



FOCUS ON
HEALTH

Multidisciplinary

Self-study CPD activity

Activity Reference Number

G1(25)

Topic

Ozempic

Article(s)

Semaglutide – Hype Validation The Great, the Good but keep the Bad in mind

Profession(s)

All Professions

You can complete any part or all parts of this activity, but we advise completing the entire activity.

This is because the way the MCQs were developed, for some questions in a specific part of the activity you may need to read the next article to complete the MCQs in that part.

Part 1 of this activity is approved for **TWO (2) Clinical** Continuing Education Units (CEU's)

Part 2 of this activity is approved for **TWO (2) Clinical** Continuing Education Units (CEU's)

Part 3 of this activity is approved for **TWO (2) Clinical** Continuing Education Units (CEU's)

Part 4 of this activity is approved for **TWO (2) Clinical** Continuing Education Units (CEU's)

Part 5 of this activity is approved for **THREE (3) Clinical** Continuing Education Units (CEU's)

Part 6 of this activity is approved for **THREE (3) Clinical** Continuing Education Units (CEU's)

Part 7 of this activity is approved for **TWO (2) Clinical** Continuing Education Units (CEU's)

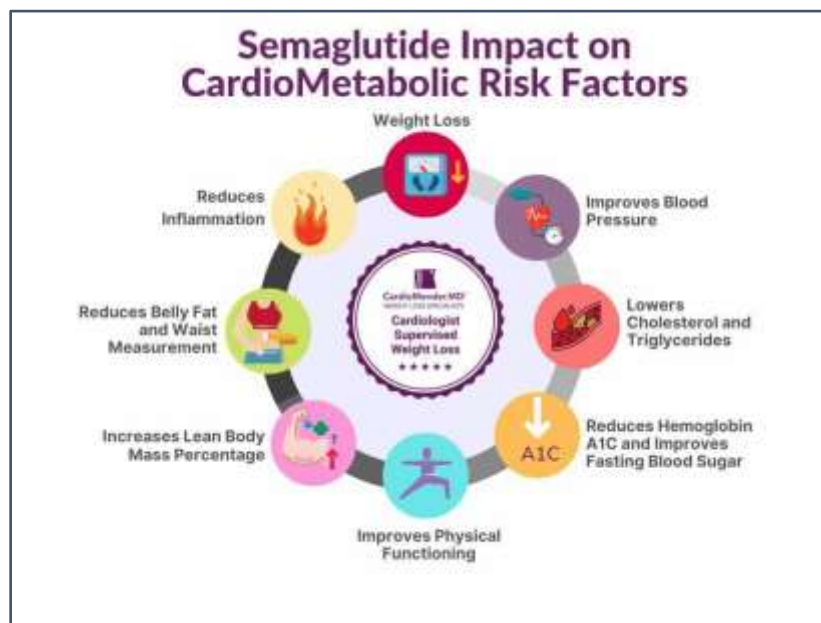
Semaglutide – Hype Validation

The Great, the Good but keep the Bad in mind



If you've been paying attention only to the headlines, when you think of "Ozempic" you'll think of a few things: a blockbuster weight loss drug or the tip of the spear of a completely new industry — A drug so popular that the people it was invented for (those with diabetes) struggled to get it.

Ozempic and other GLP-1 receptor agonists are undeniable game changers. It does not only affect diabetes but reaches much further.



Beginnings and Background

To give you an idea of where it all started here is an extract from the article:

The Discovery and Development of Liraglutide and Semaglutide

B.L Knudsen and J. Lau. 2019. Front. Endocrinol. 10:155.doi: 10.3389/fendo.2019.00155.

INTRODUCTION

Bayliss and Starling first described the connection between the pancreas, the gut and incretin hormones in the early part of the twentieth century. The discovery of glucagon-like peptide-1 (GLP-1), an incretin hormone with important effects on glycaemic control and body weight regulation, led to efforts to extend its half-life and make it therapeutically effective in people with type 2 diabetes (T2D). The development of short- and then long-acting GLP-1 receptor agonists (GLP-1RAs) followed. Significant weight loss, through an effect to reduce energy intake, led to the approval of liraglutide (3.0mg) for the treatment of obesity, an indication currently under investigation with semaglutide.

THE DISCOVERY OF LIRAGLUTIDE

GLP-1 is a 30 amino acid peptide hormone with a short half-life (1.5 min following intravenous dosing and 1.5 h following subcutaneous dosing in humans). These properties have posed challenges to the pharmaceutical use of GLP-1, where a constantly high and stable plasma level is required. Furthermore, native GLP-1 is subject to fibrillation, as best described for glucagon. In attempts to prolong the half-life of GLP-1 and develop a suitable compound for therapeutic use, some pharmaceutical companies chose to optimize the exendin-4 peptide (a naturally occurring peptide obtained from Heloderma lizard venom, with 53% homology to human GLP-1), which leads to an intravenous half-life of ~30min. Human GLP-1 was used as the starting point for the drug discovery program.

As it was very important to increase the intravenous half-life of GLP-1 beyond that which could be obtained with dipeptidyl peptidase IV (DPP-IV) stabilization, fatty-acid derivatization was employed.

Based on these initial studies and comprehensive characterization, liraglutide was selected as having the best properties, combining high receptor potency with pharmacokinetics (PK) that are optimum for once daily (OD) dosing. A key property of liraglutide is its partial protection from rapid DPP-IV degradation, despite the His-Ala N-terminal being unchanged.

THE DISCOVERY OF SEMAGLUTIDE

Successful clinical trials with exenatide and liraglutide led to an increased interest in GLP-1-based therapies. As daily injections are a barrier for some patients with T2D, there was a focus on improving convenience, ideally with an effective GLP-1 analogue that could be administered once weekly. Several technologies have been explored to discover and develop a GLP-1RA applicable for once-weekly (OW) dosing.

THE PHARMACOLOGY OF LIRAGLUTIDE AND SEMAGLUTIDE

Liraglutide and semaglutide are both long-acting GLP-1RAs that, despite differing administration intervals and doses, have pharmacodynamic (PD) effects for 24 h/day. Liraglutide was developed for OD administration, and is available as an OD injection of up to 1.8mg, whereas semaglutide is available as a OW injection of up to 1.0mg —both for the treatment of T2D. Liraglutide is additionally

approved for the treatment of obesity, at a dose of 3.0mg, while semaglutide is in clinical development as a treatment for obesity (phase 3) and NASH (phase 2). Furthermore, phase 3 clinical trials in T2D are ongoing with semaglutide administered orally (in a co-formulation with an absorption enhancer).

Using fatty acids engineered onto a peptide, thereby facilitating binding to albumin, is a novel concept for drug protraction. Eleven fatty-acid binding sites are described on human albumin and, as the human albumin concentration is ~0.6mM and the exposure levels of liraglutide and semaglutide are in the 20–40 nM range, there appears to be a large surplus in binding capacity on albumin. Consequently, no apparent safety issues have arisen from this approach. No interactions with other albumin-binding drugs have been shown, likely because most other drugs do not bind to the fatty-acid binding sites.

Glucose Lowering

Liraglutide was the first long-acting GLP-1RA to become available for the treatment of T2D, receiving market authorization in 2009 in the EU, 4 years after the short-acting GLP-1RA, exenatide, was first approved in the US. Semaglutide was approved in 2017. The pharmacology of short- and long-acting GLP-1RAs differ. Short-acting GLP-1RAs are administered before a meal and have a greater effect on gastric emptying and postprandial glucose, primarily after the meal, whereas long-acting GLP-1RAs have less of an effect on gastric emptying and postprandial glucose excursions, but a more pronounced effect on fasting blood glucose and weight loss (140). These differences were first illustrated in LEAD and AWARD, the phase 3 clinical trial programs for liraglutide and dulaglutide, respectively. While semaglutide was primarily designed as a longer-acting compound compared with liraglutide, it has been shown to provide benefits beyond its protraction; studies have demonstrated greater glucose-lowering and weight-loss effects with semaglutide compared with other GLP-1RAs, including liraglutide.

The glucose-lowering mechanisms of action of GLP-1RAs are well-characterized. Initially, GLP-1 was described as an incretin hormone that stimulates glucose-dependent insulin secretion, increases insulin biosynthesis, improves beta-cell function and

acts as a glucagonostatic regulator. Physiologically, however, the primary effect of GLP-1 is most likely the reduction of gastric emptying, with the effects on insulin and glucagon being of lesser relevance (95). There has been some controversy regarding the glucagonostatic effect of GLP-1RAs, and whether such an effect exists. Some studies have indicated a neutral, or even an increased, response. The challenge may lie in measuring glucagon, which can be very difficult. For semaglutide, however, the reductions in glucagon (both postprandial and fasting) are clear. Indeed, plasma glucagon was shown to be significantly reduced at week 56 with semaglutide vs. sitagliptin or exenatide ER.

Weight Loss

Several studies document the weight-loss effect and mechanism of liraglutide and semaglutide: these are outlined below. Clinical data have shown liraglutide to provide greater reductions in body weight compared with short- and long-acting exenatide, short-acting lixisenatide and long-acting dulaglutide, with markedly greater reductions vs. albiglutide. Trials with liraglutide 1.8mg have shown weight loss of up to 3.6% (3.3 kg) at 26 weeks and 4.7% (5.0 kg) at 56 weeks in subjects with T2D, while trials with liraglutide 3.0mg have shown weight loss of between 7.9% (8.9 kg) and 8.2% (7.3 kg) at 56 weeks in subjects with obesity. Furthermore, with a run-in phase of a low-calorie diet, total weight loss of up to 12.5 kg can be achieved (of which half [6.2%] was observed during the liraglutide 3.0mg treatment period) in subjects with obesity.

EFFECTS IN THE BRAIN, WEIGHT LOSS AND BEYOND?

Studies with semaglutide indicate that it has a better uptake in the brain compared with liraglutide but whether this completely explains the difference in weight-loss effects has not been established. What is established is that the reduction in energy intake observed with semaglutide is approximately twice that with liraglutide. It is worth mentioning that the role of GLP-1 as a neuropeptide may be broader than currently recognized and may go beyond mediating body weight and food intake lowering. GLP-1Rs in the brain have been described as being involved in, but not essential for, memory and learning, as well as depression and anxiety.

CV Risk Reduction

GLP-1 has several effects, other than glucose and body weight reduction, that may impact CV outcomes beneficially. Effects documented clinically include decreased BP, reduced postprandial lipid levels [triglycerides (TGs), apolipoprotein B48 (ApoB48)] and a smaller effect on fasting lipids and reduced inflammation.

Inflammation

Inflammation is an established risk factor for CV disease (238). While C-reactive protein (CRP) is the most established systemic inflammatory CV risk marker, recent data indicate that inflammatory markers in vascular tissue [matrix metalloproteinases (MMP), osteopontin (OPN), and cathepsin D] may be more specific measures of plaque instability. Elevated circulating levels of OPN, a proinflammatory cytokine with a role in immune cell recruitment, have been associated with increased CV disease risk in patients with T2D. The genes affected by semaglutide included markers of inflammation and plaque stability that are associated with leukocyte recruitment [e.g., interleukin-1 (IL-1) receptor antagonist, IL-6, monocyte chemoattractant protein (CCL2), OPN], leukocyte adhesion [selectin E, vascular cell adhesion molecule-1 (VCAM1)], leukocyte extravasation and plaque stability (e.g., MMP3, MMP13, CCL2), and plaque rupture and haemorrhage (CD163). Several of these markers are hypothesized to be of relevance in CV disease (IL-1 receptor antagonist, IL-1 receptor, MMP3, CD163, IL-6 and its receptor). Clinical studies have shown that liraglutide lowers levels of markers associated with inflammation.

THE TECHNOLOGY BEHIND ORAL SEMAGLUTIDE, AND THE MECHANISM OF ITS ABSORPTION

Historically, peptides and proteins have offered efficacious treatment options either as replacements in diseases where the native peptide- or protein-based hormone is not being produced endogenously, or it is being produced or secreted in smaller amounts than required (e.g., insulin in type 1 diabetes, growth hormone in growth disorders,

factor VIII in haemophilia disorders). Insulin was discovered as a life-saving drug for the treatment of type 1 diabetes and has also had a profound impact on the treatment of T2D. Despite various delivery mechanisms being tested (e.g., pulmonary, buccal, and sublingual), low bioavailability and uncertainty in terms of safety have limited the development and, as such, almost all available insulins are injectable. In the past 15 years, GLP-1RAs have emerged as efficacious therapies in T2D and obesity, with evidence also indicating potential in CV disease and NASH. Due to the relatively larger safety window of GLP-1, compared with insulin, oral delivery of GLP-1 now appears to be feasible. Oral delivery is known as a desirable approach in terms of patient convenience, but it has not been possible to achieve acceptable bioavailability of large hydrophilic peptides and proteins via this approach; oral absorption typically requires a low molecular weight and a certain hydrophobicity.

Oral absorption principally occurs via two mechanisms: Transcellular and paracellular. The absorption of semaglutide and SNAC is primarily transcellular, as shown in vitro using gastric mucosa in a chamber setup, **a gastric cell line to document intracellular uptake and EDTA as a control enhancer facilitating paracellular uptake**. Transcellular uptake of semaglutide was demonstrated in vivo in dog gastric mucosa and confirmed at the electron micrograph level in rats. The molecular mechanism for transcellular uptake appears to involve SNAC partitioning into the cell membrane, due to its lipophilic nature, and affecting membrane fluidity. This results in the rapid absorption of both semaglutide and SNAC. The effect is transient, and appears not to cause damage, probably because cell turnover in the gastric mucosa is rapid—as observed following ethanol absorption in the stomach.

In conclusion, through a variety of tests (cell lines, tissue cultures, in vivo animal models, IHC including at the electron micrograph level, imaging) and clinical trials (scintigraphy imaging, drug-drug interactions), oral semaglutide co-formulated with SNAC has been shown to be absorbed in the stomach in a localized, transient, transcellular process, where a local increase in pH provides solubility and protection against enzymatic degradation.

