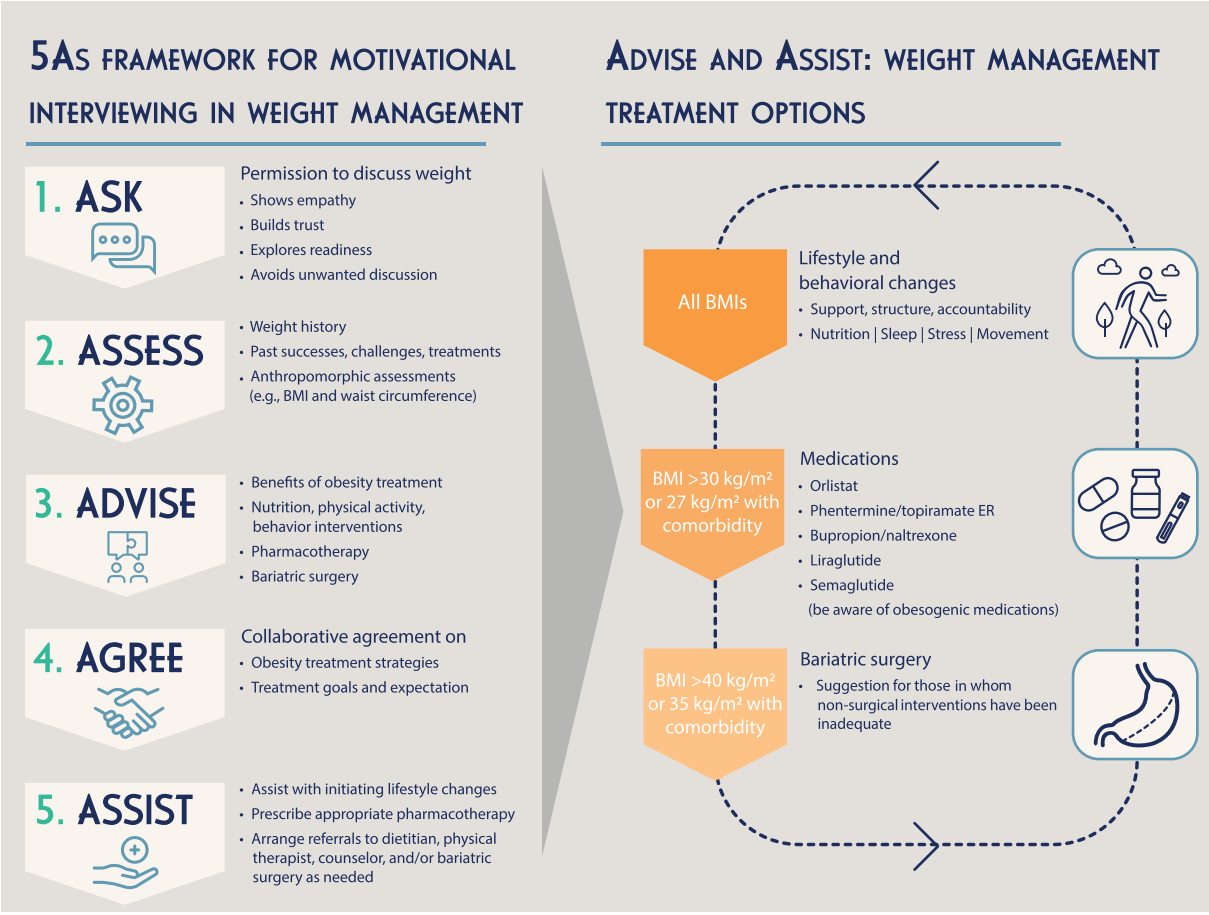

Figure 1. Framework for initial and ongoing discussions with patients as part of individualized obesity management [3–6,13,15–18].
BMI, body mass index.

(3) Bariatric surgery if BMI is ≥40 kg/m^2, or if BMI is ≥35 kg/m^2 with weight-related complications. This approach is recommended for those for whom non-surgical interventions have been inadequate.

Key clinical take-homepoints: Clinical practice guidelines for weight management

- PCPs have a pivotal role in the treatment of obesity.
- Treatment for obesity should be tailored to individual patients' needs and preferences.
- Patients should not be made to feel stigmatized or shamed about their weight because obesity is a serious, chronic, and progressive disease caused by complex abnormalities in body weight regulation.
- The 5 As framework is recommended to optimize the patient–PCP relationship.
- Basic diagnosis of obesity relies on BMI measurements, but other factors should be considered, such as the patient's history, current lifestyle patterns, general health, comorbid conditions, and wellbeing.
- Treatment options include lifestyle changes, pharmacotherapy, or bariatric surgery, all depending on the severity of obesity, and based on the patient's values.

