Semaglutide (Ozempic®): a comprehensive review of its pharmacology, efficacy, and safety profile in type 2 diabetes mellitus and weight management

SD Vambe, W Zulu, E Hough, MJ Luvhimbi, S Rwizi, E Bronkhorst

School of Pharmacy, Department of Clinical Pharmacy, Sefako Makgatho Health Sciences University, South Africa

Corresponding author, email: elmien.bronkhorst@smu.ac.za

Semaglutide, sold under the trade name Ozempic®, is a modified human glucagon-like peptide-1 receptor agonist (GLP-1 RA) indicated for the treatment of type 2 diabetes mellitus (T2DM). Glucagon-like peptide-1 receptor-agonists have shown improved renal and cardiovascular outcomes in patients with chronic kidney disease and established atherosclerotic cardiovascular disease (ASCVD). They work by binding to GLP-1 receptors which are found in different locations in the body. In the brain, they decrease appetite, increase the gastric emptying time in the gastrointestinal tract and promote weight loss. Due to the increased use of semaglutide, there has been a significant increase in reporting of adverse effects (AEs), such as pancreatitis, thyroid tumours, and hypersensitivity. Prescribing semaglutide for weight loss is seen as an off-label use since it is not registered in South Africa for weight management.

Keywords: semaglutide, glucagon-like peptide-1 receptor agonist (GLP-1 RA), type 2 diabetes mellitus, weight-loss

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Introduction

Sub-Saharan Africa has recorded a notable rise in obesity due to lifestyle changes and urbanisation.[1] In South Africa, 68% of women and 31% of men are overweight or obese.[1] The association of weight gain with increased risk of developing life-threatening conditions such as type 2 diabetes mellitus (T2DM), hypertension, heart failure, and non-alcoholic liver disease has imposed a great economic and health burden.[2] This necessitates the need to develop effective, yet non-invasive pharmacotherapeutic options to assist with weight loss.[2] The management of obesity primarily consists of four forms of therapy: lifestyle modification (i.e. diet and exercise), cognitive behavioural therapy, pharmacotherapy, and bariatric surgery.[3] However, socioeconomic factors play a role in the most preferred weight loss options, for example, the majority of those who undergo bariatric surgery have private insurance (e.g. non-government-funded insurance) and a higher median income.[4] When patients with obesity find difficulty in achieving sufficient benefit from lifestyle intervention, pharmacotherapy serves as a good adjunct therapy.[5]

The US Food and Drug Administration (FDA) has approved five agents for weight loss, namely orlistat, phentermine/topiramate, naltrexone/bupropion, semaglutide, and liraglutide respectively, with semaglutide suggested to have superior efficacy.[6] Semaglutide, sold under the trade name Ozempic®, is a modified human glucagon-like peptide-1 (GLP-1 RA) analogue, indicated for the treatment of T2DM.[7] Following the FDA approval of the first GLP-1 RA, exenatide in 2005, six additional subcutaneously administered GLP-1 RAs (semaglutide, dulaglutide, albiglutide, and extended-release exenatide, liraglutide, lixisenatide, and tirzepatide) were introduced on the market.[8] Semaglutide has demonstrated greater efficacy when administered as a weekly dose of 0.5 mg or 1 mg as compared to a combination of oral antidiabetics, insulin glargine, sitagliptin, dulaglutide and semaglutide.[9]

Apart from the management of T2DM through significantly reducing haemoglobin A1c (HbA1c), GLP-1 RAs have proven to improve renal and cardiovascular outcomes, especially in patients with chronic kidney disease and established atherosclerotic cardiovascular disease (ASCVD) and to promote weight loss.[8] In countries such as Canada, the UK, and the USA, once-weekly subcutaneous semaglutide 2.4 mg has been approved for chronic weight management in overweight adults (with weight-related comorbidities) or obesity.[10] However, its use in other regions is still restricted due to issues such as limited effectiveness, apprehensions regarding safety, and high costs.[11] There has been a rise in the use of semaglutide for off-label use in weight loss, with both subcutaneous and oral formulations currently available.[12] Trials of high-dose injectable semaglutide in patients without diabetes have demonstrated confidence in the safety of oral semaglutide in patients without diabetes. However, the impact of high-dose semaglutide may be limited by cost and scant insurance coverage for "weight loss" medications.[13] While the question of safety is underway, given the beneficial metabolic and cardiovascular actions of semaglutide, and the low risk for severe adverse events, semaglutide has an overall favourable risk/benefit profile for patients with T2DM, with less to no record of negative implications in those without T2DM.[12]