SUMMARY

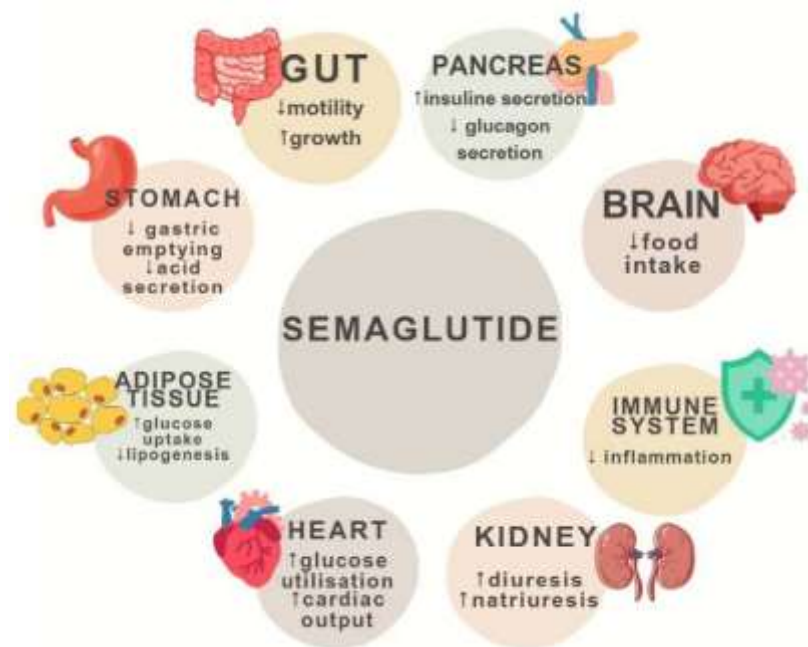
The development of the long-acting GLP-1 analogues liraglutide and semaglutide, using albumin binding to extend the half-life represents a significant advance

in GLP-1-based therapies The improvement in glycemic control and reduction in body weight with these compounds offer benefits to patients with T2D, with liraglutide (3.0mg) also providing a treatment option for those with obesity and semaglutide under investigation for this indication. Furthermore, both liraglutide and semaglutide have been shown to reduce CV risk in patients with T2D, a

finding that has not been observed with short-acting GLP-1RAs. Given that CV complications remain a leading cause of morbidity and mortality in people with T2D, despite substantial efforts to reduce risk using CV medications, the availability of antidiabetes medications that can contribute to risk reduction is a significant advance.

Research and Beyond

A great deal of research has been done since the discovery of semaglutide and liraglutide because of their possible far-reaching effects. Although initially meant for the treatment of type 2 diabetes mellitus, they show significant performance on weight reduction and in other areas.



Semaglutide and Obesity



Here are extracts from two articles relating to the effect of semaglutide on obesity.

Long-term weight loss effects of semaglutide in obesity without diabetes in the SELECT trial

D.H. Ryan et al. 2024, nature medicine; doi.org/10.1038/s41591-024-02996-)

INTRODUCTION

The worldwide obesity prevalence, defined by body mass index (BMI) ≥ 30 kg m⁻², has nearly tripled since 1975. BMI is a good surveillance measure for population changes over time, given its strong correlation with body fat amount on a population level, but it may not accurately indicate the amount or location of body fat at the individual level. In fact, the World Health Organization defines clinical obesity as ‘abnormal or excessive fat accumulation that may impair health’. Excess abnormal body fat, especially visceral adiposity and ectopic fat, is a driver of cardiovascular (CV) disease (CVD), and contributes to the global chronic disease burden of diabetes, chronic kidney disease, cancer and other chronic conditions.

Remediating the adverse health effects of excess abnormal body fat through weight loss is a priority in addressing the global chronic disease burden. Improvements in CV risk factors, glycemia and quality-of-life measures including personal well-being and physical functioning generally begin with modest weight loss of 5%, whereas greater weight loss is associated with more improvement in these measures. Producing and sustaining durable and clinically significant weight loss with lifestyle intervention alone has been challenging. However, weight-management medications that modify appetite can make attaining and sustaining clinically meaningful weight loss of $\geq 10\%$ more likely.

Recently, weight-management medications, particularly those comprising glucagon-like peptide-1 receptor agonists, that help people achieve greater and more sustainable weight loss have been developed. Once-weekly subcutaneous semaglutide 2.4 mg, a glucagon-like peptide-1 receptor agonist, is approved for chronic weight management and at doses of up to 2.0 mg is approved for type 2 diabetes treatment. In patients with type 2 diabetes and high CV risk, semaglutide at doses of 0.5 mg and 1.0 mg has been shown to significantly lower the risk of CV events (20). The SELECT trial (Semaglutide Effects on Heart Disease and Stroke in Patients with Overweight or Obesity) studied patients with established CVD and overweight or obese but without diabetes. In SELECT, semaglutide was associated with a 20% reduction in major adverse CV events (hazard ratio 0.80, 95% confidence interval (CI) 0.72 to 0.90).

DISCUSSION

The analyses of weight effects of the SELECT study presented here reveal that patients assigned to once-weekly subcutaneous semaglutide 2.4 mg lost significantly more weight than those receiving placebo. The weight-loss trajectory with semaglutide occurred **over 65 weeks** and was sustained up to 4 years. Likewise, there were similar improvements in the semaglutide group for anthropometrics (WC and WHtR). **The weight loss was associated with a greater proportion of patients receiving semaglutide achieving improvement in BMI**

category, healthy BMI (<25 kg m⁻²) and falling below the WC cutoff point above which increased cardiometabolic risk for the sex and race is greater.

Furthermore, both sexes, all races, all body sizes and those from all geographic regions were able to achieve clinically meaningful weight loss. The implications of weight loss of this degree in such a diverse population suggest that it may be possible to impact the public health burden of the multiple morbidities associated with obesity. Although our trial focused on CV events, many chronic diseases would benefit from effective weight management.

The overall safety profile did not reveal any new signals from prior studies, and there were no BMI category-related associations **with AE reporting**. The analysis did reveal that tolerability may differ among specific BMI classes since more discontinuations occurred with semaglutide among lower BMI classes. Potential contributors may include a possibility of higher drug exposure in lower BMI classes, although other explanations, including differences in motivation and cultural mores regarding body size, cannot be excluded.

An interesting observation from this SELECT weight loss data is that when BMI is ≤ 30 kg m⁻², weight loss on a percentage basis is less than that observed across higher classes of BMI severity. Furthermore, as BMI exceeds 30 kg m⁻², weight loss amounts are more similar for class I, II and III obesity. This was also observed in Look AHEAD, a lifestyle intervention study for weight loss (30). The proportion (percentage) of weight loss seems to be less, on average, in the BMI <30 kg m⁻²

category relative to higher BMI categories, despite their receiving the same treatment and even potentially higher exposure to the drug for weight loss (30). Weight loss cannot continue indefinitely. There is a plateau of weight that occurs after weight loss with all treatments for weight management. This plateau has been termed the 'set point' or 'settling point', a body weight that is in harmony with the genetic and environmental determinants of body weight and adiposity (31). Perhaps persons with BMI <30 kg m⁻² are closer to their settling point and have less weight to lose to reach it. Furthermore, the cardiometabolic benefits of weight loss are driven by reduction in the abnormal ectopic and visceral depots of fat, not by reduction of subcutaneous fat stores in the hips and thighs. The phenotype of cardiometabolic disease but lower BMI (<30 kg m⁻²) may be one where reduction of excess abnormal and dysfunctional body fat does not require as much body mass reduction to achieve health improvement. We suspect this may be the case and suggest further studies to explore this aspect of weight-loss physiology.

This analysis of the SELECT study supports the broad use of once-weekly subcutaneous semaglutide 2.4 mg as an aid to CV event reduction in individuals with overweight or obese without diabetes but with preexisting CVD. Semaglutide 2.4 mg safely and effectively produced clinically significant weight loss in all subgroups based on age, sex, race, glycemia, renal function and anthropometric categories. Furthermore, the weight loss was sustained over 4 years during the trial.

Two-year effects of semaglutide in adults with overweight or obesity: the STEP 5 trial

W.T. Garvey et al. 2022. Nature medicine; /doi.org/10.1038/s41591-022-02026-4

INTRODUCTION

Behavioural intervention incorporating modifications in diet and physical activity remains the foundation of treatment for overweight and obesity. However, because behavioural intervention is often not associated

with clinically meaningful and sustainable weight loss, pharmacotherapy is recommended as an additional tool for long-term weight management in people with a body mass index (BMI) of at least 30 kg m⁻², or at least 27 kg m⁻² in those with weight-related comorbidities (1). Semaglutide is a glucagon-like peptide-1 (GLP-1) analogue approved for the

treatment of type 2 diabetes (oral semaglutide and subcutaneous semaglutide) and for reducing the risk of cardiovascular events in people with type 2 diabetes and cardiovascular disease (subcutaneous semaglutide only). At a dose of 2.4 mg once weekly, subcutaneous semaglutide was approved in the United States, Europe, the United Kingdom and Canada for weight management in adults with overweight (BMI ≥ 27 kg m⁻² with at least one weight-related comorbidity) or obesity (BMI ≥ 30 kg m⁻²), based on results from the Semaglutide Treatment Effect in People with Obesity (STEP) clinical trial program

DISCUSSION

In STEP 5, once-weekly treatment with semaglutide 2.4 mg as an adjunct to behavioural intervention in adults with overweight (with at least one weight-related comorbidity) or obesity led to a substantial initial reduction in weight, which plateaued after approximately week 60 and was maintained for the remainder of the study. At week 104, participants in the semaglutide group achieved a mean weight loss of 15.2% from baseline—a difference of 12.6 percentage points versus placebo plus behavioural intervention.

This weight loss is comparable to the mean reduction of 14.9% (placebo-corrected weight loss of 12.4 percentage points) seen at week 68 in the STEP 1 trial of semaglutide 2.4 mg versus placebo (both plus behavioural intervention). Thus, our findings indicate that the substantial weight losses reported during 68 weeks' treatment with semaglutide 2.4 mg in prior STEP trials can be maintained with continued semaglutide treatment up to at least 104 weeks. The mean weight loss of ~15% achieved with semaglutide 2.4 mg at week 104 in STEP 5 exceeds weight loss reported at similar time points in trials with other pharmacotherapies for weight management in adults with overweight or obesity.

Obesity is a chronic, relapsing disease that requires continuous effort to control. With all nonsurgical interventions and to some extent with bariatric surgery, weight regain after initial weight loss is common. In contrast to findings with behavioural and other pharmacological interventions, the similar mean weight loss achieved with semaglutide 2.4 mg in STEP 5 at weeks 52 and 104 (–15.6% and –15.2%, respectively) suggests that, on average, there is minimal weight regain over 104 weeks when once-

weekly semaglutide therapy is continued. When interpreted together with the findings of the STEP 4 withdrawal trial and STEP 1 off-treatment extension study, which both showed weight regain after semaglutide discontinuation (after 20 weeks' treatment in STEP 4 and 68-weeks' treatment in STEP 1), these results support the benefit of continued semaglutide treatment for sustained weight loss.

Prior 68-week trials in adults with overweight or obesity have reported cardiometabolic improvements with semaglutide 2.4 mg. Consistent with these findings, in STEP 5 semaglutide treatment improved a range of cardiometabolic risk parameters, including waist circumference, systolic and diastolic blood pressure, HbA1c levels, total cholesterol, low-density lipoprotein cholesterol, very-low-density lipoprotein cholesterol and triglycerides. Collectively, these results indicate a beneficial effect of treatment on overall patient health. In addition, semaglutide treatment reduced C-reactive protein levels, a marker of systemic inflammation that is known to be elevated in patients with obesity. The reduction in fasting insulin and glucose with semaglutide is indicative of an increase in insulin sensitivity.

SAFETY AND TOLERABILITY

Adverse events leading to discontinuation of trial product were reported by nine participants (5.9%) in the semaglutide group and seven participants (4.6%) in the placebo group. Gastrointestinal disorders, namely nausea, diarrhoea, vomiting and constipation were the most frequently reported adverse events and occurred in more participants treated with semaglutide than with placebo (125 (82.2%) of 152 versus 82 (53.9%) of 152, respectively). Most gastrointestinal adverse events were mild-to-moderate and transient, and such events led to permanent treatment discontinuation in six (3.9%) participants in the semaglutide group and one (0.7%) participant in the placebo group.

In conclusion, treatment with once-weekly subcutaneous semaglutide in conjunction with behavioural intervention in adults with overweight (with at least one weight-related comorbidity) or obesity (without diabetes) was associated with clinically impactful and sustained weight loss of 15.2% at week 104, along with improvements in

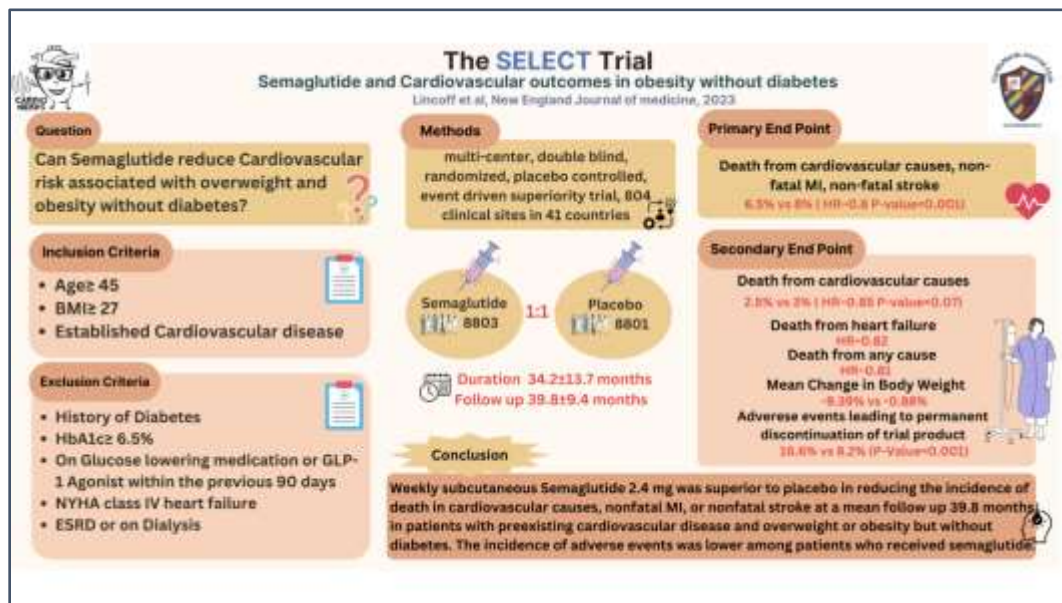
weight-related cardiometabolic risk factors.

Semaglutide and Cardiovascular outcomes

Inter-related to obesity, which impacts cardiovascular health, here is an extract from the article:

Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes

A.M Lincoff, M.D. et al. 2023 N Engl J Med 2023;389:2221-32.DOI: 10.1056/NEJMoa2307563



BACKGROUND

Semaglutide, a glucagon-like peptide-1 receptor agonist, has been shown to reduce the risk of adverse cardiovascular events in patients with diabetes. Whether semaglutide can reduce cardiovascular risk associated with overweight and obesity in the absence of diabetes is unknown. More than half the world population is projected to be overweight or obese by the year 2035. High body mass index (BMI) is estimated to have accounted for 4 million deaths globally in 2015, more than two-thirds of which were caused by cardiovascular diseases. Overweight and obesity are independently associated with an increased risk of cardiovascular events, even after the influence of metabolic cardiovascular risk factors linked to excess weight

has been accounted for. Although reducing the risk of cardiovascular disease by treating dyslipidemia, hypertension, and diabetes is standard evidence-based practice, the concept of treating obesity to reduce the risk of cardiovascular complications has been hampered by the lack of evidence from trials indicating that lifestyle or pharmacologic interventions for overweight or obesity improve cardiovascular outcomes.