3. The role of lifestyle in weight management

Nutrition remains the most important pillar in weight management, with many theories surrounding nutrition-based weight loss. While a negative energy balance has traditionally been the focus in weight management [13,33] and has typically been recommended as a key component of weight-loss interventions [4,5], the carbohydrate–insulin model is an alternative theory which proposes that excess fat storage is due to hormonal responses to a high-glycemic-load diet [34]. Understanding insulin as the main driver of energy storage, a nutritional approach that aims to minimize insulin response may decrease fat storage and improve metabolic syndrome, even in the absence of total weight loss [18].

Recent guidelines, such as those from The Obesity Medicine Association and Obesity Canada, have progressed toward the adoption of a personalized approach to meet individual preferences for a nutritionally adequate, well-formulated dietary intervention, rather than relying solely on set calorific deficits [18,33,35]. Optimal interventions incorporate the patient's preferences, lifestyle, and cultural and socioeconomic factors, are evidence-based, nutritionally sound, and can be maintained successfully over the long-term [18]. Regardless of dietary plan, the healthiest advice encourages patients to increase consumption of real, whole foods, and

reduce intake of ultra-processed foods, juices, and sugary drinks. Ultra-processed food and drinks provide less satiety than whole foods, can be addictive, and are more likely to trigger a higher insulin response, leading to increased fat storage [36–38]. Furthermore, ultra-processed food has been linked to higher rates of overall cardiovascular disease, cerebrovascular disease, and all-cause mortality [39,40].

Sustaining weight loss can also be a challenge for patients, as a range of homeostatic mechanisms in the body act against decreasing weight [28]. As weight is lost, the basal metabolic rate decreases and systemic appetite regulation is altered. As a result, fewer calories are expended during the day and hunger increases, counteracting efforts to maintain the perceived energy deficit [28]. These mechanisms, which were evolutionarily beneficial in times of food scarcity, make sustaining weight loss difficult [33]. Understanding this can promote empathy and help the provider and patient re-evaluate goals and treatment plans in cases of weight loss plateau or weight regain.

While weight loss is often driven by dietary changes, exercise is an important part of improving body composition and maintaining weight loss. Guidelines recommend interventions to increase physical activity, and while any physical activity is beneficial, adults are recommended to exercise for at least 150–300 minutes (2.5–5 hours) at moderate intensity, or 75–150 minutes (1.25–2.5 hours) at vigorous intensity, spread throughout the week in combination with strength training. However, it is important to assess patients' current level of activity, ability, and readiness, and to use this information to set realistic goals for physical activity, both as exercise and non-exercise activity [18].

Key clinical take-home points: The role of lifestyle in weight management

- Nutrition based on real, whole foods, while avoiding ultra-processed foods, is recommended, with less focus being put on simple calorie restriction.
- Nutritional advice should align with patients' preferences, lifestyle, and cultural and socioeconomic factors.
- PCPs should be aware of the counteractive physiological changes that occur in response to weight loss and have empathy for patients when they struggle to maintain weight loss.
- Physical activity plays an important part in maintaining weight loss. Realistic goals should be set for increasing physical activity based on patients' current abilities and preferences.

4. The role of behavioral therapy in weight management

A well-thought-out behavioral approach is integral to weight management – this can take many different forms and the choice of which behavioral therapy to use will vary depending on individual patient's needs and preferences, along with available resources. Behavioral intervention can include motivational interviewing, which is important to actively engage patients and is much more effective than telling people what they need to do. Psychological therapies, including cognitive behavioral therapy, have been used to help facilitate carrying out behavioral goals [5,6,16,35]. Behavioral interventions should be tailored to the patient's individual goals [13,16] and ideally utilize a multidisciplinary team [5]. If a multidisciplinary team is not available, alternative approaches can include motivational apps, coaching (available through some health insurance providers or employers), and peer support groups. Interventions that involve an average of 5 to 16 contacts over 9 to 12 months, depending on their intensity, increase the likelihood of success [41]. Multiple contacts over time improves patient motivation, adherence, and accountability, which is ultimately associated with the best long-term outcomes [35]. Interestingly, results from the STEP 1 [37] and STEP 3 [38] trials comparing semaglutide 2.4 mg with placebo showed similar magnitudes of weight loss despite differences in lifestyle modification intensity, which could be related to the high efficacy of semaglutide 2.4 mg treatment.

Key clinical take-home points: The role of behavioral therapy in weight management

- Behavioral interventions for weight management include motivational interviewing, cognitive behavioral therapy, and other psychological therapies.
- The frequency and intensity of behavioral therapy is likely to depend on individual patients' needs, preferences and access to resources, but regular follow-up is associated with better outcomes.