A case-control analysis done by Bezin et al.[14] on patients treated with GLP-1 RAs specifically exenatide, liraglutide, and dulaglutide for one to three years found that patients had a significantly higher risk for thyroid cancer and medullary thyroid cancer. At the time when Bezin et al.[14] did the analysis, data on semaglutide was

Table I: Contraindications, warnings and precautions and interactions

Contraindications	Warnings and precautions	Interactions
• Personal or family history of medullary thyroid carcinoma or in patients with multiple endocrine neoplasia syndrome type 2. • Known hypersensitivity to Ozempic® or any of the product components. • Gastroparesis. • Inflammatory bowel disease.	• Pancreatitis has been reported in clinical trials. Discontinue promptly if pancreatitis is suspected. Do not restart if pancreatitis is confirmed. • Diabetic retinopathy complications have been reported in a clinical trial. Patients with a history of diabetic retinopathy should be monitored. • Never share an Ozempic® pen between patients, even if the needle is changed. • Hypoglycaemia, when Ozempic® is used with an insulin secretagogue or insulin, consider lowering the dose of the secretagogue or insulin to reduce the risk of hypoglycaemia. • Can result in acute kidney injury. Monitor renal function in patients with renal impairment reporting severe adverse gastrointestinal reactions. • If signs of hypersensitivity occur, stop using Ozempic® immediately and promptly consult a healthcare professional for guidance. • There have been no clinical trials confirming definitive evidence of semaglutide reducing risks associated with macrovascular outcomes.	• Oral medications interact with Ozempic®, causing delays in gastric emptying. May impact absorption of concomitantly administered oral medications.

missing.[15] Unlike other GLP-1 RAs, there has been no link found between the use of semaglutide and the development of cancer in patients according to the findings of systematic review and meta-analysis. The semaglutide group had no higher risk of developing pancreatic cancer, thyroid cancer, or any other neoplasm than the placebo or active group in the studies that were reviewed.[15] Another systematic review narrowed in on the incident risk for thyroid cancer with semaglutide use and reported a less than 1% chance.[16] These findings correlate with the results found in another study that also demonstrated the advantage that semaglutide has over other GLP-1 Ras.[15]

Class and Mode of Action

Semaglutide belongs to a class of antidiabetic treatments known as GLP-1 RAs, which have similar pharmacokinetic properties as endogenous glucagon-like peptide 1 (GLP-1).[17] In the body, GLP-1, an incretin hormone, is produced from the proglucagon gene and this peptide closely resembles glucagon in structure but has glucose-dependent lowering activity.[18,19] Glucagon is one of the hormones that regulate glucose in the blood by signalling for the breakdown of stored glycogen to release glucose.[19]

GLP-1 RAs work by binding to GLP-1 receptors, which are found in different locations in the body, namely in the islet cells of the pancreas, cells of the kidney, lungs, heart, brain and gastrointestinal tract (GIT)[17] (Refer to Figure 1). In beta cells of the pancreas, the GLP-1 RAs cause an enhanced release of insulin, which is dependent on the glucose in the serum, by activation of the adenylyl cyclase enzyme. This action results in glucose uptake by the cells leading to a decrease in the serum glucose level.[20] Additionally, the GLP-1 RAs will travel to the brain where it decreases appetite and increases the gastric emptying time in the GIT.[20,21]

Due to the overall decreased appetite, semaglutide causes a decrease in body weight and body fat mass, resulting from the lowered energy intake. Additionally, semaglutide causes a change in food preference to foods with less fats.[21]

Indications

Semaglutide initially was developed solely for the management of T2DM but has gradually shifted in terms of its indication. Semaglutide is marketed for its efficacy in the management of obesity, especially in obese adults and adolescents who couldn't achieve significant weight loss without surgical intervention.[23]

Semaglutide is not registered in South Africa for weight management. Registered South African indications include:[21]

Inadequate management of T2DM (in addition to diet and exercise). Lowering the risk of major adverse cardiovascular events in patients with T2DM and existing cardiovascular disease, such as