DISCUSSION

GLP-1 receptor agonists are recognized to have cardioprotective effects in patients with type 2

diabetes. We conducted this trial to determine whether semaglutide, a potent long-acting medication in this class (25), would diminish the excess cardiovascular risk associated with overweight or obesity in patients with no history of diabetes.

Among 17,604 patients with a BMI of 27 or greater and preexisting cardiovascular disease but without diabetes, treatment with once-weekly subcutaneous semaglutide at a dose of 2.4 mg for a mean duration of 33 months reduced the risk of a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke by 20% (hazard ratio, 0.80; 95% CI, 0.72 to 0.90). The effects of semaglutide occurred early after the initiation of treatment and were directionally similar across cardiovascular endpoints and among prespecified patient subgroups.

Semaglutide was associated with decreases in body weight and waist circumference, findings consistent with the known metabolic effects of this class of medications. Semaglutide improved cardiovascular outcomes in this trial, whereas lifestyle and pharmacologic interventions for overweight or obesity tested in previous trials have uniformly failed to do so. The reductions in body weight achieved with other nonsurgical approaches have been substantially lower than the mean 9.4% decrease observed with semaglutide in this trial, and a post hoc analysis of data from a previous trial has suggested that cardiovascular risk might be decreased among patients who lose at least 10% of their body weight. Similarly, bariatric surgery, in which reductions in body weight of more than 20% can be achieved, has been associated with fewer cardiovascular events than usual care.

Recommendations for the treatment of type 2 diabetes have long targeted cardiovascular risk reduction, and current guidelines recommend the use of GLP-1 receptor agonists in patients with diabetes who need cardiovascular risk reduction, weight management, or both (38,39). Major adverse cardiovascular events were reduced by approximately 14% in a meta-analysis of GLP-1 receptor agonists (hazard ratio, 0.86; 95% CI, 0.80 to 0.93) among patients with type 2 diabetes and preexisting cardiovascular disease or cardiovascular risk factors, with similar benefits observed in these patient groups in trials of subcutaneous or oral semaglutide (hazard ratios of 0.74 and 0.79, respectively). The estimated global prevalence of diabetes is approximately 30% among patients with chronic coronary syndromes, and thus most people with cardiovascular disease do not have diabetes.

The magnitude of the effect of semaglutide in the current trial was similar to that among patients with diabetes in previous studies (within the constraints of between-trial comparisons), which suggests that treatment with semaglutide could be applied more broadly for secondary prevention of cardiovascular events in the expanding population of patients with overweight and obesity and atherosclerotic vascular disease.

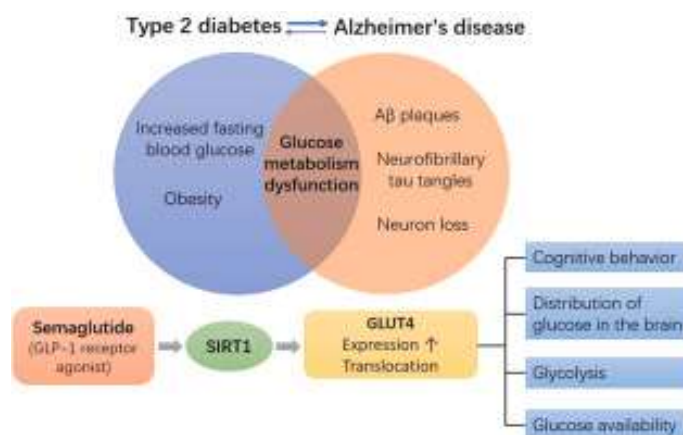
In this randomized, placebo-controlled trial involving patients with preexisting cardiovascular disease and overweight or obesity but without diabetes, weekly subcutaneous semaglutide at a dose of 2.4 mg was superior to placebo in reducing the incidence of a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke at a mean follow-up of 39.8 months.

Semaglutide and the brain

Clinical trial evidence suggests that semaglutide possibly protects against neurodegeneration and neuroinflammation and therefore could have the ability to protect against Alzheimer's disease. There are also potential beneficial effects on various substance use disorders such as cannabis use disorder and alcohol and smoking addiction. Here are extracts from articles on this matter.

Glucagon-like peptide-1 class drugs show clear protective effects in Parkinson's and Alzheimer's disease clinical trials: A revolution in the making?

Christian Hölscher.2024.Neuropharmacology, Vol 253 doi.org/10.1016/j.neuropharm.2024.109952



ABSTRACT

Parkinson's disease (PD) is a complex syndrome for which there is no disease-modifying treatment on the market. However, a group of drugs from the glucagon-like peptide-1 (GLP-1) class have shown impressive improvements in clinical phase II trials. Exendin-4 (Bydureon), Liraglutide (Victoza, Saxenda) and Lixisenatide (Adlyxin), drugs that are on the market as treatments for diabetes, have shown clear effects in improving motor activity in patients with PD in phase II clinical trials. In addition, Liraglutide has shown improvement in cognition and brain shrinkage in a phase II trial in patients with Alzheimer's disease (AD). Two phase III trials testing the GLP-1 drug semaglutide (Wegovy, Ozempic, Rybelsus) are ongoing. We are at a crossroads where GLP-1 class drugs are emerging as a new treatment strategy for PD and for AD. Newer drugs that have been designed to enter the brain easier are being developed and already show improved effects in preclinical studies compared with the older GLP-1 class drugs that had been developed to treat diabetes. The future looks bright for new treatments for AD and PD.

DISCUSSION

The reasons for the failure of previous drug discovery projects are manifold, ranging from wrong hypotheses to misleading data from animal experiments. One key issue is that many approaches to treat AD or PD assume for each a monocausal origin of the disease. The aim to 'fix' one biomarker that correlates with the disease, and therefore must be the cause of the disease, appears to be a common misconception that almost always guarantees failure. We know that the pathologies that underlie PD and AD are complex and involve very disparate systems such as the chronic inflammation response, loss of energy utilization, loss of synaptic activity, impaired autophagy and responses to oxidative stress (Johnson et al., 2019; Reich and Hölscher, 2022). Any successful treatment will have to involve a multi-pronged approach that simultaneously improves many different physiological systems and underlying disease mechanisms.

Based on the impressive protective effects in different preclinical models and the approval for the use of some GLP-1 class drugs as a treatment for humans, numerous clinical trials have been conducted or are currently ongoing in AD and PD. The first clinical trial outcomes show clear neuroprotective and disease-modifying effects.

What is the underlying mechanism of GLP-1 drug action?

It appears that a lot of people in the field are unsure what to make of the results of these clinical studies, even though quite a lot of research on the underlying mechanisms has been conducted in this area. Since the role and function of GLP-1 signalling in the brain are still unknown to most neuroscientists and neurologists, the main question often is how does GLP-1 achieve this impressive result, what is the underlying mechanism? We actually know a lot about the molecular processes that are activated by GLP-1 in neurons.

Cell culture and animal studies demonstrate that when activating the GLP-1 or GIP receptors in the brain, energy utilization in neurons is normalized, cell repair and gene expression returns to normal, synaptic activity is normalized, the chronic inflammation response in the brain is reduced, and more (Hölscher, 2022a; Reich and Hölscher, 2022). This is due to the loss of growth factor signalling, in particular insulin. Insulin is an important growth factor in the brain, and previous studies have shown that insulin signalling is impaired in the brains of PD patients (Bassil et al., 2022; Cheong et al., 2020; Morris et al., 2011). GLP-1 is a growth factor as well and can compensate for the loss of insulin signalling, and can re-sensitize insulin signalling in the brain (Long-Smith et al., 2013; Yassine et al., 2022). In diabetes patients, GLP-1 mimetics can improve insulin sensitization (Doyle and Egan, 2003; Müller et al., 2019; Yang et al., 2022) and in patients with AD or PD, they can, too (Athauda et al., 2022; Cheong et al., 2020; Long-Smith et al., 2013; Talbot, 2014; Talbot and Wang, 2023).

There are several other mechanisms, such as the reduction of the chronic inflammation response found in the brains of PD patients (Hirsch and Hunot, 2009; Orr et al., 2002). GLP-1 mimetics such as exendin-4, liraglutide and lixisenatide have shown good effects in reducing the inflammation response (Kim et al., 2009; Liu et al., 2015; Parthasarathy and Holscher, 2013; Solmaz et al., 2015; Yang et al., 2022). Other mechanisms of action include improvement of mitochondrial activity, synaptic activity, normalization of autophagy to remove

misfolded proteins, and reduction of oxidative stress. See (Hölscher, 2022a, 2022b; Reich and Hölscher, 2022) for comprehensive reviews. Therefore, it is important to note that there is no single mechanism of action that underlies the improvements observed in the brain.

CONCLUSION

GLP-1 class drugs that are on the market to treat diabetes showed clear neuroprotective effects in the first clinical trials in AD and PD patients. This is a clear proof of concept that this strategy is viable and that extensive drug discovery research is warranted in this area. Drugs designed to enter the brain may be more effective than the older drugs that have been designed to treat diabetes.

Currently, there are no drugs available to treat PD that can modify disease progression. The research in this area seems to focus mainly on the theory of misfolded proteins and on the protein alpha-synuclein that appears to aggregate in some, but not all patients with PD.

All clinical trials that tested the effects of antibodies directed against alpha-synuclein showed a complete lack of improvements in PD patients. The antibody Prasinezumab had been tested (Roche and Prothena) and showed no effect (Pagano et al., 2022). Cinpanemab (Biogen) had been shelved in 2021, due to lack of efficacy (Lang et al., 2022). AbbVie discontinued their drug development program of the antibody ABBV-0805 for the same reason (AbbVie, 2022). Other trials in this space are ongoing (Teng et al., 2021), though it is unlikely that this approach will bear fruit.

In contrast, the first clinical trials of GLP-1 receptor agonists that originally have been developed to treat diabetes have already shown significant protective effects in patients with AD or PD. Three different GLP-1 receptor agonists (Exendin-4, Liraglutide, Lixisenatide) in three separate clinical trials showed clear and meaningful improvements in PD, even after washout, and Liraglutide showed improvements in AD patients, too. This is a clear proof of concept that the GLP-1 strategy is effective and treatment with such drugs is making a clear difference in disease progression. This is only the beginning, and drugs are being developed that can

cross the BBB better and show improved protective effects compared to older drugs that had been developed to treat diabetes. We are entering a new era of drug discovery that already has shown success

in the clinic and could bring novel drug treatments to the market that are effective and potentially stop disease progression. The future looks bright for patients with AD or PD.

Associations of semaglutide with first-time diagnosis of Alzheimer's disease in patients with type 2 diabetes: Target trial emulation using nationwide real-world data in the US

W. Wang et al. 2024. *Alzheimer's Dement.* 2024;1–12. DOI: 10.1002/alz.14313



BACKGROUND

An estimated 6.9 million Americans aged 65 and older will be living with Alzheimer's disease (AD) in 2024, a number that is projected to increase to 13.8 million by 2060. AD has no cure, and about 40% of cases are linked to modifiable risk factors.² Given its growing prevalence, profound societal and economic impact, and absence of a cure, targeting these modifiable risk factors is crucial to prevent or delay AD and related dementia. Semaglutide, a glucagon-like peptide-1 receptor agonist (GLP-1RA), was approved by the US Food and Drug Administration (FDA) for type 2 diabetes mellitus (T2DM) in 2017 and for weight loss in 2021. Both T2DM and obesity are significant modifiable risk factors for AD. Furthermore, semaglutide has demonstrated benefits in managing various other health conditions such as cardiovascular factors, alcohol use, smoking, and depression,^{5–9} many of which are also linked to AD risk.² Given its ability to target these risk factors, we hypothesize that semaglutide may reduce the risk of developing AD in high-risk patients. Two placebo-controlled trials are currently assessing semaglutide's neuroprotective effects in early AD, alongside a study on its impact on the immune

system in AD patients. However, there are no clinical trials investigating whether semaglutide can delay or prevent the onset of AD. In this study, we conducted an emulation target trial using realworld electronic health records (EHRs) of T2DM patients without prior AD diagnosis. Our aim was to determine whether semaglutide is associated with a reduced risk for first-time diagnoses of AD in a high-risk population, stratified by gender, age groups, and obesity status.

DISCUSSION

In our study of real-world populations with T2DM, a high-risk group for AD, semaglutide showed a lower risk of first-time AD diagnosis or AD-related medication prescriptions compared to insulin, other non-insulin/non-GLP-1RAs, and other GLP-1RAs. These results were similar for older patients, both genders, and those with and without obesity. Cumulative incidence curves began to diverge within 30 days and continued to separate thereafter, indicating semaglutide's potential to delay or slow AD development with sustained effects.

Our study findings align with recent evidence suggesting GLP1RAs like semaglutide may protect cognitive function. Preclinical research indicates semaglutide's potential in reducing A β -mediated neurotoxicity, enhancing autophagy, improving brain glucose uptake, and reducing A β plaques and tau tangles. Clinical data, including studies with dulaglutide, show GLP-1RAs can reduce cognitive impairment in patients with T2DM. Data pooled from three randomized, placebo-controlled trials and nationwide prescription registers from Denmark showed that GLP-1RAs were associated with a 53% reduction in all-cause dementia in patients with T2DM. Our large-scale study of 1,094,761 US patients with T2DM found semaglutide associated with a 40% to 70% decrease in first-time AD diagnoses, including a 40% reduction compared to other GLP-1RAs. Ongoing randomized trials are assessing semaglutide's therapeutic effects in early AD. Our findings support conducting future prevention trials to determine semaglutide's ability to delay or slow down the onset of AD.

AD pathology is multifactorial and complex. GLP receptors are expressed in various organs, influencing multiple intracellular responses that could directly affect AD development or progression in the brain. Insulin dysregulation affects key pathological features of AD.³¹ Antidiabetic medications have shown promise in improving cognition, A β clearance, tau phosphorylation, neurotransmitter turnover, synaptic loss, bioenergetics, vascular function, inflammation, and lipid metabolism in AD. Our study shows that semaglutide significantly reduces first-time AD diagnoses compared to other antidiabetic medications, suggesting potential benefits beyond insulin resistance improvement. This is further supported by the data comparing semaglutide with SGLT2i. Indeed, SGLT2i reduces blood glucose independent of insulin sensitivity and secretion. SGLT2i crosses the blood-brain barrier and has neuroprotective effects by reducing neuroinflammation, oxidative stress, mitochondrial dysfunction, and increasing brain-derived neurotrophic factors. A recent large population-based cohort study showed that SGLT2i was associated with a lower risk of dementia compared with DPP-4i. Our study shows that semaglutide was associated with significantly lower AD first-time diagnosis compared with SGLT2i, with an effect more profound than that of DPP4i. These findings align

with prior research suggesting semaglutide may offer neuroprotective effects via pathways like neuroinflammation and mitochondrial function beyond insulin resistance improvement.