5. The role of pharmacotherapy in weight management

Clinical guidelines recommend pharmacotherapy as an option for patients with a BMI ≥30 kg/m^2, or a BMI ≥27 kg/m^2 with weight-related complications, who have not achieved successful sustained weight loss with lifestyle modification alone [4–6,13,16]. Pharmacotherapy is recommended to augment lifestyle interventions and is not a substitute for lifestyle intervention [5,6]. Robust evidence shows that pharmacotherapy, when used as an adjunct to lifestyle modification, leads to greater initial weight loss and greater sustained weight loss over time than lifestyle interventions alone [4,5]. There are a number of pharmacotherapy options for long-term obesity treatment [4,5,13] (Table 1). Weight loss observed with once-weekly semaglutide 2.4 mg as an adjunct to lifestyle modification was 14.9% in STEP 1 [42], and the medication was subsequently approved by the US Food and Drug Administration (FDA) in June 2021 for the treatment of obesity [43]. Other FDA-approved medications approved for obesity treatment, specifically bupropion/naltrexone, liraglutide, orlistat, and phentermine/topiramate extended-release, have been shown to give rise to weight loss of 4.0% to 10.9% [11]. Research into other medications is ongoing and may lead to expansion of the approved medications for obesity management. For example, tirzepatide is an agonist of the GLP-1 and glucose-dependent insulinotropic polypeptide receptors, which is currently approved by the FDA for the treatment of T2D [44]. Tirzepatide has demonstrated substantial reductions in body weight in the SURMOUNT-1 trial of people with obesity [44] and a new drug application for tirzepatide in adults with obesity or overweight is anticipated in the coming year [45].

Table 1. FDA-approved pharmacotherapies for long-term weight management.

Medication	Orlistat [46]	Phentermine/topiramate ER [47]	Bupropion/naltrexone [48]	Liraglutide [49]	Semaglutide [36]
Commercial name	XENICAL®	QSYMIA®	CONTRAVE®	SAXENDA®	WEGOVY®
Mechanism of action	Gastrointestinal lipase inhibitor	Noradrenergic + GABA receptor activator, kainite/AMPA glutamate receptor inhibitor	Opioid receptor antagonist + dopamine/ norepinephrine reuptake inhibitor	GLP-1RA	GLP-1RA
Route of administration	Oral	Oral	Oral	Subcutaneous	Subcutaneous
1-year weight change relative to placebo, kg (95% CI)[a]	Adults: −3.4 kg (−3.2 to −3.6) Adolescents: −2.6 kg	For 7.5/46 mg/d: −6.7 kg (−5.9 to −7.5) For 15/92 mg/d: −8.9 kg (−8.3 to −9.4)	−4.9 kg (−4.6 to −5.1)	Adults: −5.2 kg (−4.9 to −5.6) Adolescents: −4.5 kg (−7.2 to −1.8)	−6.1 kg to −12.7 kg
Indication	In conjunction with a reduced-calorie diet for the treatment of people with BMI ≥30 kg/m^2, or ≥27 kg/m^2 with associated risk factors (hypertension, diabetes or dyslipidemia)	As an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with a BMI of ≥30 kg/m^2 or ≥27 kg/m^2 in the presence of at least one weight-related comorbidity (e.g. hypertension, T2D, or dyslipidemia)	As an adjunct to a reduced-calorie diet and increased physical activity for weight management in adults with an initial BMI of ≥30 kg/m^2 or ≥27kg/m^2 to <30 kg/m^2 in the presence of at least one weight-related comorbidity (e.g. T2D, dyslipidemia, or controlled hypertension)	As an adjunct to a reduced-calorie diet and increased physical activity for weight management in adults with an initial BMI of ≥30 kg/m^2 or ≥27 kg/m^2 to <30 kg/m^2 in the presence of at least one weight-related comorbidity, (e.g. dysglycemia [prediabetes or T2D], hypertension, dyslipidemia, or obstructive sleep apnea)	As an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial BMI of ≥30 kg/m^2 or ≥27 kg/m^2 in the presence of at least one weight-related comorbidity (e.g. hypertension, T2D, or dyslipidemia)
Contraindications	Pregnancy; chronic malabsorption syndrome; cholestasis; breastfeeding	Pregnancy; glaucoma; hyperthyroidism; during or within 14 days of taking monoamine oxidase inhibitors	Pregnancy; uncontrolled hypertension; current seizure disorder or a history of seizures; known central nervous system tumor; acute alcohol or benzodiazepine withdrawal; history of bipolar disorder; concomitant treatment containing bupropion or naltrexone; current or previous diagnosis of bulimia or anorexia nervosa; dependent on chronic opioids or opiate agonists (e.g. methadone) or in acute opiate withdrawal; concomitant administration of MAOI; severe hepatic impairment; end-stage renal failure	Pregnancy; a personal or family history of MTC or MEN 2; hypersensitivity to liraglutide or to any of the excipients	Pregnancy; a personal or family history of MTC or in patients with MEN 2; prior serious hypersensitivity reactions to semaglutide or to any of the excipients
Common side effects	Gastrointestinal events	Paresthesia; dizziness; dysgeusia; insomnia; constipation; dry mouth	Nausea; constipation; vomiting; dizziness; dry mouth	Gastrointestinal events	Gastrointestinal events
Notes	Discontinue after 12 weeks if patients have been unable to lose at least 5% of body weight [46]	The effect of Qsymia on cardiovascular morbidity and mortality has not been established	Discontinue after 12 weeks if patients have been unable to lose at least 5% of body weight	Discontinue after 16 weeks if patients have been unable to lose at least 4% of body weight	Discontinue if patients cannot tolerate the 2.4 mg dose

