British Cardiovascular Society
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Semaglutide: Friend or Foe?

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Take Home Messages

- Semaglutide shows significant promise in managing obesity and Type 2 diabetes mellitus, offering substantial improvements in weight loss, glycaemic control and cardiovascular outcomes.
- Long-term studies are essential to fully assess its safety, efficacy, and broader applicability in diverse patient populations.
- Careful prescribing is essential to prevent its misuse, maximise benefits and reduce risks.

Introduction

Obesity remains one of the most pervasive and stigmatized health conditions of the 21st century. It is a complex, multifactorial disease influenced by genetics, environment, and behaviour. Despite this, individuals living with obesity often face profound social stigma. This stigma, coupled with well-documented health concerns such as an increased risk of cardiovascular disease, diabetes mellitus, and certain cancers, adds to the challenges faced by patients and healthcare providers. For decades, medical science has sought a breakthrough solution for effective obesity management.

Amid this pursuit, Semaglutide, a glucagon-like peptide-1 (GLP-1) receptor agonist, has emerged as a potential game-changer. Originally developed for type 2 diabetes, the drug's remarkable impact on weight loss has sparked hope that it might be the wonder drug we've been waiting for. But does it truly live up to the promise, or does it come with strings attached? This editorial explores the ongoing debate surrounding Semaglutide, examining its potential benefits as a groundbreaking tool in obesity and diabetes management alongside the challenges and controversies it presents.

Mechanism of Action

Semaglutide is currently the only GLP-1 receptor agonist available in both subcutaneously injectable and oral formulation. It is structurally 94% homologous to native human GLP-1 (1). It stimulates GLP-1 receptors in the gastrointestinal tract, pancreas, and brain, resulting in potentiation of glucose-stimulated insulin secretion, delayed gastric emptying, enhanced pancreatic β-cell proliferation, and decreased glucagon release (2). Furthermore, its interaction with GLP-1 receptors in the hypothalamus reduces hunger and improves satiety (2).

Table 1-Indications for Semaglutide

Regulatory Body	**Indication for Semaglutide**
MHRA (UK)	Approved for weight management in adults with: - BMI ≥30 kg/m² (obesity) - BMI ≥27 kg/m² with weight-related comorbidities (e.g., type 2 diabetes, hypertension, dyslipidaemia) (3).
NICE (UK)	Approved as an adjunct to a reduced-calorie diet and increased physical activity for weight management in adults with at least 1 weight-related comorbidity and: - BMI ≥35 kg/m² or - BMI 30-34.9 kg/m² who meet the criteria for referral to specialist weight management services (1).
FDA (US)	**Wegovy®** Approved for weight management in adults with: - BMI ≥30 kg/m² (obesity) - BMI ≥27 kg/m² with at least one weight-related comorbidity (e.g., type 2 diabetes, hypertension, dyslipidaemia) **Ozempic® and Rybelsus®**: Different Formulations-Approved for type 2 diabetes management, not weight loss (2).

MHRA; Medicines and Healthcare products Regulatory Agency, NICE; National Institute for Health and Care Excellence, FDA; Food and Drug Administration

Scientific Trials

The SUSTAIN trials demonstrated Semaglutide's effectiveness in reducing HbA1c levels in type 2 diabetes patients against placebo (SUSTAIN 1), sitagliptin (SUSTAIN 2), exenatide extended-release (SUSTAIN 3), daily insulin glargine with metformin and/or a sulfonylurea (SUSTAIN 4), and basal insulin with or without metformin (SUSTAIN 5) (4-8). In the SUSTAIN-6 trial, Semaglutide significantly reduced the risk of major adverse cardiovascular events in patients with Type 2 diabetes at high cardiovascular risk over a follow up period of 104 weeks. The primary composite outcome—cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke occurred in 6.6% of patients receiving Semaglutide compared to 8.9% in the placebo group, resulting in a hazard ratio (HR) of 0.74 (95% confidence interval [CI], 0.58 to 0.95; P<0.001 for noninferiority (9). This lower risk was principally driven by a significant (39%) decrease in the rate of nonfatal stroke and a nonsignificant (26%) decrease in nonfatal myocardial infarction, with no significant difference in the rate of cardiovascular death.