While the underlying mechanisms of the observed association of semaglutide and reduced risk of AD are unknown, they could also reflect semaglutide's improvement of AD risk factors such as T2DM, obesity, cardiovascular diseases, smoking, alcohol drinking, and depression, among others. Semaglutide was shown to improve cardiovascular health in patients with T2DM or obesity.^{5,6} We recently reported that semaglutide was associated with reduced risks for alcohol use disorders⁷ and tobacco use disorders. A large cohort study in the United States showed that GLP-1RAs including semaglutide were correlated with lower risk of depression and anxiety. Findings from this study support the idea that semaglutide could help delay or prevent the onset of AD by mitigating these modifiable risk factors.

In addition, GLP-1RAs have been reported to influence many pathways associated with the progression of AD, including oxidative stress, mitochondrial dysfunction, altered glycation status, and inflammation. GLP-1 receptors have been identified in neurons, astrocytes, and microglia, all of which have been implicated in the cascade of events that drive the pathology of AD. These receptors also exist on macrophages and on cells derived from the macrophage lineage such as microglia and astrocytes, where their activation can reduce secretion of pro-inflammatory cytokines and increase anti-inflammatory mediators. A recent study showed that semaglutide reduces the severity of polymicrobial inflammation and neuroinflammation through central neuronal GLP-1 receptors. However, it is not possible from our studies to implicate any of these in the delay or prevention of an AD diagnosis, though it seems likely that the mechanism involves more than vigorous blood sugar control, given our comparison of antidiabetic drugs and weight loss given our subgroup analysis by obesity status. Obesity is now recognized as a major modifiable risk factor for AD and related dementias in the United States. Semaglutide was approved as Ozempic for treating T2DM in December 2017 and as Wegovy for weight loss in June 2021. Our study population comprised patients with T2DM prescribed semaglutide between December 2017 and May 2021, before its approval for weight loss. Due to

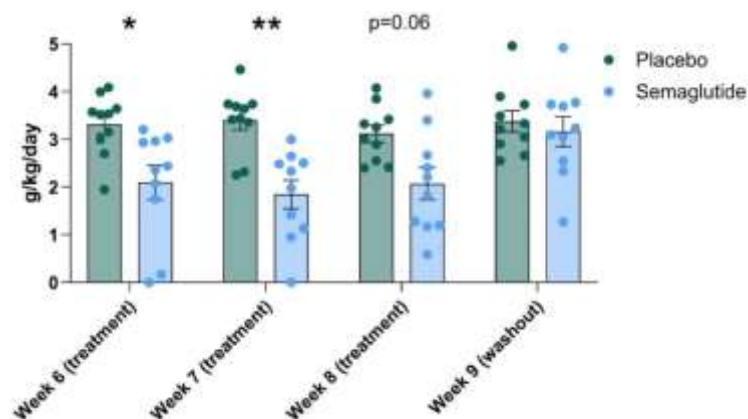
sample size limitations and a shorter follow-up time, we did not include patients prescribed semaglutide as Wegovy for obesity. However, we conducted stratified analyses by obesity status among T2DM patients and found a consistent decrease in first-time AD diagnosis regardless of obesity status. These findings suggest that semaglutide may have beneficial effects on delaying the onset of AD through mechanisms beyond weight loss. Further research is needed to investigate semaglutide's effects in patients with obesity, both with and without T2DM.

A recent randomized placebo-controlled clinical trial of 204 patients with mild AD showed that liraglutide, a first-generation GLP-1RA, slowed the reduction in whole cortical grey matter and frontal, temporal,

and parietal lobe volume compared to placebo. These findings suggest that semaglutide could offer a promising therapeutic approach to treating AD. Our findings support further clinical evaluation of semaglutide's role in mitigating AD initiation and development in patients with T2DM. Future research should explore its effects in mild cognitive impairment, other dementias, and neurodegenerative diseases, as well as investigate other GLP-1RAs like tirzepatide and combination therapies with other antidiabetic medications. Additional preclinical and clinical study articles are needed to shed light on the mechanisms of the potential benefits of semaglutide in preventing or delaying the onset of AD and establish causal effects through randomized trials.

Association of semaglutide with reduced incidence and relapse of cannabis use disorder in real-world populations: a retrospective cohort study

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INTRODUCTION

Cannabis is the most widely used illicit substance worldwide, with estimates from the United Nations Office on Drugs and Crime (UNODC) that in 2020,

209 million people or 4% of the global adult population, had used cannabis (range: 141 million–256 million). In the United States, the increased

legalization of recreational and medical cannabis by the States has expanded the number of users who consume cannabis regularly and at higher doses, which is driven both by the availability of higher-potency cannabis products and access to diverse formulations (e.g., edibles, beverages, vaping, and dabbing) .. Indeed, in the United States between 2008 and 2019, the number of past-year cannabis users increased from 22.6 million to 45.0 million, that of daily or near-daily users increased from 3.6 to 9.8 million, and the number of adults with cannabis use disorder (CUD) increased from 3.4 to 4.1 million.

Nearly a quarter of cannabis users who meet the DSM-5 (the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition) criteria for CUD have a severe disorder that interferes with their everyday lives. Moreover, CUD has been associated with a higher risk for psychotic disorders, self-harm, and suicidal behaviours. Despite the high prevalence of CUD and its negative consequences, there are currently no FDA-approved medications. Treatment of CUD is managed by tapering marijuana use and providing support to combat withdrawal symptoms alongside behavioural interventions. However, behavioral therapies such as contingency management, cognitive-behavioral, and motivational enhancement therapies, are only moderately effective. Thus, there is an urgency to develop medications that can help treat CUD.

DISCUSSION

Currently, several registered clinical trials are ongoing to evaluate the effect of semaglutide on alcohol consumption and on smoking. Preclinical studies have investigated the effects of semaglutide or other GLP1R agonists on nicotine, alcohol, cocaine or opioids. However, little attention has been placed on the effects of semaglutide or other GLP1R agonists on cannabis consumption even though the prevalence of cannabis use is even higher than that of tobacco use among certain demographics. Preclinical and preliminary clinical evidence of semaglutide's potential beneficial effects in various substance use disorders led us to evaluate if it could extend to CUD.

The potential beneficial effects of semaglutide (and presumably other GLP1R agonists) in the treatment of CUD deserve attention in that currently there are no approved medications for its treatment. As such

the only available proven effective therapeutic alternatives are psychosocial interventions, but their effects tend to be limited. Thus, our results support conducting preclinical studies of semaglutide (and other GLP1R agonists) on THC and randomized clinical trials to evaluate the therapeutic benefits of semaglutide in CUD in individuals with obesity or T2D as well as in patients with CUD who don't have these co-morbid conditions.

Though the mechanism(s) underlying the decreased risk of incident and recurrent CUD with semaglutide is unclear, several mechanisms could be involved. Since our results document not just a reduction in relapse but also in the incidence of CUD, one could question the mechanism by which semaglutide prevents the transition from cannabis use to CUD. Though the majority of cannabis users do not proceed to develop a CUD, approximately 10% do, and among young users, the risk can increase to 30%. This transition is typically associated with an increase in the regularity and frequency of use. In the case of nicotine, preclinical studies showed evidence that the rewarding effects of nicotine are reduced by stimulation of GLP-1 receptors in the medial habenula, which is a brain region that mediates nicotine's aversive effects; whereas exenatide a GLP-1R agonist drug attenuated nicotine's activation of dopamine reward circuitry.

Whether similar mechanisms pertain to cannabis is unclear since there are no studies that have evaluated the effects of GLP1 signalling in the aversive or rewarding effects of THC. Cannabinoid receptor 1 (CB1R) is expressed in presynaptic and postsynaptic neuronal sites in the lateral habenula, where they modulate behavioural responses to stress exposure, such that CB1R blockade reduced anxiety-like behaviours and also in GABAergic cells in the ventral tegmental area (VTA) and their stimulation increases the firing of dopamine neurons, which modulate reward. Indeed endocannabinoid signaling through CB1R regulates the activity of dopamine (DA) neurons in the VTA, which projects to the nucleus accumbens, a key brain reward region activated by addictive drugs including THC. CB1R signalling also inhibits the excitatory stimulation from the infralimbic cortex in response to stressful stimuli relayed via the bed nucleus of the stria terminalis (BNST). Since the BNST also expresses GLP1R and their ablation reduces anxiety-like behaviours, this could provide another potential convergence mechanism by which

semaglutide or other GLP1R could affect cannabis consumption. Though to our knowledge there are no studies on interactions between GLP-1 and CB1 receptors in the habenula, VTA or other brain regions, there is evidence of reciprocal functional interactions between these two receptors peripherally.

In juxtaposition, the high prevalence of cannabis use alongside the rise in prescriptions of semaglutide for diabetes and obesity has led to concerns among cannabis users that their cannabis use could interfere with semaglutide therapeutic effects. Even though there is no evidence of interactions between semaglutide and cannabis nor of reports of reduced efficacy, this is an area that requires monitoring. In particular, since CB1Rs, the main target for the rewarding effects of cannabis, are expressed on incretin-secreting cells in rodents and may play a role in regulating GLP-1 secretion. In fact, CB1R antagonist drugs increased GLP-1 release and improved the response to GLP-1RA in rats with diet-induced obesity. Since THC is a partial CB1R agonist, a concern could be that it might inhibit GLP-1 release and attenuate the effects of semaglutide. On the other hand, and seemingly paradoxically in rats the CB1R agonist WIN 55,212-2 enhanced the anorexic effects of subthreshold doses of the

GLP1-RA exendin-4 resulting in a significant decrease in food intake and body weight in rats. Similar effects for an agonist and antagonist on food intake could reflect the dose dependency of cannabinoid effects on food intake, such that decreased intake is reported after high doses whereas low doses increase food consumption.

Our study population included patients who had recent medical encounters for the diagnosis of obesity or T2D and were subsequently prescribed semaglutide or other anti-obesity or anti-diabetes medications, suggesting that patients had active obesity or T2D that needed medical attention and treatments. However, patients may discontinue medications for reasons such as financial burden, drug side effects, or lack of efficacy.

In summary, our results show that semaglutide was associated with a lower risk for both incident and relapse of CUD compared to non-GLP-1 RA anti-obesity and anti-diabetes medications. While these findings provide preliminary evidence of the potential benefit of semaglutide in CUD in real-world populations further preclinical studies are warranted to understand the underlying mechanism and randomized clinical trials are needed to support its use clinically for CUD.

Exploring the Potential Impact of GLP-1 Receptor Agonists on Substance Use, Compulsive Behavior, and Libido: Insights from Social Media Using a Mixed-Methods Approach

Davide Arillotta et al. Brain Sci. 2024, 14, 617. <https://doi.org/10.3390/brainsci14060617>

INTRODUCTION

Glucagon-like peptide-1 (GLP-1) is a multifaceted incretin hormone that plays a crucial role in glucose homeostasis and metabolic regulation. Its primary function is to stimulate insulin secretion in a glucose-dependent manner, which helps to reduce blood glucose levels. This action is achieved through the activation of GLP-1 receptors (GLP-1 Rs) on pancreatic beta cells, leading to increased insulin synthesis and secretion. This incretin activity has resulted in the approval of GLP-1 receptor agonists

(GLP-1 RAs) for the management of type II diabetes [1]. Notably, GLP-1 is also involved in various independent central and peripheral pathways related to appetite regulation due to its anorexic properties. To date, given their proven efficacy in producing weight loss, two GLP-1 RAs (e.g., liraglutide and semaglutide) are also being prescribed with this purpose GLP-1 RAs such as semaglutide have shown a potential and significant influence in reshaping bodies, hence impacting the

medical practice, food economy, and culture. Apart from their social and economic impacts, GLP-1 RAs' use goes beyond their conventional application in treating diabetes and obesity, potentially involving addictive and compulsive behaviours.

Substantial preclinical evidence in rodents and non-human primates has shown that GLP-1 RAs can modulate compulsive and reward-related behaviours in both the seeking and consumption aspects relating to various commonly abused substances (e.g., alcohol, nicotine, opioids and cocaine). GLP-1 RAs, at the central nervous system level, can impact the release of dopamine in the nucleus accumbens, thus modulating the rewarding effects of substance abuse, influencing drug-seeking behaviour, diminishing responsiveness to drug cues, and probably alleviating the withdrawal symptoms' experience. The biological effects of GLP-1, mimicked by GLP-1 RAs (e.g., lixisenatide, liraglutide, exenatide, dulaglutide, and semaglutide), largely depend on the activation of GLP-1 Rs. GLP-1 Rs are expressed in multiple organs and tissues such as the pancreas, kidney, lung, immune system, stomach, bowel, cardiovascular system, and neurons within the enteric, central, and peripheral nervous systems [9]. Acute and chronic GLP-1 Rs' activation triggers a complex network of intracellular signalling pathways (involving, e.g., cyclic adenosine monophosphate (cAMP), protein kinase A (PKA), protein kinase C (PKC), and calcium). These specific signalling patterns depend on the index GLP-1 RA; the target tissue; and the cellular context. In the central nervous system (CNS), GLP-1 Rs are expressed in the cerebral cortex, hypothalamus, hippocampus, thalamus, substantia nigra, circumventricular organ, cerebellum, and brainstem nucleus, with GLP-1 Rs' gene expression pattern evident in rodents, non-human primates, and humans. Acting in these CNS structures, GLP-1 RAs exert a wide range of effects, including those on satiety, energy homeostasis, and neurogenesis. Based on their ability to modulate the mesolimbic reward system and food intake, different authors have hypothesized that GLP-1 RAs might regulate drug-motivated behaviours and drug-reward mechanisms.

Moreover, according to recent studies, some GLP-1 RAs, due to their extended half-lives, exhibited the capability of crossing the blood-brain barrier and exerting effects in the brain that could differ from those of endogenous GLP-1. GLP-1 RAs may potentially be involved in further neurotransmitter

(e.g., serotonin; dopamine) activities. It has been suggested that food intake and substance use disorder share common neurobiological mechanisms [15]. The reward system is a complex network, presenting interactions between the opioid, dopamine, endocannabinoid, and serotonin systems; indeed, food may act as a stimulus to feeding due to its rewarding nature.