[a]Weight changes relative to placebo (95% CI) using intent-to-treat analyses for each medication at 1 year for orlistat, phentermine-topiramate, naltrexone-bupropion-ER, and liraglutide are found in prior reports that performed meta-analyses [50–53]. At present, there is only one large, placebo-controlled trial for adolescents using liraglutide [54]. Semaglutide weight change is described in the papers as occurring at week 68, after 52 weeks at full dose [42,55,56]. Total weight losses (not relative to placebo) are somewhat greater and generally reflect the intensity of the lifestyle modification program offered.

AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; BMI, body mass index; CI, confidence interval; d, day; EMA, European Medicines Agency; ER, extended-release; FDA, US Food and Drug Administration; GABA, gamma-aminobutyric acid; GLP-1RA, glucagon-like peptide-1 receptor agonist; MAOI, monoamine oxidase inhibitor; MEN 2, multiple endocrine neoplasia syndrome type 2; MTC, medullary thyroid carcinoma; T2D, type 2 diabetes.

Key clinical take-home points: The role of pharmacotherapy in weight management

- Pharmacotherapy is recommended for patients who have not been able to lose weight through lifestyle modifications alone.
- It is important to realize that pharmacotherapy should be used to augment lifestyle changes such as healthy nutrition and increased physical activity.
- Pharmacotherapies for long-term obesity treatment include bupro- pion/naltrexone, liraglutide, orlistat, phentermine/topiramate extended-release, and semaglutide.
- Weight loss with semaglutide 2.4 mg as an adjunct to lifestyle modification was 14.9% in the STEP 1 trial and is around 4.0% to 10.9% with other approved anti-obesity medications.

6. Key considerations for the use of once-weekly semaglutide 2.4 mg for weight management in clinical practice

Once-weekly subcutaneous injections of semaglutide 2.4 mg for weight management should be used as part of a well-thought-out weight-management plan, ideally including counseling on nutrition and physical activity, as well as behavioral therapy (see Figure 2).

6.1. Assessing which patients would be most suitable for treatment with once-weekly semaglutide 2.4 mg for weight management

Once permission to discuss the patient's body weight has been established, the next step is to assess the stage of overweight or obesity to determine the best course of treatment. If the patient has a BMI of ≥27 kg/m^2 (overweight) with ≥1 weight-related comorbid condition (e.g. hypertension, type 2 diabetes, or dyslipidemia), or a BMI of ≥30 kg/m^2 (obesity), once-weekly semaglutide 2.4 mg could be considered as an adjunctive pharmacotherapy to augment increased physical activity and a well-formulated nutrition intervention [43].

6.1.1. Patients with T2D taking concomitant oral glucose-lowering drugs or insulin

T2D is one of the most common weight-related comorbidities and it is important to assess glycemic status as part of the patient's initial contact and ongoing treatment plan [13]. In people with T2D, once-weekly semaglutide 2.4 mg has been shown to be effective in reducing body weight, with estimated mean reductions of 9.6% after 68 weeks of treatment [55]. Patients with T2D may therefore benefit from treatment with once-weekly semaglutide 2.4 mg for weight management. If the patient is already receiving pharmacotherapy for T2D, there are some important considerations to take into account when initiating once-weekly semaglutide 2.4 mg. Semaglutide lowers blood glucose by stimulating insulin in a glucose-dependent manner, conferring an overall low risk of hypoglycemia. However, the risk of hypoglycemia is increased when semaglutide is used in combination with insulin secretagogues (e.g. sulfonylureas) or insulin. In these cases, a dose reduction of any concomitant insulin secretagogues or insulin may be necessary [43]. As such, in the STEP 2 trial, doses of these agents were decreased by up to 50% at the investigator's discretion based on baseline glycemic status [55]. Since semaglutide 2.4 mg is a GLP-1RA, any other GLP-1RA or agents that act on the same pathway, such as DPP-4 inhibitors, should be discontinued when initiating semaglutide 2.4 mg [43]. In addition, rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy. The effect of long-term glycemic control with semaglutide on diabetic retinopathy complications is currently being studied in the FOCUS trial (NCT03811561), and any patient with a history of diabetic retinopathy receiving semaglutide should be monitored for progression of the condition [43].