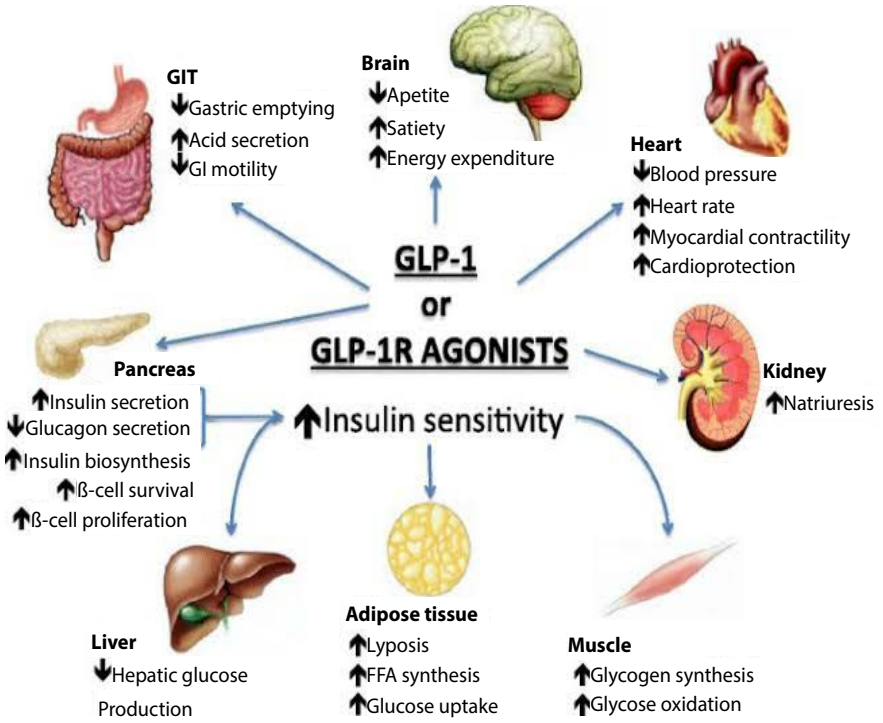

Figure 1: Effects of GLP1/GLP1-RAs on the different organs in the body.[22]

Table II: Common side effects

Frequent	Less frequent
• Nausea • Diarrhoea • Stomach or abdominal pain • Vomiting • Constipation • Rebound weight gain after discontinuation of semaglutide	• Ozempic face (most commonly in the middle-aged and older patients) • Gastroparesis (stomach paralysis) • Nasopharyngitis

non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death.

In terms of possible future indications for semaglutide, it is currently undergoing clinical trials to determine its viability as a possible treatment for a range of health issues such as kidney and heart failure, addiction, Alzheimer's disease, Parkinson's disease and metabolic-related steatohepatitis in obese and non-obese patients.[23]

Contraindications, precautions and drug interactions

The Table I summarises the complications, warnings and precautions, and interactions of semaglutide:[24]

Side effects and adverse drug reactions

Common side effects of semaglutide may resolve after a few days or weeks.[25,26] The side effects of semaglutide can be classified as common side effects, serious side effects, and adverse drug reactions (ADR) as shown in Tables II and III.[27]

The most common side effects of semaglutide are listed in Table II.

Management of side effects

Nausea, vomiting and diarrhoea

Consuming bland, low-fat foods such as dry toast, crackers, rice, soups, gelatin, and ice-cold drinks is recommended to reduce the risk of nausea, vomiting and diarrhoea.[25,27,28] It is also advisable to avoid deep-fried, greasy, oily, or sweet foods, eat slowly, refrain from lying down immediately after eating, and opt for fresh air outdoors rather than staying indoors after meals.[27,28]

Thyroid cancer (boxed warning)

Currently, the risk of developing thyroid cancer is low. However, symptoms such as a lump or swelling in the neck, hoarseness, shortness of breath, or difficulty swallowing, require seeking medical attention immediately, as these may indicate thyroid cancer.[27,16]

Abdominal pain and gallbladder disease

When patients are prescribed semaglutide, it is important to monitor symptoms, such as persistent gastro-intestinal pain, radiating from the abdomen to the back, accompanied by vomiting, that may require immediate medical attention.[29] Furthermore, patients should be monitored for fever, jaundice or clay-coloured stools, as it may indicate gallbladder impairment and will need prompt attention.[27]