DISCUSSION

To the best of our knowledge, this is the first paper aiming at exploring, with a mixed-method approach, the potential impact of GLP-1 RAs on substance-related and behavioural addictions. The focus was here on both legal (alcohol, caffeine, nicotine) and recreational (cannabinoids, psychostimulants, and other substances) drugs. Data relating to possible changes in compulsive shopping activities and sexual drive were provided here as well.

Social media analysis has the potential to provide valuable real-time data for researchers, clinicians, and stakeholders across various fields. The usability, accessibility, and immediacy of social media platforms create a unique opportunity for individuals to share experiences, connect with others, and access resources. When applied to drug abuse and behavioural research, social media analysis could potentially contribute to expanding clinicians' knowledge in diagnosing and treating potential addiction issues.

Indeed, lifestyle changes may well be associated with reduced levels of psychotropic substance consumption. Furthermore, both the beneficial effect of GLP-1 RAs on psychopathological aspects (e.g., improved mood) and the significant weight loss-related improvement in one's appearance could also be hypothesized as being significant factors contributing to reduced drug consumption levels. Previous research has also suggested both direct and indirect effects of GLP-1 RAs on craving, pleasure circuits, and extended networks of substance abuse-related receptor mechanisms.

Finally, the direct adverse effects of GLP-1 RAs in the context of alcohol abuse are likely to be mainly of gastroenterological relevance, hence acting as anti-addictive/aversive stimuli. Moreover, even if GLP-1 RAs might temporarily help in preventing the occurrence of alcohol-related incidents during the

early stages of therapy, they may not be suitable for all individuals with alcohol use disorder because of these molecules' potential adverse effects (e.g., malaise and risk of pancreatitis), particularly in individuals with low body weight or pre-existing pancreatic conditions.

Nicotine and cannabis-derived products. Preliminary studies suggest that GLP-1 RAs have the potential to reduce the nicotine reward, decrease the nicotine intake, and potentially increase smoking abstinence rates. Interestingly, molecules such as dulaglutide have demonstrated benefits in preventing post-cessation weight gain, suggesting that these medications could help in managing the metabolic issues that often accompany quitting Smoking. In relation to cannabis, recent findings showed preliminary evidence of the potential benefit of semaglutide in cannabis use disorder in distinct populations with obesity and type 2 diabetes. Current data may confirm the occurrence of a possible reduction in cannabis intake levels in association with semaglutide.

Cocaine and remaining stimulants. Preclinical findings showed promising results supporting GLP-1 RAs as potential cocaine use disorder medications. Among the underlying mechanisms, some authors hypothesized that GLP-1 RAs can attenuate the cocaine reward by both regulating some neurotransmitter release (e.g., dopamine, GABA, glutamate) and reducing inflammation. To date, however, there is no clear evidence that GLP-1 RAs have an effect on changes in stimulant misuse levels in a clinical setting.

Indeed, some authors highlighted the relationships between binge eating and stimulant abuse, whilst others aimed at clarifying the role of dopamine in the binge eating context [70]. In humans, GLP-1 RAs may not have a significant effect on pervasive and typical stimulant behavioural sensitisation. Rather than substantially affecting dopamine reuptake, one could then argue that these molecules may be able to modulate it only partially or indirectly, and this is consistent with current findings. Similar considerations could be made for amphetamine-type substances, which have indeed been discussed as popular weight-loss agents.

Sexual drive. Little is known about GLP-1 RAs' potential effects on libido and sexual behaviour.

Whilst the GLP-1 receptor activation may reduce the levels of sexual interactions in mice, improvements in libido and sexual function have been observed in males using GLP-1 RAs. Indeed, long-acting GLP-1 RAs may present the potential to boost erectile function in males with type 2 diabetes mellitus. Current clinical evidence shows promising results in both female and male fertility levels, due to weight loss and/or direct actions on the reproductive system.

General considerations regarding reward-related/compulsive behaviours (e.g., food eating, shopping, gaming, internet addiction). GLP-1 RAs' effects seemed to extend not only to food satiety but also to drug craving and various other behavioural disorders (e.g., compulsive shopping), involving the perceived pleasure of substance use and the aversion to excessive patterns in a transversal way. The following questions, therefore, arise: (a) how much/many impulsivity/compulsive mechanisms is/are involved; (b) is there is an influence of GLP-1 RAs on emotional aspects/stress; and (c) what is the specific role of the different GLP1-RAs in modifying behaviours, habits, and chemical dependencies. As we refer to a dual diagnosis (substance use disorder plus a psychiatric disorder), a triple diagnosis (metabolic disease plus substance use disorder plus psychiatric disorder) clinical cluster may be emerging as well. Indeed, individuals should be considered as a composite unit, and it is more appropriate to stratify for different risk factors, subpopulations, and biotypes.

A more integrated perspective should include contributions from eating disorders; inflammation; food addiction; and impulsivity studies. All these issues may shed some light on the interpretation of some of the current results. In this context, whilst the ability of GLP-1 RAs agonists to cross the blood-brain barrier is still controversial, the potential importance of its integrity, e.g., in terms of gut–microbiome–brain axis crosstalk, dysbiosis in obesity, alcoholism, substance use disorders, and systemic inflammations, may be of particular interest. Current data suggest that the benefits of GLP-1 RAs may be evident from their first ingestions and appear to last as long as GLP-1 RAs are being administered.

Some concerns emerged here in relation to the non-prescribed intake of further medications in combination with GLP1-RAs, e.g., with the appetite suppressant tesofensine, or with other molecules

taken with the intention to manage GLP-1 RAs' side effects/consequences, such as skin loss. Particular attention should be paid to certain populations at risk of GLP1-RAs abuse, such as pregnant/lactating women; underweight subjects taking psychostimulants; eating-disordered individuals; the elderly; and people with reduced muscle mass levels .

The overlap between food and substance cravings at a neural level shows the intricate connection between brain reward pathways. GLP-1 RAs could offer a new way to address this overlap by modulating these pathways, potentially reducing the reinforcing effects of both food and substances. By targeting GLP-1 receptors in the brain, these drugs can affect the reward system and areas linked to impulse control and decision-making, suggesting a “dual action” on appetite regulation and addictive

behaviours. Overall, targeting “noise” associated with cravings for food and substances with GLP-1 RAs could offer new avenues for managing addictive behaviours and promoting healthier habits.

CONCLUSIONS

GLP-1 RAs such as semaglutide and tirzepatide were suggested to possess levels of positive effects on reducing both substance- (e.g., alcohol; nicotine; and caffeine) and non-substance-related (e.g., compulsive shopping) behaviours. The intricate interplay between a wide range of factors, including body image, sexual health, individual characteristics, and the GLP-1 RAs' effects, suggests the need for a holistic understanding of these interrelated issues.

Semaglutide and Tirzepatide reduce alcohol consumption in individuals with obesity

Fatima Quddos et al. Scientific Reports | (2023) 13:20998. doi.org/10.1038/s41598-023-48267-2



INTRODUCTION

Alcohol Use Disorder (AUD) is a multi-faceted chronic relapsing brain disorder and contributes greatly to global mortality, yet it remains one of the most undertreated conditions. The only FDA-approved treatments (disulfiram, naltrexone, and acamprosate) have been modestly successful in treating AUD (e.g., naltrexone reduces relapse rates by 5%) (for a detailed review and meta-analysis), but still are severely under-prescribed. Further, 2/3 of patients relapse within the first year in abstinence-based treatment models.

A meta-analysis reported that, at maximum, 50% of individuals diagnosed with AUD achieve remission during extended follow-up periods. Therefore, a crucial need for novel and effective AUD treatments still remains.

GLP-1 peptides, FDA-approved for type-2 diabetes (e.g., Semaglutide and Exenatide) and weight loss (Semaglutide) have been studied for their effects on alcohol use in both preclinical and clinical studies (for a detailed review: 10). GLP-1/GIP peptide

(Tirzepatide) has also been FDA-approved for treating type-2 diabetes. However, to our knowledge, there have been no research studies to investigate the effects of Tirzepatide on alcohol consumption.

While administration of GLP-1 agonists has convincingly shown to reduce alcohol intake in preclinical models, more clinical data is crucial to understanding the efficacy and mechanism of several GLP-1 agonists and other related drug classes (e.g., Tirzepatide) on alcohol intake. In this article, we systematically analyzed social media discussions centred around GLP-1 agonists to generate insights and characterize the real-world evidence regarding the effects on alcohol consumption in a substantial number of social media texts, replicating the workflow from. Next, to gain detailed information on the impact of GLP-1 medication on alcohol consumption, we surveyed individuals with and without Semaglutide or Tirzepatide medications and assessed their historical and contemporary self-reports of alcohol usage and its direct effects. First, for the social media analysis, we retrieved all posts containing keywords related to GLP-1 agonists from Reddit and categorized them by employing a machine learning algorithm to identify major themes of discussions. Next, we identified all alcohol-related posts and categorized them by impact on alcohol. Second, for the detailed reports on alcohol usage, we conducted a between and within participant remote survey among individuals taking Semaglutide or Tirzepatide or neither of these medications, who had a BMI greater than 30 and drank alcohol. Note heretofore, there have been no other reports of Tirzepatide effects on alcohol consumption. We hypothesize reduced alcohol intake and less impact of the self-reported effects of alcohol, in individuals on Semaglutide or Tirzepatide medications, as compared to those not taking these medications.

DISCUSSION

Here, we report a novel analysis of GLP-1 agonist and drinking related posts made to the social media platform reddit. Case studies and media articles have hinted at unexpected side effects of GLP-1 agonist medications, i.e. the suppression of addictive behaviours and desire to consume alcohol. The machine learning-based analysis here provides preliminary empirical support of these phenomena by classifying and quantifying these experiences.

We further report a reduction in alcohol consumption in a cohort of people self-reporting alcohol use and taking Semaglutide or Tirzepatide compared to controls. Participants endorsing Semaglutide and Tirzepatide use reported fewer drinks as measured by the TLFB, fewer binge episodes, and lower AUDIT scores compared to controls and compared to before starting their medication. Participants also reported less stimulating and less sedative effects of alcohol than before starting their medication and when compared to controls.

In contrast to self-reported surveys, passive observation has higher accuracy in areas where self-reporting doesn't, such as recall area and social desirability bias. By integrating both methodologies, we adopt a multifaceted approach wherein the qualitative analysis corroborates the outcomes of our self-reported survey, thereby diminishing potential biases. In our case, we find that not only is there a self-reported decrease in alcohol use in individuals as evidenced by self-reports in our remote study but also a notable association of a decrease in appetite of alcohol with individuals in the comprehensive qualitative social media analysis.

The mechanism by which GLP-1 agonists reduce alcohol intake in humans is currently unknown, though a recent RCT reported reduced alcohol cue reactivity in the nucleus accumbens (NAc), a key region associated with alcohol's rewarding properties, after treatment with the GLP-1 agonist Exenatide. This is in accordance with preclinical studies demonstrating the ventral tegmental area and NAc as key areas mediating the effects of GLP-1 receptor agonists on alcohol intake. Recent studies using fluorescently labelled semaglutide have demonstrated binding in the nucleus accumbens. Furthermore, infusion of Exendin-4 in NAc has been shown to attenuate alcohol self-administration and related behaviours in mice and rats.

While GLP-1 agonists have been shown to have central nervous system action, another possible mechanism is slowed gastric emptying, which could increase fullness and reduce alcohol consumption. This could explain the prevalence of "nausea" and "appetite suppression" terms in our social media study

Additionally, oxidation of alcohol to acetaldehyde can occur in the stomach, potentially explaining the

increase in negative effects of alcohol reported in the social media study. In contrast, intraduodenal ethanol rapidly increases blood alcohol levels³⁶. Therefore, slowed gastric emptying from the stomach to the upper intestine (duodenum) observed after GLP-1 agonist administration could lead to increased levels of acetaldehyde and an altered or blunted rise in blood alcohol content (BAC). Altering the rising curve of a drug greatly decreases its subjective effects and abuse potential. A decrease in the rewarding effects of alcohol could be driving the decrease in AUDIT scores and drinks per week observed in our remote study. Reduced BAC could also explain the decreased sedative and stimulating effects reported by the participants, here. However, some reports suggest that gastric emptying may return to baseline levels over time.

Further mechanistic studies are needed to test these hypotheses and explore potential mechanisms of action of GIP analogues, such as Tirzepatide tested here, for reducing alcohol intake.

CONCLUSIONS

Semaglutide or Tirzepatide in our remote study. These findings add to a growing literature detailing a reduction in alcohol intake after GLP-1 agonist medications. To our knowledge, this is the first report of decreased alcohol consumption following Tirzepatide use. Further RCTs are needed to fully explore the therapeutic potential of GLP-1 agonists and GIP/GLP-1 combination drugs for the treatment of Alcohol Use Disorder.

Semaglutide – Safety, efficacy, misuse and cost-effectiveness

Semaglutide has the world excited with good reason, but is it safe to use and affordable for people who really need it? Here are extracts of a few articles relating to these concerns.

Is There a Risk for Semaglutide Misuse? Focus on the Food and Drug Administration's FDA Adverse Events Reporting System (FAERS) Pharmacovigilance Dataset

Stefania Chiappini et al. 2023. *Pharmaceuticals* 2023, 16, 994. <https://doi.org/10.3390/ph16070994>

ABSTRACT

Recent media reports commented about a possible issue of the misuse of antidiabetics related to molecules promoted as a weight-loss treatment in non-obese people.

INTRODUCTION

In the absence of contraindications, metformin has traditionally been considered the first-line medication in T2DM patients; however, it promotes

modest weight reduction. Conversely, invasive bariatric surgery has been the primary approach to treat severely obese individuals. More recently, the emergence of agents impacting the brain satiety centres' function may provide effective, non-invasive treatment of obesity for individuals with and without diabetes. The long-acting glucagon-like peptide-1 receptor agonist (GLP-1 RA) semaglutide, and tirzepatide, a dual-agonist at both the receptors for glucagon-like peptide-1 (GLP-1) and the glucose-dependent insulinotropic polypeptide (GIP), are now approaching the success seen with bariatric surgery;

in association with these molecules, decreasing body weight (e.g., by >10% in most patients), with a favorable safety profile, is being observed. Indeed, tirzepatide showed even better dose-dependent efficacy (e.g., greater reduction in hemoglobin A1c/HbA1c and body weight) than placebo, basal insulin, and the two GLP-1 analogues dulaglutide and semaglutide. The principal role of the incretins GIP and GLP-1 has generally been thought to stimulate insulin secretion. GLP-1 improves fasting blood glucose due to its direct action on pancreatic islets and decreases postprandial hyperglycemia due to inhibition of gastric emptying, and thus reducing levels of glucose entry into the circulation. GIP directly stimulates insulin secretion through the α cell GIP receptors. Indirectly, GIP potentiates β cell activity to enhance α to β cell communication through the GLP-1R/glucagon receptor (GcgR), thus indirectly stimulating insulin secretion through the β cell. Among other incretin mimetics, both liraglutide, at a maximum daily dose of 3.0 mg, and semaglutide, at a maximum weekly maintenance dose of 2.4 mg, have already received regulatory approval for the treatment of obesity, whilst tirzepatide is currently being assessed for this indication [10,16]. In the United Kingdom (UK), semaglutide received approval as a weight-loss medication to be prescribed on the National Health System (NHS) as of March 2023. With these medications, a range of gastrointestinal adverse effects have been reported, e.g., nausea and diarrhea; conversely, severe hypoglycemia, fatal adverse events, acute pancreatitis, cholelithiasis, and cholecystitis are considered rare events.