6.1.2. Patients with cardiovascular disease or at high cardiovascular risk

People with overweight or obesity have an increased risk of developing cardiovascular disease [6]. The second article in this supplement by Amaro et al. described the effects of once-weekly semaglutide 2.4 mg on cardiometabolic and cardiovascular risk factors. In the STEP 1–4 trials, favorable effects were observed with once-weekly semaglutide 2.4 mg compared with placebo for most of the cardiometabolic and cardiovascular risk factors assessed, including waist circumference, blood pressure, lipid profile, and C-reactive protein [42,49,55,56]. Treatment with once-weekly semaglutide 2.4 mg may therefore be beneficial in patients at risk of developing weight-related cardiometabolic complications.

Once-weekly semaglutide 1.0 mg for the treatment of T2D reduced the risk of major adverse cardiovascular events in adults with T2D and established cardiovascular disease in the SUSTAIN-6 trial, and is indicated for use in these patients [57,58]. Once-weekly semaglutide 2.4 mg for weight management is currently being investigated in a cardiovascular outcomes trial (SELECT; NCT03574597) to determine whether it reduces the risk of major adverse cardiovascular events versus placebo in people with obesity but without diabetes [59].

6.1.3. Patients already taking an anti-obesity medication

If a patient is already on another anti-obesity medication, it may be beneficial to re-evaluate their existing treatment, taking into consideration weight loss progress and any negative side effects. If there has been inadequate clinical improvement (i.e. ≤4–5% reduction of baseline body weight) with their current anti-obesity medication after 12–16 weeks, then PCPs can consider dose adjustment or discussing alternative pharmacotherapeutic options with their patient [18]. Once-weekly semaglutide 2.4 mg may be a suitable alternative option for patients not achieving at least a ≤4–5% baseline body weight reduction on other

Indication	Once-weekly semaglutide 2.4 mg is indicated as an adjunctive pharmacotherapy to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with an initial BMI of ≥30 kg/m² (obesity), or ≥27 kg/m² (overweight) with ≥1 weight-related comorbid condition, e.g. T2D.

Special populations	*Children*	The safety and efficacy of semaglutide 2.4 mg has not been established in children or adolescents.
	Elderly	No overall differences were seen in efficacy or safety between younger or older subjects, but greater sensitivity of some older individuals cannot be ruled out.
	Pregnancy	Potential risks to the fetus from exposure to semaglutide during pregnancy. Discontinue semaglutide as soon as a pregnancy is recognized. Discontinue at least 2 months prior to a planned pregnancy for women of reproductive age.
	Renal impairment	Individuals with renal impairment may be at greater risk of acute kidney injury requiring renal function to be monitored for volume depletion.
	Hepatic impairment	No dose adjustment is required for patients with renal or hepatic impairment.
Interactions	*Insulin or insulin secretagogues*	A dose reduction of any concomitant insulin secretagogues (e.g. sulfonylureas) or insulin may be required. Do not combine semaglutide with any other GLP-1RA or DPP-4 inhibitors.
Contraindications	*Thyroid C-cell tumors*	Any personal or family history of MTC or in patients with MEN 2.
Pre-treatment counseling	*Gastrointestinal adverse events*	Inform the patient of the dose-escalation strategy. Advise on other strategies (smaller, more frequent meals, avoid high-fat meals).
	Injectable pen	Advise on how to self-administer, weekly dosing schedule, and how to handle missed doses.
Initiation and dose escalation	*Dose-escalation schedule*	Once-weekly injection dose of 0.25 mg for 4 weeks and gradually, every 4 weeks the dose increases until the target dose of 2.4 mg is reached.
	Dose adjustments	In case of tolerability issues during the escalation period, delay dose escalation for 4 weeks. If the target maintenance dose of 2.4 mg once weekly causes tolerability issues, temporarily decrease to 1.7 mg once weekly, for a maximum of 4 weeks and return to 2.4 mg. Discontinue semaglutide if the patient continues to not tolerate 2.4 mg.
Monitoring	*T2D*	The risk of hypoglycemia in patients taking concomitant administration of insulin secretagogues (e.g. sulfonylureas) or insulin requires regular monitoring of blood glucose levels. Patients with a history of diabetic retinopathy should be monitored for progression of diabetic retinopathy.
	Acute kidney injury	Monitor renal function when initiating or escalating doses in patients reporting severe adverse gastrointestinal reactions as they can potentially lead to volume depletion. Monitor renal function in patients with renal impairment reporting any adverse events that could lead to volume depletion.
	Acute pancreatitis	Inform patient to be aware of severe abdominal pain that may radiate to the back, which may or may not be accompanied by vomiting. Acute pancreatitis should be suspected, and treatment discontinued immediately.
	Suicidal behavior and depression	Monitor a patient who presents with an emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior. Discontinue treatment for any experience of suicidal ideation or behaviors.
	Increased heart rate	Monitor a patient's resting heart rate consistent with usual clinical practice and discontinue treatment if the patient experiences a sustained increase. Instruct patients to inform their healthcare providers of palpitations or feelings of a racing heartbeat while at rest during treatment with semaglutide 2.4 mg.