Table III: Serious side effects and adverse drug reactions ADRs

Serious side effects	ADRs
• Hypoglycaemia (low blood sugar) • Acute kidney injury/kidney failure • Vision changes	• Pancreatitis (inflammation of the pancreas) • Acute gallbladder disease • Possible thyroid C-cell tumours, including cancer • Hypersensitivity (serious allergic reaction) • Bleeding, blistering, and burning (rare) • Ileus (temporary inhibition of the gastrointestinal contraction)

Visual changes

During treatment with semaglutide, monitor patients for vision changes. It is recommended to provide a comprehensive dilated eye exam at least once a year.[25]

Hypoglycaemia

Semaglutide, in combination with other hypoglycaemic medicine, such as sulfonylureas (glibenclamide) or insulin, should be used with caution, as it may increase the risk of developing hypoglycaemia.[25] Some signs and symptoms of hypoglycaemia include excessive hunger, shakiness, confusion, light-headedness, blurred vision, fast heartbeat, and mood changes.[27] Regular blood glucose monitoring may mitigate the risk of developing hypoglycaemia.[26]

Kidney impairment

Excessive fluid loss caused by diarrhoea, nausea, and vomiting may lead to dehydration, which can worsen kidney damage or pre-existing kidney impairment.[27] Patients must be counselled to drink plenty of fluids to reduce the risk of dehydration.[28]

Hypersensitivity

Patients may develop symptoms of a severe hypersensitivity or allergic reaction, such as rash, itchiness, swollen facial features (lips, tongue or throat), difficulty in breathing or swallowing, fainting or feeling lightheaded, with elevated rapid heartrate.[27,28] Even after discontinuation of semaglutide, side effects may persist, especially when used at the maximum dose of 2 milligrams.[26]

Ongoing research is being conducted to determine the potential long-term side effects of semaglutide for type 2 diabetes and off-label weight loss.[28] The focus is mainly on how the drug could impact the thyroid and gastrointestinal tract.[28] As of January 2024, the FDA reported gastrointestinal disorders, particularly nausea, as the most reported side effect of semaglutide.[26] The FDA continuously reviews the drug's reported side effects while it is on the market. Therefore, it is highly recommended that everyone who is undergoing drug treatment pays close attention and reports any side effects that do not subside over a few weeks.[28]

Use or abuse of semaglutide

A USA study observed a total of 31 542 adverse effects and of these reported, 26.1% (n = 8 249) were from semaglutide use during the period from January 2018 to December 2022. Additionally, semaglutide had the most drug use, abuse and withdrawal-related AEs reported when compared with the other GLP-1 RAs (dulaglutide, liraglutide, exenatide, lixisenatide, tirzepatide, and albiglutide). The increased rate of off-label use of semaglutide, which is not seen with the other GLP-1 RA's, raised concerns about increased misuse or abuse of the drug.[30]

In the South African context, we are one of the countries in sub-Saharan Africa burdened with overweight and obese patients.[31] Owing to that, shortages have been reported of semaglutide for diabetic patients, which may indicate high off-label use driven by a similar weight-loss popularity trend seen in countries like the USA and Britain.[32] The scale of the unmet demands for semaglutide prompted a media release from the South African Health Products Regulatory Authority (SAHPRA) on the 11th of October 2023 warning customers against counterfeit, unregistered drugs available in the market.[32] There is still a need for further studies to be conducted to quantify the use or misuse of semaglutide in South Africa.

Conclusion

Despite its indications for T2DM, semaglutide is used worldwide as a weight-loss drug. If used independently, semaglutide lowers blood sugar levels without raising the risk of hypoglycaemia and slows gastric emptying, which prolongs the sensation of fullness after eating, and functions as an appetite suppressant by focusing on the brain regions that are responsible for hunger and cravings. Writing a semaglutide prescription for weight loss is seen as an off-label use.[33]

In the case of any complaints or experienced side-effects, you are encouraged to report the side effects experienced to the following number: +27 83 379 2104.

Before reporting a side effect, contact your local doctor or another medical health expert if you or the person you are reporting on behalf of is experiencing serious side effects.

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