DISCUSSION

To the best of our knowledge, this is the first study documenting the misuse and abuse potential of semaglutide in comparison with both remaining GLP-1 analogues (dulaglutide, liraglutide, exenatide, lixisenatide, tirzepatide, and albiglutide) and the phentermine–topiramate combination.

Consistent with this, in the years previous to the timeframe considered here (i.e., 2018–2022), prescriptions for all the molecules selected increased, and this was especially true for those relating to liraglutide, dulaglutide, and Semaglutide.

As expected, for both semaglutide and the other GLP-1 analogues, most reported AERs involved gastrointestinal adverse events [40]. Conversely, the phentermine–topiramate AERs most typically involve dizziness, headache, blurred vision, hypoesthesia, and paresthesia, which have all been reported for topiramate. In relation to the AERs registered for the phentermine/topiramate combination, it is interesting that no significant data on misuse/abuse are reported, despite clinicians' concerns regarding the use of single phentermine. Given both the low risk of semaglutide severe adverse events (e.g., mostly mild-to-moderate and transient), and its beneficial metabolic and cardiovascular actions, the molecule is considered to possess an overall favorable risk/benefit profile for patients with T2DM. It may be a reason of concern, however, that an off-label prescription issue for semaglutide, but not for the remaining GLP-1 analogues, was identified here. This may happen when a drug is being used for an unapproved indication/population or at an unapproved dosage. Off-label use of a medication is at times associated with its misuse potential. In line with this, and in contrast with remaining GLP-1-RA analogues, semaglutide appeared here to be associated with significantly higher levels of (i) abuse, (ii) intentional product use issues, and (iii) use without a prescription. To the best of our knowledge, this finding has never been reported before in the medical literature and is fully consistent with the vast range of anecdotal, unconfirmed magazine and newspaper reports.

Semaglutide and GLP-1 RAs as Molecules Acting on the Reward System?

One could wonder if there is a neurobiological issue putatively associated with the decreased appetite and improved levels of satiety, and hence with the significant weight loss, associated with GLP-1 RA in general and semaglutide in particular. In the central nervous system (CNS), GLP-1Rs are expressed in several brain regions involved in the regulation of metabolism and energy balance. The reward-related brain regions that regulate appetitive and consumption behaviours include the mesolimbic regions' nucleus accumbens (NAc), ventral tegmental area (VTA), and amygdala, with GLP-1Rs being located in the mesolimbic system.

Furthermore, the gut-brain axis peptide ghrelin enhances dopamine release in the VTA. Hence, one

could wonder if the withdrawal symptoms associated here with semaglutide may be conceivably related to its effect on the reward system; this is consistent with a range of anecdotal Redditors' observations highlighting both rebound and craving phenomena after withdrawing from semaglutide. In line with this, a recent randomized controlled trial showed that 1 year after having withdrawn from a weekly treatment of 2.4 mg of semaglutide, participants regained two-thirds of their weight loss. Indeed, GLP-1 analogues may reduce the rewarding effects of palatable food intake and the food-related brain responses in both T2DM and obese subjects in the insula, amygdala, putamen, and orbitofrontal cortex. Consistent with these observations, GLP-1 RA can reduce cue and drug-induced fentanyl seeking; physical and behavioural effects of morphine withdrawal; cue-, stress-, and drug-induced heroin seeking; and use of cocaine, amphetamine, alcohol, and nicotine in animals when administered over several days or weeks. In one randomized controlled trial, exenatide, administered weekly in combination with nicotine replacement therapy, improved smoking abstinence, reduced craving and withdrawal symptoms, and decreased weight gain among abstainers.

Another study demonstrated that weekly exenatide significantly reduced heavy drinking days and total alcohol intake in a subgroup of obese patients. Therefore, GLP-1 RA is gaining increasing attention as a new therapeutic agent for the treatment of reward-system-related disorders.

The Potential Use of GLP-1 RA in Neurology

Preclinical studies suggest that exenatide can normalize dopaminergic function, showing its potential protective action against cytokine-

mediating apoptosis and its substantial therapeutic utility in diseases where neuroinflammation may play a significant role, such as Parkinson's disease (PD) [70], Alzheimer's disease (AD), diabetes, and strokes. Consistently, exenatide administered weekly had positive effects on practically defined off-medication motor scores in PD, and this outcome was sustained beyond the period of exposure. Interestingly, the GLP-1 RA exenatide, in its extended-release formulation, has been successfully employed to alleviate the motor symptoms of PD patients [73], a condition characterized by a deficit in dopaminergic neurotransmission, a critical axis of the reward system. Notably, in preclinical models of brain ageing and neurodegeneration, the same compound has been shown to positively affect the signalling of the brain-derived neurotrophic factor (BDNF) and modulate synaptic plasticity thereby introducing the possibility of long-lasting behavioural effects driven by the long-term structural brain and neural modifications.

LIMITATIONS

Despite the interest of the current findings, they may need to be interpreted with caution. First, although disproportionality analysis is a suitable tool for quantifying signs of drug abuse/misuse, it has a limited ability to differentiate the type or reason for abuse (e.g., recreational and self-medication). Furthermore, confounding factors such as comorbidities, dosages/routes of administration, and concomitant drugs consumed cannot be adequately assessed with a pharmacovigilance approach.

CONCLUSIONS

The current findings, which indicate a possible semaglutide misuse/abuse issue, will need to be confirmed by further empirical investigations.

Efficacy and safety of subcutaneous semaglutide in adults with overweight or obese: a subgroup meta-analysis of randomized controlled trials

Rui Zhang et al. 2023.Front. Endocrinol..doi: 10.3389/fendo.2023.1132004



ABSTRACT

Semaglutide shows significant performance on weight reduction in several clinical trials. However, it is not clear what kind of administration frequency or

dosage will achieve better effects. This study aims to explore the different therapeutic effect of semaglutide on weight control under the diverse administration circumstances



INTRODUCTION

Maintaining long-term weight control is challenging due to the metabolism variation and non-adherence to lifestyle modification. Traditional diet restriction and exercise interventions for weight reduction are sometimes difficult to adhere to, and likely to rebound. Therefore, it becomes increasingly urgent to seek a more safe, effective, and long-term way of weight control. Currently, many guidelines and recommendations encourage the use of anti-obese medications to achieve this goal.

Several anti-obesity drugs, such as orlistat, naltrexone-bupropion, phentermine-topiramate and

liraglutide, have provided sufficient evidence on weight loss for adults. A comprehensive network meta-analysis of pharmacotherapy compared with lifestyle modification only demonstrated phentermine-topiramate and GLP-1 RAs achieved the best effects (14). GLP-1 is an incretin hormone secreted mainly by intestinal L cells, which can increase the insulin release and inhibit the glucagon release in a manner of glucose-dependent way. The mechanisms are mainly focused on appetite restriction and food intake reduction by turning up the satiation signals and turning down the hunger signals in the arcuate nucleus of the hypothalamus.

Semaglutide, a novel, long-acting GLP-1 RAs, shows significant performance on weight reduction in several clinical trials. Besides the good performance on weight loss and hypoglycemic effect, it also demonstrates cardio-protective potential, greatly broadening its applications on type 2 diabetes treatment only. Compared with exenatide, dulaglutide and liraglutide, semaglutide shows a superior capability of weight-lowering with a similar low risk of adverse events. Therefore, FDA has officially approved it for use for adults with overweight or obese in June 2021. In view of the good performance on weight management and maintenance, many trials with different administration ways (oral or subcutaneous, high or low dosages, long or short treatment durations) have been implemented across North America, Europe and Asia. Up to now, it is known that the effect of subcutaneous injection of semaglutide is far better than that of oral medication. However, there is no clear conclusion on the therapeutic effect of semaglutide under the diverse application circumstances (dosages, administration frequencies, trial durations, etc.).

DISCUSSION

Several subcutaneous semaglutide randomized controlled trials have shown a great reduction in weight loss, blood glucose and blood pressure, as well as a low rate of adverse events, under different medication treatments. However, which treatment scheme is to be superior, safer, and more durable, especially under diverse and complex personal situations, rare research is reported.

There were four main findings in our analysis as follows. Firstly, subcutaneous semaglutide showed significant weight loss and cardiometabolic benefits, as well as improvements in the quality of life in adults with overweight or obese. Secondly, subcutaneous semaglutide was relatively safe with the consideration of overall adverse events. Thirdly, consistent with the occurrence of side effects in the GLP-1 RAs, gastrointestinal disorders and

hypoglycemia were the most common adverse events. Finally, the efficacy and safety of subcutaneous semaglutide varied depending on treatment dosage, administration frequency, trial duration, baseline obesity level and whether accompanied by lifestyle intervention

Lifestyle interventions were the foundation of all obesity treatments according to most of the recommendations and guidelines. Although those participants without lifestyle intervention achieved more on the weight loss goal of 5%, they had a higher incidence of hypoglycemia actually, compared with those with lifestyle modification. In terms of cardiovascular benefit, greater improvement in TG was seen in the group along with lifestyle intervention. So, we believe that diet and exercise modification can be helpful for the stabilization of blood glucose and serum lipids, especially accompanied by anti-obesity drug usage. Maintaining a healthy lifestyle was not only beneficial for weight management but also good for reducing hypoglycemia, and optimizing lipid metabolism when applied with obesity treatment simultaneously. Therefore, we recommend lifestyle interventions in parallel with semaglutide administration.

Our review provided a systematic assessment of the efficacy and safety of subcutaneous semaglutide in the treatment of adults with overweight or obesity, especially comparing the effects under various situations, like different baseline BMI, administration dosages, delivery frequencies, trial duration, with or without lifestyle interventions, hoping to give useful information to clinical practice on pharmacological purpose. The results showed that subcutaneous semaglutide treatment had a great beneficial effect on body weight control, with additional improvements in cardiovascular and metabolic profiles. Based on subgroup analysis, we recommend semaglutide to be coupled with lifestyle interventions and be administered subcutaneously with a target dosage of 2.0 mg or more, once weekly.

Effectiveness of Oral versus Injectable Semaglutide in Adults with Type 2 Diabetes: Results from a Retrospective Observational Study in Croatia

Sanja Klobučar et al. 2024. *Diabetology* 2024, 5, 60–68. <https://doi.org/10.3390/diabetology5010005>

The number of people with type 2 diabetes is increasing daily, and therefore, effective therapy is needed to successfully regulate glycemia and reduce the risk of associated complications. Recently, an oral formulation of the glucagon-like peptide-1 receptor agonist (GLP-1 RA) semaglutide has become available.

INTRODUCTION

According to the International Diabetes Federation, it is estimated that 537 million people worldwide have diabetes, and the vast majority of cases are type 2 diabetes (T2D). In addition, there are around 541 million people who have impaired glucose tolerance. It is predicted that by 2045, the number of diabetes cases will reach 783 million. By all accounts, diabetes is certainly one of the fastest-growing global health issues of the 21st century.

According to a recent systematic review, the leading cause of mortality and comorbidity in people with diabetes is cardiovascular disease (CVD), which accounts for 50.3% of all deaths. It is assessed that in the U.S., around USD 37.3 billion per year is spent on treating cardiovascular-related complications associated with diabetes. A great number of people with type 2 diabetes have cardiometabolic risk factors that can be modified, such as diet, smoking, sedentary lifestyle, dyslipidemia, hypertension, and obesity.

Over the past decade, a number of clinical trials have been published with results showing that modern therapies, including glucagon-like peptide-1 receptor agonists (GLP-1 RA) and SGLT-2 inhibitors, achieve significant and consistent cardiometabolic benefits. GLP-1 RAs have been shown to be an effective treatment for patients with type 2 diabetes. Remarkable clinical benefits of GLP-1 RAs have been demonstrated, not only in maintaining glycemic control and protecting against hypoglycemia, but also in significant weight loss, lowering blood pressure, and improving lipid profiles. Moreover, their use has been associated

with a reduced risk of major cardiovascular events (MACE), cardiovascular death, nonfatal myocardial infarction, and nonfatal ischemic stroke in patients with T2D.

Semaglutide is the only GLP-1 RA available in both injectable and oral formulations. Impaired absorption of orally administered peptides has been overcome by co-formulation with the absorption enhancer sodium N-(8-[2-hydroxybenzoyl]amino)caprylate (SNAC) which protects semaglutide through local buffering and leads to facilitated absorption across the gastric epithelium. The first oral formulation of GLP-1 RA semaglutide (Rybelsus) was approved by the U.S. Food and Drug Administration (FDA) in September 2019 and by the European Medicines Agency (EMA) in April 2020. Due to the lower bioavailability of oral semaglutide compared to the subcutaneous formulation, a higher dose of 7 mg to 14 mg/day versus 1 mg to 2 mg/week of the subcutaneous formulation is required.

DISCUSSION

Our study is the first direct comparison between the two semaglutide formulations in a real-world setting as add-on therapy to ongoing antihyperglycemic treatment in patients with inadequately controlled type 2 diabetes who had not previously received GLP-1 RA. Both formulations of semaglutide have been shown to be nearly equally effective in achieving HbA1c reduction (IS −1.1% vs. OS −1.4%) and weight loss (IS −6.5 kg vs. OS −5.9 kg).

Across the SUSTAIN program, once-weekly subcutaneous semaglutide 1.0 mg reduced HbA1c by 1.5–1.8% after 30–56 weeks, while once-daily oral semaglutide 14 mg reduced HbA1c by 1.0–1.4% across the PIONEER program. In addition, subcutaneous semaglutide reduced body weight by 4.5 kg to 6.5 kg, significantly more than all active comparators tested, while oral semaglutide reduced

body weight more than sitagliptin and liraglutide and to a similar extent as empagliflozin, namely between 2.6 kg and 4.4 kg. In a clinical trial conducted by Gibbons et al., people with a BMI of 20–38 kg/m² had less food cravings, had greater control over their diet, and consumed less food at each meal of the day with oral formulation of semaglutide versus the placebo. Overall, after 12 weeks of treatment, the mean body weight decreased by 2.7 kg with oral semaglutide and 0.1 kg with placebo, mostly attributable to body fat mass loss.