Figure 2. Key considerations for integrating semaglutide 2.4 mg into obesity management [41].

BMI, body mass index; GLP-1RA, glucagon-like peptide-1 receptor agonist; MTC, medullary thyroid carcinoma; MEN 2, multiple endocrine neoplasia syndrome type 2; T2D, type 2 diabetes.

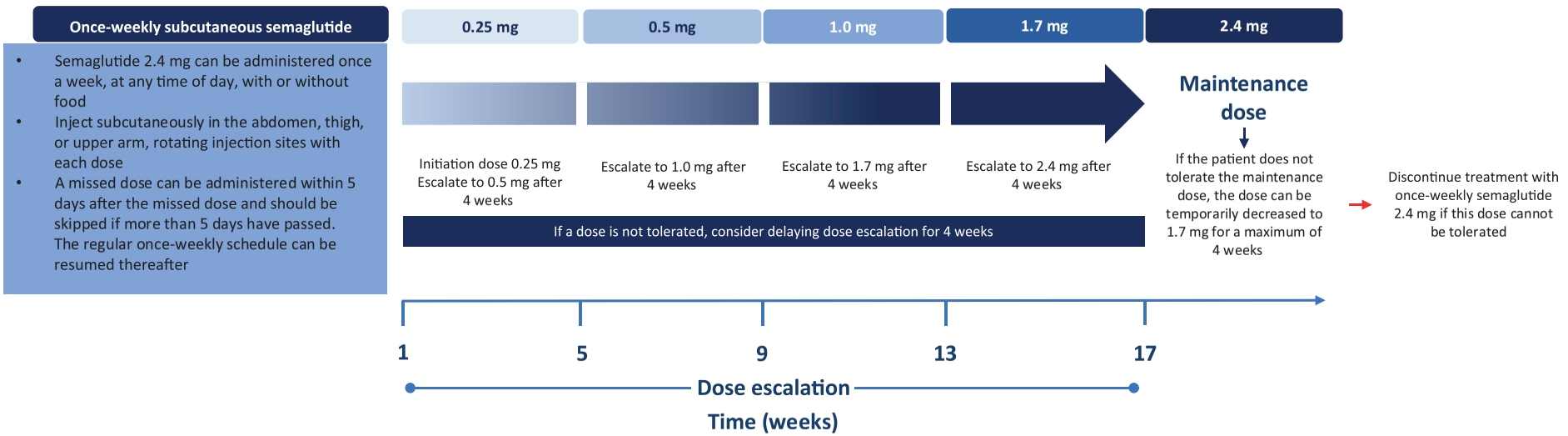

Figure 3. Once-weekly semaglutide 2.4 mg dosing schedule [43].

anti-obesity medications, given the high proportions of participants achieving 5% and 10% reductions in clinical trials of once-weekly semaglutide 2.4 mg [42,49,55,56].

The combination of once-weekly semaglutide 2.4 mg with other weight loss medications has not been investigated [43].

6.1.4. Special populations

Semaglutide is not currently indicated for the management of overweight and obesity in children or adolescents [60], but research in adolescent populations is underway. The safety and efficacy of semaglutide 2.4 mg is being investigated in adolescents aged 12–17 years in the STEP TEENS trial (NCT04102189) [61]. The once-daily GLP-1RA, liraglutide, is currently indicated for weight management in this age group [60]. Elderly individuals (over 65 years of age) were included in the trials [42,49,55,56]. No overall differences were seen in efficacy or safety between younger or older adults, and a study of once-weekly semaglutide 1.0 mg for the treatment of T2D found that the efficacy and safety were comparable between elderly and non-elderly patients [62]. However, as with most medications, greater sensitivity of some older individuals to once-weekly semaglutide 2.4 mg is possible [43].

Semaglutide is not recommended for use during pregnancy, so this should be made clear if caring for adults who may become pregnant. Due to its long half-life, semaglutide should not be initiated in the 2 months prior to attempting pregnancy in women of reproductive age [43]. If once-weekly semaglutide 2.4 mg has already been initiated and a patient becomes pregnant, it is recommended to discontinue semaglutide as soon as the pregnancy is suspected, since animal studies have demonstrated that there may be potential risks to the fetus from exposure to semaglutide in utero [43]. There is a registry that monitors pregnancy outcomes in women exposed to semaglutide during pregnancy. Pregnant women exposed to semaglutide and healthcare providers are encouraged to contact Novo Nordisk at 1-800-727-6500. Women of reproductive age taking semaglutide 2.4 mg should be informed that weight loss can improve fertility and increase risk of pregnancy [63].