In the SELECT trial, involving 17,604 adults with preexisting cardiovascular disease (defined as previous myocardial infarction, previous stroke, or symptomatic peripheral arterial disease and obesity (BMI 27 or >), but without diabetes, participants were randomized to receive either Semaglutide or placebo. Over a mean follow-up period of approximately 39.8 months, the primary composite endpoint—comprising cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke—occurred in 6.5% of patients in the Semaglutide group and 8.0% in the placebo group. This corresponds to a hazard ratio of 0.80 (95% confidence interval, 0.72 to 0.90; P<0.001), indicating a 20% relative risk reduction in major adverse cardiovascular events for those treated with Semaglutide (10).

The PIONEER trials were crucial in establishing oral semaglutide (Rybelsus) as an effective option for blood glucose control and weight management in patients with Type 2 Diabetes

Mellitus. Across multiple studies, Semaglutide demonstrated superior HbA1c reduction and greater weight loss compared to placebo and other antidiabetic drugs (11-17). The PIONEER 6 was a cardiovascular outcome trial designed to assess the safety of oral semaglutide in patients with type 2 diabetes**.** This cardiovascular outcome trial met its primary objective of ruling out an 80% excess cardiovascular risk with oral Semaglutide, confirming noninferiority to placebo for the primary outcome (hazard ratio, 0.79; 95% CI, 0.57 to 1.11) and the absence of excess cardiovascular risk (18).

The Semaglutide Treatment Effect in People with Obesity (STEP) trials have focused on the effects of weekly subcutaneous Wegovy® on weight loss. These trials revealed that 2.4 mg weekly injection significantly improved weight loss in adults with obesity or those with comorbid conditions (19-24). Step HFpEF trial demonstrated that for patients with obesity-related heart failure with preserved ejection fraction and type 2 diabetes mellitus, weekly injectable semaglutide reduced heart failure-related symptoms and physical limitation and led to greater weight loss compared to placebo at one year (25).

Oral Formulation

Oral semaglutide tablets (Rybelsus®) are a modified version of the drug that includes the absorption enhancer sodium N-(8-[2-hydroxybenzoyl] amino) caprylate (SNAC). Peptide-based drugs like Semaglutide face significant challenges in oral delivery due to the acidic environment of the gastrointestinal tract, rapid degradation by proteolytic enzymes and limited permeability through the intestinal epithelium. SNAC helps overcome these barriers by temporarily loosening the tight junctions between epithelial cells, facilitating its absorption into the bloodstream (26).

Challenges and Controversies

Despite the promising benefits of Semaglutide in managing obesity and type 2 diabetes, several controversies surround its use:

1. **Cost and Accessibility:** It is expensive, and high cost may limit access for many patients, particularly in lower-income populations or regions with restricted healthcare coverage.

2. **Long-Term Safety:** There is still limited data on its long-term safety, particularly in patients without diabetes. Concerns about its potential to increase the risk of thyroid cancer, pancreatitis, and gallbladder issues, diabetic retinopathy (27) have been raised, though these risks have not been conclusively proven in the general population.

3. **Side Effects:** Common side effects include hypoglycaemia and gastrointestinal issues such as nausea, vomiting, and diarrhoea (27).

4. **Misuse for Weight Loss:** The increasing popularity of semaglutide as a weight-loss drug has led to concerns about misuse in individuals without obesity or diabetes. Its off-label use for cosmetic weight loss, often through online platforms and unregulated clinics, raises medical concerns and can lead to serious side effects.

5. **Counterfeit Products:** Its rising demand for weight loss has resulted in the proliferation of counterfeit and compounded versions, which may be ineffective or dangerous. This poses a significant risk to patient safety and complicates efforts to regulate and control the drug's distribution.

6. **Ethical Concerns:** There are ethical debates surrounding the use of semaglutide for weight loss. The drug's marketing and its use in non-obese individuals may inadvertently promote unrealistic body image standards, potentially fostering unhealthy expectations and pressures related to physical appearance.

7. **Regulatory Issues:** The different indications and dosing regimens for semaglutide across its formulations have created confusion and may complicate its clinical application. There is also concern about the clarity of regulatory guidelines for its use in weight management.

Conclusions

To conclude, Semaglutide offers promising advancements in obesity and type 2 diabetes management, with significant weight loss and cardiovascular benefits. However, its high cost, long-term safety concerns, potential misuse, and ethical issues surrounding its use pose notable challenges. As its role in clinical practice expands, further research into long term hard outcomes is needed to ensure its safe and effective use. Careful patient selection, cost reduction, improved accessibility, and prevention of misuse are key strategies to maximize the benefits and minimize associated risks of the drug.

Disclosures

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