Our results suggest that the antihyperglycemic potential of oral semaglutide in a real-world setting is consistent with that demonstrated in randomized clinical trials. However, the potential for weight reduction was more pronounced than in the PIONEER program. On the other hand, the HbA_{1c} reduction achieved with the injectable form was slightly weaker than expected, but with body weight loss consistent with that in the SUSTAIN program. Moreover, the safety profile of the two formulations was similar. As commonly observed with GLP-1 Ras, the most common adverse side effect was nausea, which was generally mild to moderate and transient. Excessive belching was reported by 14% of patients taking oral semaglutide and by none of the patients taking the injectable form.

Many patients are reluctant to initiate treatment with injectable medications due to fear of pain during injection and a sense of failure related to disease progression. A possible disadvantage of taking semaglutide orally is that the tablet must be taken on an empty stomach 30 min before a meal, drink, or taking other medications to ensure unimpeded absorption [17]. On the other hand, for injectable semaglutide, it does not matter whether

food or liquid has been consumed before or after the injection. Therefore, selection of the most appropriate formulation needs to be made on an individual basis to best suit the patient's preferences and needs.

Our study suggests that semaglutide offers the benefits of a highly effective GLP-1 RA in both injectable and oral formulations. However, since this is a single-center retrospective observational study, the findings should be interpreted accordingly. It was conducted on a relatively small sample of respondents. Furthermore, due to the study design, the researchers had no control over exposures and interventions or absolute medication adherence. Likewise, there is the possibility of various confounding effects, such as background therapy and comorbidities. Nonetheless, our results have shown that orally administered semaglutide may be as effective an option for improving glycemic target attainment and supporting weight loss in adults with T2D as the injectable formulation, particularly in patients who are reluctant to take injectable medications.

CONCLUSIONS

In a real-world setting, oral semaglutide as an add-on therapy to ongoing antihyperglycemic treatment in patients with inadequately controlled type 2 diabetes who had not previously received GLP-1 RA demonstrated the same effectiveness as injectable semaglutide in terms of glycemic control and weight loss after 6 months of treatment. Considering the almost equal effect, the oral formulation of semaglutide could make it easier for patients to use since there is no injection burden.

A Real-World Study of the Effectiveness and Safety of Semaglutide for Weight Loss

P. Tzoulis et al. 2024 Cureus 16(5): e59558. DOI 10.7759/cureus.59558

INTRODUCTION

Obesity is nowadays recognized as a multifactorial, chronic, relapsing, progressive disease. It is

characterized by the presence of excessive adipose tissue, most commonly defined as a body mass index (BMI) greater than or equal to 30 kg/m², calculated as weight in kilograms divided by height in meters squared (kg/m²). Obesity is associated with an

increased risk for several diseases, such as type 2 diabetes mellitus (DM), dyslipidemia, hypertension, cardiovascular disease, several types of cancer, hepatobiliary disease, obstructive sleep apnea, osteoarthritis, and excess mortality. Over the last three decades, there has been an exponential increase in rates of obesity, which has become a global epidemic and a major public health problem.

People with obesity should receive personalized care from a multidisciplinary team, including a combination of medical nutrition therapy and physical activity, supplemented by psychological and behavioural interventions. In most cases, lifestyle interventions have limited efficacy and durability with the long-term maintenance of weight loss remaining a big challenge. Despite this unmet clinical need, anti-obesity medications (AOMs) have been underutilized in routine clinical practice, with less than 1.5% of those eligible for pharmacotherapy having received AOMs.

In 2021, semaglutide was approved by both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for chronic weight management in patients with either a BMI greater than 30 kg/m² or a BMI greater than 27 kg/m² and at least one weight-related condition. This indication followed its initial approval for the treatment of type 2 diabetes mellitus (DM) in 2017. Semaglutide, a weekly injectable GLP-1 agonist, reduces appetite and increases satiety through the activation of GLP-1 receptors in the hypothalamus and the hindbrain, leading to reduced energy intake. A global program of phase 3 clinical trials evaluating the effect of semaglutide use for weight management in people with obesity, the Semaglutide Treatment Effect in People with Obesity (STEP) trials, has reported an average placebo-subtracted weight loss percentage of 12.5%, with more than half of the participants achieving 15% or more weight loss. Therefore, semaglutide has become the first AOM that results in a greater than 10% average weight loss over that attributable to lifestyle interventions, generating widespread public interest and leading to global supply shortages. Besides semaglutide, numerous studies are currently exploring the potential synergistic effect of targeting multiple gut peptides.

In addition, oral formulations of GLP-1 agonists, such as once-daily oral semaglutide and orforglipron, have led to similar weight loss to that of injectable

semaglutide. These promising results suggest that a variety of novel pharmacotherapies will become available in the next few years, revolutionizing the treatment of obesity.

A series of randomized controlled trials (RCTs) have consistently demonstrated the great efficacy of semaglutide for weight management. Despite the wealth of high-quality evidence, there is a paucity of real-life data limited to one cohort study. The aim of this real-world retrospective study was to evaluate the effectiveness and adverse events of semaglutide therapy for weight management in individuals with obesity in day-to-day clinical practice.

ADVERSE EVENTS

Out of 40 participants, 26 individuals (65%) reported adverse events, including 55% experiencing gastrointestinal side effects, with the most frequent being nausea, constipation, abdominal pain, diarrhea, and dyspeptic symptoms, as illustrated in Table 2. In most cases, gastrointestinal events were mild to moderate and had a short duration of less than four weeks. Severe adverse events were noted only in three patients (7.5%), with vomiting resolved in two cases within four weeks. The semaglutide discontinuation rate due to adverse events was 2.5%, with only one patient discontinuing semaglutide after seven weeks due to persistent vomiting and acute abdominal pain. The patient fully recovered, while acute pancreatitis and gallbladder-related diseases were excluded. In total, no cases of cholelithiasis, cholecystitis, or acute pancreatitis were reported.

DISCUSSION

This real-world retrospective study of semaglutide therapy for weight loss in adults without DM demonstrated a significant median six-month weight loss of 13.3% (14.9 kg), with 68% (17 out of 25 individuals) achieving at least 10% weight loss, in combination with a favourable safety profile. In almost two-thirds of the participants, substantial weight loss was produced despite being treated with 1 mg weekly, lower than the maintenance-licensed semaglutide dose of 2.4 mg weekly.

This study reported semaglutide-related percentage weight loss of 6.6% (7.4 kg) and 13.3% (14.9 kg) in three

and six months, in line with the mean 6.3% and 11.8% in three and six months, respectively, observed in a similar real-world cohort study in the United States. These weight loss outcomes are comparable with a three-month percentage weight loss of 6%-6.5% and a six-month of 10.6%-12% reported in STEP 1 and STEP 4 trials [7,8], suggesting that semaglutide achieves a similar effect in routine clinical practice with that observed in RCTs. Therefore, an efficacy-effectiveness gap does not exist with respect to semaglutide in weight management, supporting the generalizability of RCT findings.

This real-world study showed an early improvement in glycemic markers, confirming the glucose-lowering effect reported in STEP studies. In addition, semaglutide improves numerous cardiovascular risk factors, including the reduction of blood pressure, total and LDL cholesterol, and triglycerides and a significant decrease in C-reactive protein (CRP) concentration. In November 2023, the long-awaited results of the Semaglutide Effects on Heart Disease and Stroke in Patients with Overweight or Obesity (SELECT) trial were published, showing that semaglutide results in the 20% reduction of a composite cardiovascular endpoint, including death from cardiovascular causes, non-fatal myocardial infarction, and non-fatal stroke, in patients who are overweight or obese and with preexisting cardiovascular disease but without DM. It remains unclear to what extent weight loss, the improvement of metabolic risk factors, and possible pleiotropic anti-atherosclerotic effects contribute to the semaglutide-related reduction of cardiovascular risk.

In this real-life study, the rate of gastrointestinal side effects was 55%, mostly mild to moderate with only 7.5% of individuals experiencing serious adverse events, compared to a 74%-84% rate for gastrointestinal side effects and 7.9%-9.8% for serious side effects in STEP trials. The discontinuation rate in this study was low at 2.5%, similar to the 2.9% reported in another real-world study and lower than 5.9%-7.7% in STEP trials, but this difference might be explained by the longer follow-up period in RCTs. No cases of pancreatitis or gallbladder-related disease were recorded in this cohort in line with another real-world study, while STEP trials reported an increased likelihood for cholelithiasis at a rate of 0.8%-3.5%.

Due to its substantial and durable weight loss effect, semaglutide may herald a new era in the management of obesity, using percentage weight loss as a biomarker and applying a treat-to-target approach, in line with other chronic diseases, to prevent and treat weight-related complications. Additionally, recent high-quality evidence about the cardiovascular benefit of semaglutide, indicating for the first time that the long-term use of an AOM reduces the rate of cardiovascular events, may lead to a paradigm shift, characterized by the widespread chronic administration of AOMs in individuals with obesity based not only on durable weight loss but also on cardiovascular benefit. In the future, the availability of numerous potent AOMs could usher in an era of precision medicine with the application of personalized treatment strategies, based on predictive models, encompassing age, gender, different obesity phenotypes, coexisting complications, genotype, and predictors of response to each treatment modality.

Further research is needed to address several aspects of chronic semaglutide use for weight management, such as the durability of semaglutide-induced weight loss beyond two years, the optimal duration of treatment, and strategies to prevent or, at least, ameliorate weight regain occurring after semaglutide discontinuation.

Marked variability in the therapeutic result of semaglutide highlights the need to identify the predictors of response and assess the efficacy of lower semaglutide doses, facilitating personalized decision-making. Future research efforts should not only evaluate the potential synergistic effect of combining semaglutide with other AOMs and different lifestyle interventions but also explore its use as neoadjuvant or adjuvant therapy along with bariatric surgery. In addition, a new generation of studies should recognize distinct obesity phenotypes and evaluate the use of semaglutide for weight management in patient subgroups with different main comorbidities with primary endpoints other than weight, for example, the progression of liver steatohepatitis or the regression of liver fibrosis. In view of the potential widespread use of semaglutide, cost-effectiveness studies are of paramount importance, as well as head-to-head studies with other AOMs. Despite the favourable risk profile of semaglutide in STEP trials, postmarketing surveillance with the employment of prospective databases should assess whether semaglutide is

associated with an increased risk for gastroparesis and gastrointestinal ileus, as suggested by a recent study [30], or alters the risk for rare complications with a long latency period, such as the incidence of malignancies. Finally, concerns about the possible association of semaglutide-induced weight loss with sarcopenia and the loss of bone density should be addressed, and if needed, strategies should be developed to ameliorate these unwanted effects.

CONCLUSIONS

This study showed the great effectiveness of semaglutide in a real-life setting, leading to a median three-month and six-month weight loss of 6.6% (7.4 kg) and 13.3% (14.9 kg), respectively, with 68% (17 out of 25 individuals) attaining 10% weight loss over six months. Therefore, the advent of semaglutide could represent a paradigm shift in obesity care, encompassing the widespread long-term use of pharmacotherapy across lifestyle interventions and employing a personalized treat-to-target approach, similar to the contemporary management of type 2 DM, in order to prevent and treat weight-related complications.

What Are the Bad Side Effects of Ozempic?



Semaglutide

Sharath Kommu; Philip Whitfield. 2024. National Library of Medicine.NBK603723 | PMID: 38753931
| <https://www.ncbi.nlm.nih.gov/books/NBK603723/>

ADVERSE EFFECTS

Adverse Drug Reactions

Adverse drug reactions caused by semaglutide are listed below.

Hypoglycemia: GLP-1 agonists lower blood glucose and may cause hypoglycemia. The risk of

hypoglycemia significantly increases with escalating doses and when semaglutide is administered with other anti-hyperglycemic medications such as sulfonylureas, metformin, or insulin.

Gastrointestinal: The adverse effects most frequently reported and most associated with discontinuation of semaglutide include nausea, vomiting, abdominal pain, constipation, and diarrhea. Nearly one-fifth of all patients in clinical trials with Ozempic® and Rybelsus® experienced nausea, which is the most prevalent adverse effect, whereas 44% of patients treated with Wegovy® reported the same adverse effects. In addition, decreased appetite, dysgeusia, and dyspepsia have been documented. Although the precise mechanism behind these effects is not entirely elucidated, it may stem from delayed gastric emptying or the activation of brain centres implicated in appetite regulation, satiety, and nausea. Higher doses and dose escalations are associated with the risk of these adverse effects.

Renal: Semaglutide can result in acute kidney injury. Patients who experienced nausea, vomiting, diarrhoea, or dehydration during the treatment were at the highest risk of acute kidney injury, with volume depletion being the suspected link. Discontinuation or dose reduction of semaglutide is recommended rather than relying solely on symptomatic treatment of volume depletion.

Gallbladder disorders: Semaglutide has been associated with gallbladder and biliary tract issues, including cholelithiasis and cholecystitis. The exact mechanism behind this adverse effect is not entirely understood. Animal studies and in vitro data suggest that GLP-1 enhances cholangiocyte proliferation and functional activity, which could contribute to gallbladder diseases. Some authors have proposed that semaglutide can potentially suppress cholecystokinin secretion, reduce gallbladder emptying, and prolong gallbladder refilling, or a combination of these factors contributing to gallbladder disease.

Anaphylaxis and angioedema: GLP-1 receptor agonists (GLP-1 RAs) can induce severe type 1 hypersensitivity reactions, such as anaphylaxis and angioedema. A possibility of cross-reactivity among different GLP-1 receptor agonists exists. Therefore, caution is advised when prescribing semaglutide to patients with a history of anaphylaxis or angioedema

in response to other GLP-1 receptor agonists, pending further studies.

Pancreatitis: Although cases of acute pancreatitis have been associated with semaglutide use, findings from the SUSTAIN 6 trial indicate a similar incidence rate of pancreatitis with semaglutide compared to the placebo group. The causal relationship between semaglutide and acute pancreatitis has not been definitively established. GLP-1 receptor agonists directly stimulate GLP-1 receptors in pancreatic islet beta cells and exocrine duct cells. Researchers suggest that this stimulation may lead to the overgrowth of cells covering smaller ducts, causing hyperplasia, increased pancreatic weight, duct occlusion, back pressure, and subsequent acute or chronic inflammation.

Diabetic retinopathy: Semaglutide use may potentially elevate the risk of diabetic retinopathy, particularly in patients with retinopathy at baseline. The exact relationship between semaglutide and the development or exacerbation of diabetic retinopathy remains incompletely understood. However, it may be associated with rapid improvements in glucose control, as identified in other studies.