In addition, semaglutide is contraindicated in people with a personal or family history of medullary thyroid carcinoma, people with multiple endocrine neoplasia syndrome type 2, or people with known hypersensitivity to semaglutide or its excipients [43].

6.2. Pre-treatment counseling

It is necessary to set realistic patient expectations, both in terms of weight-loss magnitude and timeframe, and to advise patients on potential adverse events with the provision of strategies to mitigate and manage [13,16,64,65]. Gastrointestinal adverse events are common with the GLP-1RA class as a whole [43,60]. To minimize potential gastrointestinal adverse events, gradual dose escalation is recommended. Other strategies to help mitigate potential gastrointestinal adverse events include counseling patients to avoid high-fat meals, to stop eating as soon as they feel full, as well as reducing meal size and food intake to help prevent nausea and vomiting [64–67]. Wharton et al (2021) recommend using the 3 'E's to help manage gastrointestinal adverse effects – 1. Education and explanation; 2. Escalation to an appropriate dose; and 3. Effective management of gastrointestinal side effects. We kindly refer readers to Wharton et al for more practical information on the 3 'E's [64].

Semaglutide is supplied as a single-dose disposable injectable pen, which requires training in how to self-administer injections in the abdomen, thigh, or upper arm. Advice should be given about the weekly dosing schedule (i.e. on the same day each week, any time of day with or without meals), and how to handle missed doses (i.e. if the patient misses a dose, take the missed dose as soon as possible unless the next scheduled dose is less than 2 days away, in which case the missed dose should not be administered and the next dose should be taken on the next scheduled day) (Figure 3) [43].

6.3. Initiation and dose escalation of once-weekly semaglutide 2.4 mg for weight management

Gradual dose escalation of semaglutide 2.4 mg is necessary to mitigate the risk of gastrointestinal side effects. As part of the clinical development program for semaglutide, the STEP trials included a slow dose escalation of semaglutide over a 16-week period [68]. The recommended 16-week escalation regimen starts with a once-weekly injection dose of 0.25 mg for 4 weeks followed by 0.5 mg (weeks 5–8), 1.0 mg (weeks 9–12), then 1.7 mg (weeks 13–16), until the maintenance dose of 2.4 mg is reached (week 17 onwards) [43] (Figure 3). If patients have tolerability issues during the escalation period, consider delaying dose escalation for 4 weeks, or if patients do not tolerate the maintenance 2.4 mg once-weekly dose, the dose can be temporarily decreased to 1.7 mg once weekly. If a patient cannot tolerate the 2.4 mg dose, semaglutide should be discontinued [43] (Figure 3). However, in the authors' experience, a slower dose escalation than specified here has often enabled patients to reach the target dose of 2.4 mg with fewer difficulties.

6.4. Follow-up, monitoring, and maintenance treatment

6.4.1. Practical guidance on when and how to follow up with patients after initiation of once-weekly semaglutide 2.4 mg

The importance of continued and individualized follow-up and reassessment of interventions for weight management, in terms of effects on weight, goal attainment, and weight-related complications is well recognized [5,13]. Follow-up encourages adherence to lifestyle modification along with adherence to continued medication use. An early follow-up assessment during the first month of treatment is important for physicians to evaluate the progress of the patient, assess for side effects, and to sustain motivation. Thereafter, follow-up can be spaced to monthly intervals, and eventually to every 3 months. Determining the frequency of follow-up requires shared decision-making with the patient to ensure the care plan is tailored to the patient and fits their lifestyle. At the follow-up visits, it is important to review not only the achieved benefits but also identify challenges with lifestyle modification program, and the medication's efficacy and tolerability [3,69]. Physical activity is an integral component of

weight maintenance, as it decreases the risk of many diseases including diabetes, cardiovascular disease, cancer, and mood disorders, and enhances quality of life. Therefore, a discussion of concrete strategies for enhancing success around both physical activity and nutrition is important.

Effective weight loss is defined as ≥5% loss of body weight at 3 months. Most pharmacotherapeutic agents for weight management include recommendations on when to stop the treatment if there is a lack of response (defined as <5% weight loss at 3 months). If ≥5% weight loss has been achieved within 3 months and there have been no tolerability issues, the medication can be continued [69]. The prescribing information for once-weekly semaglutide 2.4 mg does not include recommendations on when to discontinue treatment as a result of insufficient response [43]. The STEP studies indicate that weight losses continue to accrue with once-weekly semaglutide 2.4 mg after 3 months [42,49,55,56,70], and therefore the authors recommend a longer timeframe at maximal dose in some cases to determine response or non-response.

6.4.2. Monitoring patients after once-weekly semaglutide 2.4 mg has been initiated

Monitoring is individualized to patients' needs. For patients with T2D, regular monitoring of blood glucose levels should be done due to the risk of hypoglycemia in patients with concomitant use of insulin secretagogues (e.g. sulfonylureas) or insulin with once-weekly semaglutide 2.4 mg [43].

It is important to be aware that although infrequent, acute pancreatitis has been observed in both the clinical trials and post-marketing experience with the GLP-1RA class as a whole [43]. In addition, individuals with renal impairment may be at greater risk of acute kidney injury requiring renal function to be monitored for volume depletion, particularly if patients report severe gastrointestinal symptoms and have decreased fluid intake. No dose adjustment is required, however, for patients with renal or hepatic impairment [43]. Patients should be monitored for adverse reactions that may indicate acute pancreatitis or acute kidney injury and semaglutide should be discontinued if either of these is suspected [43].

In clinical trials, mean increases in resting heart rate of 1–4 beats per minute were observed in semaglutide-treated patients compared with placebo [42,55,56].

6.4.3. Maintenance treatment with once-weekly semaglutide 2.4 mg

Obesity is a chronic disease and maintenance treatment with pharmacotherapies is required to sustain weight loss. Short-term (3–6-month) treatment is not recommended in clinical guidelines as it does not provide long-term benefits [5]. Consistent with this, continued maintenance treatment with semaglutide 2.4 mg has been shown to sustain weight losses. If patients stop treatment after achieving initial weight loss with semaglutide, they are likely to regain weight [71]. The earlier articles in this supplement discussed this effect of semaglutide, which was specifically studied in the STEP 4 trial and discussed by Amaro et al. in the first article. In addition, the continuing benefits of semaglutide to 68 weeks included not only continued weight loss over time but also significantly better outcomes for waist circumference, systolic blood pressure, and Short Form-36 physical functioning scores versus placebo [49].

Key clinical take-home points: Considerations for initiating once-weekly semaglutide 2.4 mg in clinical practice

- Once-weekly semaglutide 2.4 mg for weight management is suitable for use in adults with:
  - BMI ≥27 kg/m^2 with ≥1 weight-related comorbid condition (e.g. hypertension, T2D, or dyslipidemia);
  - BMI ≥30 kg/m^2.
- Once-weekly semaglutide 2.4 mg may be beneficial for weight management in patients with T2D. Blood glucose levels should be monitored, particularly if there is use of concomitant insulin secretagogues (e.g. sulfonylureas) or insulin.
- Once-weekly semaglutide 2.4 mg should not be used with other GLP-1RAs or DPP-4 inhibitors.
- Treatment with once-weekly semaglutide 2.4 mg may be beneficial in patients at risk of developing weight-related cardiometabolic or cardiovascular complications.
- Once-weekly semaglutide 2.4 mg should not be used in:
  - Children;
  - Planned or current pregnancy.
- Personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2.
- Known hypersensitivity to semaglutide or its excipients.
- Patients should be counseled on how to administer injections and how to mitigate potential gastrointestinal adverse reactions before initiating treatment with once-weekly semaglutide 2.4 mg.
- Regular follow-ups with patients encourage adherence to lifestyle modification and to continued medication use.
- Patients should be monitored for adverse reactions that may indicate acute pancreatitis or acute kidney injury (i.e. volume depletion); discontinue treatment with once-weekly semaglutide 2.4 mg if either of these is suspected.
- If treatment with once-weekly semaglutide 2.4 mg is well tolerated, long-term treatment is recommended for significant and sustained weight loss.

7. Conclusions

Obesity is a multifactorial, chronic disease often requiring lifestyle modification and pharmacologic therapy for treatment and maintenance. Lifestyle changes are essential in prevention and treatment of overweight or obesity but may not be effective alone. The approval of semaglutide 2.4 mg presents an opportunity for effective treatment of overweight and obesity, with a level of both safety and efficacy beyond previously available medications. Integration of this new pharmacotherapy as an adjunct to lifestyle modification into primary care practice offers

healthcare providers an opportunity to further support their patients to achieve substantial reductions in body weight and improvements in cardiometabolic and physical health.

Abbreviations

AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid
BMI, body mass index
CI, confidence interval
d, day
DPP-4, dipeptidyl peptidase-4
EMA, European Medicines Agency
ER, extended-release
FDA, US Food and Drug Administration
GABA, gamma-aminobutyric acid
GLP-1RA, glucagon-like peptide-1 receptor agonist
MAOI, monoamine oxidase inhibitor
MEN 2, multiple endocrine neoplasia syndrome type 2
MTC, medullary thyroid carcinoma
PCP, primary care practitioner
STEP, Semaglutide Treatment Effect in People with obesity
T2D, type 2 diabetes

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ORCID

Janine V. Kyrillos http://orcid.org/0000-0002-1604-971X

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