Risk of thyroid C-cell tumours: During the initial phases of drug development, animal studies involving semaglutide revealed the development of thyroid C-cell tumours. However, the potential association between semaglutide and thyroid cancers in humans remains unclear. Individuals with a personal or family history of medullary thyroid carcinoma (MTC) or those diagnosed with multiple endocrine neoplasia type 2 (MEN 2) syndrome may face an elevated risk. The manufacturer acknowledges reported cases of MTC associated with liraglutide, which is another GLP-1 receptor agonist.

Additional adverse reactions: Other reported adverse reactions associated with semaglutide include fatigue, headache, rash, alopecia, vitreous haemorrhage in patients with diabetic retinopathy, anxiety, dizziness, discomfort at the injection site, and erythema at the injection site.

DRUG-DRUG INTERACTIONS

- Semaglutide causes a delay in gastric emptying, which may lead to delayed absorption of concurrently administered oral medications. However, clinical

pharmacology trials with subcutaneously administered semaglutide have demonstrated no significant impact on the absorption of orally administered medications. Nonetheless, cautious monitoring of the effects of oral medications is recommended when used concurrently with semaglutide, especially those with a narrow therapeutic window.

- When semaglutide is used alongside other blood-glucose-lowering agents, there is a notable risk of hypoglycemia.
- Semaglutide should not be used with other GLP-1 receptor agonists or tirzepatide, as they are contraindicated.
- When semaglutide is administered alongside insulins or insulin secretagogues, such as sulfonylureas, it is recommended to consider reducing the dosage of these medications to mitigate the risk of hypoglycemia.
- Medications that have the potential to augment the hypoglycemic effects of semaglutide include beta-blockers, monoamine oxidase inhibitors, androgens, quinolones, salicylates, selective serotonin reuptake inhibitors, and other antidiabetic medications.
- Medications that may diminish the therapeutic effects of semaglutide include furosemide, thiazide diuretics, and ritodrine.
- Semaglutide may increase the serum concentrations of levothyroxine.

CONTRAINDICATIONS

Box warning

Semaglutide has been shown to induce dose-dependent and treatment-duration-dependent thyroid C-cell tumours in rodents. However, it remains uncertain whether semaglutide poses a similar risk of cancer in humans. This aspect may become more apparent as more data on this

medication becomes available over the next few years. Given this potential risk, semaglutide is contraindicated in patients with a personal or family history of MTC or MEN 2 syndrome. Patients prescribed semaglutide should receive counselling regarding the potential risk of thyroid cancers.

Precautions

- Suicidal behaviour has been reported with other medications prescribed for weight management. Therefore, it is advisable to avoid the use of Semaglutide in individuals with a history of suicidal attempts or current suicidal ideation. Patients with suicidal ideations should seek immediate assistance.
- Semaglutide can potentially slow gastric emptying and impede the absorption of other medications.
- The multiple-dose injection pen (Ozempic®) should not be shared among individuals to mitigate the risk of infection transmitting infections.
- Semaglutide is contraindicated in patients with type 1 diabetes.
- As the effectiveness of semaglutide in combination with other weight loss medications is not established, concurrent use of this drug with other weight loss medications should be avoided.
- Patients with a history of bariatric surgery face an increased risk of gastrointestinal complications when using semaglutide. Therefore, regular monitoring for such complications is recommended.
- If the medication is discontinued after attaining weight loss, a risk of rebound weight gain exists. This was demonstrated in an extension of the STEP 1 trial, where participants, after discontinuing weekly subcutaneous semaglutide 2.4 mg and lifestyle interventions for 1 year, experienced a regain of approximately two-thirds of their initial weight loss.[\[52\]](#)

How does Ozempic affect the face?

O. Ewumi. 2023. Medical news today



Semaglutide, the generic name for Ozempic, is part of a class of medications known as incretin mimetics. These ensure the pancreas releases sufficient insulin when the blood glucose level is high. Additionally, Ozempic acts as a long-lasting and effective glucagon-like peptide-1 receptor agonist. This means it makes a person feel fuller and delays gastric emptying so they can consume fewer calories.

While Ozempic is safe to use with a doctor's recommendation, it can cause rapid weight loss that is often more pronounced on the face. Facial fat serves a protective function and affects facial aesthetics and elasticity. Weight loss can cause dermatological changes and shrinking because the fat that stretches and cushions the skin is no longer in place. The skin of the face also loses its ability to retract after an episode of rapid weight loss due to

reduced levels of elastin and collagen, which are essential for structural integrity.

As a result, people taking Ozempic may report the following facial symptoms:

- increased signs of ageing, such as more lines and wrinkles
- loss of fat, which can lead the skin to become loose and sag
- a hollowed-out appearance
- lipodystrophy, which affects how the body accumulates and stores fat

Sources

1. Arillotta D et al. Brain Sci. 2024, 14, 617. <https://doi.org/10.3390/brainsci14060617>
2. Chiappini S. et al. 2023. Pharmaceuticals 2023, 16, 994. <https://doi.org/10.3390/ph16070994>
3. Ewumi O. 2023. Medical news today. <https://www.medicalnewstoday.com/articles/drugs-ozempic-side-effects#talk-with-your-doctor>
4. Garvey W.T. et al. 2022. Nature medicine; /doi.org/10.1038/s41591-022-02026-4
5. Hölscher C.2024.Neuropharmacology, Vol 253 doi.org/10.1016/j.neuropharm.2024.109952
6. Klobučar S. et al. 2024. Diabetology 2024, 5, 60–68. <https://doi.org/10.3390/diabetology5010005>
7. Knudsen B.L and Lau.J. 2019. Front. Endocrinol. 10:155.doi: 10.3389/fendo.2019.00155
8. Kommu S.and Whitfield P. 2024. National Library of Medicine.NBK603723| PMID: 38753931 <https://www.ncbi.nlm.nih.gov/books/NBK603723>
9. Lincoff A.M, M.D. et al. 2023 N Engl J Med 2023;389:2221-32.DOI: 10.1056/NEJMoa2307563
10. Quddos F.et al. Scientific Reports | (2023) 13:20998. doi.org/10.1038/s41598-023-48267-2
11. Ryan D.H. et al. 2024, Nature Medicine; doi.org/10.1038/s41591-024-02996-7
12. Tzoulis P, Batavanis M, Baldeweg S (May 02, 2024) A Real-World Study of the Effectiveness and Safety of Semaglutide for Weight Loss. Cureus16(5): e59558. DOI 10.7759/cureus.59558
13. Wang W. et al. 2024. Alzheimer’s Dement. 2024;1–12. DOI: 10.1002/alz.14313
14. Wang W. et al. 2024. Molecular Psychiatry (2024) 29:2587–2598; doi.org/10.1038/s41380-024-02498-5
15. <https://www.medicalnewstoday.com/articles/ozempic-face#summary>
16. Zhang R. et al. 2023. Front. Endocrinol..doi: 10.3389/fendo.2023.1132004

QUESTIONNAIRE

G1(25) Part 1 of 7

Semaglutide – Hype Validation The Great, the Good but keep the Bad in mind

INSTRUCTIONS

- Read through the article and answer the multiple-choice questions provided below.
- Some questions may have more than one correct answer; in which case you must mark all the correct answers.

Beginnings and Background

The Discovery and Development of Liraglutide and Semaglutide

Introduction

Question 1: Which of the following statements is **NOT TRUE** about glucagon-like peptide-1 (GLP-1)

- A: It is an incretin hormone
- B: It has important effects on glycemic control
- C: It has no effect on body weight regulation
- D: By extending its half-life it was made therapeutically effective in people with type 2 diabetes (T2D)

Question 2: Is it **TRUE** or **FALSE** that significant weight loss, through an effect to reduce energy intake, led to the approval of liraglutide (3.0mg) for the treatment of obesity?

- A: TRUE
- B: FALSE

Question 3: Liraglutide and semaglutide are both long-acting GLP-1 receptor agonists (GLP-1RAs) that have pharmacodynamic (PD) effects for 24 h/day. Which of the following are **TRUE** about semaglutide?

- A: It was developed for once daily (OD) administration
- B: It is available as an OD injection of up to 1.8mg for the treatment of type 2 diabetes (T2D).
- C: It is available as a once weekly (OW) injection of up to 1.0mg for the treatment of T2D
- D: It is additionally approved for the treatment of obesity at a dose of 3.0mg
- E: It is in clinical development as a treatment for obesity (phase 3) and non-alcoholic steatohepatitis (NASH) (phase 2)

Question 4: Which one of the following has a greater effect on fasting blood glucose and weight loss?

- A: Short-acting GLP-1RAs
- B: Long-acting GLP-1RAs

Question 5: Which **ONE** of the following has been shown to provide benefits beyond its protraction and in greater glucose-lowering and weight-loss effects?

- A: Exenatide
- B: Semaglutide
- C: Other GLP-1RAs
- D: Liraglutide

Question 6: Which of the following is most likely the primary physiological effect of GLP-1?

- A: The stimulation of glucose-dependent insulin secretion
- B: The increase in insulin biosynthesis
- C: The improvement of beta-cell function
- D: The reduction of gastric emptying

Question 7: Trials with liraglutide 3.0mg have shown weight loss of between at 56 weeks in subjects with obesity.

- A: 3.6% and 4.7%
- B: 7.9% and 8.2%

Question 8: Oral absorption of semaglutide and sodium N-(8-[2-hydroxybenzoyl] amino) caprylate (SNAC) is primarily which of the following?

- A: Transcellular
- B: Paracellular

Summary

Question 9: Is it **TRUE** that a significant advance in GLP-1-based therapies is represented by the development of the long-acting GLP-1 analogues liraglutide and semaglutide, using albumin binding to extend the half-life?

- A: YES
- B: NO

Question 10: Which **ONE** of the following statements is **NOT TRUE**?

- A:** Both liraglutide and semaglutide, have been shown to reduce cardiovascular (CV) risk in patients with T2D
- B:** Short-acting GLP-1RAs have been found to reduce CV risk in patients with T2D
- C:** CV complications remain a leading cause of morbidity and mortality in people with T2D, despite substantial efforts to reduce risk using CV medications
- D:** The availability of antidiabetes medications that can contribute to risk reduction is a significant advance

THE END

QUESTIONNAIRE

G1(25) Part 2 of 7

Semaglutide – Hype Validation the Great, the Good but keep the Bad in mind

INSTRUCTIONS

- Read through the article and answer the multiple-choice questions provided below.
- Some questions may have more than one correct answer; in which case you must mark all the correct answers.

Research and Beyond

Semaglutide and Obesity

Long-term weight loss effects of semaglutide in obesity without diabetes in the SELECT trial

Introduction

Question 1: The worldwide obesity prevalence, defined by body mass index (BMI) ≥ 30 kg m⁻², has nearly tripled since 1975. Which of the following is **NOT TRUE** about BMI?

- A: Is a good surveillance measure for population changes over time
- B: It shows a strong correlation with body fat amount on a population level
- C: It is proven to accurately indicate the amount or location of body fat at the individual level

Question 2: Excess abnormal body fat, especially visceral adiposity and ectopic fat, is a driver of cardiovascular disease (CVD), and contributes to the global chronic disease burden of which of the following?

- A: Diabetes
- B: Seasonal allergies
- C: Chronic kidney disease
- D: Cancer
- E: Arthritis

Question 3: In patients with type 2 diabetes and high CV risk, semaglutide at doses of and has been shown to significantly lower the risk of CV events?

- A: 1.0 mg
- B: 2.4 mg
- C: 2.0 mg
- D: 0.5 mg

Discussion

Question 4: Which **ONE** of the following is **NOT** a **TRUE** representation of the analyses of weight effects of the SELECT study?

- A: Patients assigned to once-weekly subcutaneous semaglutide 2.4 mg lost significantly more weight than those receiving a placebo
- B: The weight-loss trajectory with semaglutide occurred over 65 weeks and was sustained up to 4 years
- C: Both sexes, all body sizes, those from all geographic regions, but NOT all races were able to achieve weight loss
- D: There is a possibility to impact the public health burden of the multiple morbidities associated with obesity

Question 5: Does the analysis of the SELECT study support the broad use of once-weekly subcutaneous semaglutide 2.4 mg as an aid to CV event reduction in individuals with overweight or obese without diabetes, but with preexisting CVD?

- A: YES
- B: NO

Two-year effects of semaglutide in adults with overweight or obesity: the STEP 5 trial

Introduction

Question 6: Which of the following is often not associated with clinically meaningful and sustainable weight loss?

- A: Behavioural intervention
- B: Pharmacotherapy

Discussion

Question 7: In the STEP 5 trial, at which stage of the intervention of once-weekly treatment with semaglutide 2.4 mg, did participants in the semaglutide group achieve a mean weight loss of 15.2% from baseline?

- A: Week 26
- B: Initially
- C: Week 60
- D: Week 104

Question 8: Which **ONE** of the following statements is **NOT TRUE**?

- A:** Obesity is a chronic, relapsing disease
- B:** It requires continuous effort to control
- C:** Weight regain after initial weight loss is uncommon with all nonsurgical interventions and bariatric surgery
- D:** It is suggested that, on average, there is minimal weight regain over 104 weeks when once-weekly semaglutide therapy is continued

Question 9: The results of which **ONE** of the following trials support the benefit of continued semaglutide treatment for sustained weight loss?

- A:** STEP 4 withdrawal trial
- B:** STEP 5 two-year effect trial
- C:** STEP 1 off-treatment extension study

Question 10: Adverse events leading to discontinuation of the trial product were reported. Gastrointestinal disorders were the most frequently reported and occurred in of participants treated with semaglutide?

.

- A:** 4.6%
- B:** 3.9%
- C:** 82.2%
- D:** 53.9%
- E:** 5.9%

THE END

QUESTIONNAIRE

G1(25) Part 3 of 7

Semaglutide – Hype Validation the Great, the Good but keep the Bad in mind

INSTRUCTIONS

- Read through the article and answer the multiple-choice questions provided below.
- Some questions may have more than one correct answer; in which case you must mark all the correct answers.

Semaglutide and Cardiovascular Outcomes

Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes

Background

Question 1: Which of the following statements is **NOT TRUE**?

- A:** High body mass index (BMI) is estimated to have accounted for 4 million deaths globally in 2015
- B:** More than a quarter of the world population is projected to be overweight or obese by the year 2035
- C:** More than two-thirds of deaths caused by high BMI were because of cardiovascular diseases
- D:** Overweight and obesity are independently associated with an increased risk of cardiovascular events

Discussion

Question 2: Is it **TRUE** that the trial mentioned in this article was conducted to determine whether semaglutide would diminish the excess cardiovascular risk associated with overweight or obesity in patients with no history of diabetes?

- A:** YES
- B:** NO

Question 3: Semaglutide was associated with which of the following?

- A:** A decrease in body weight
- B:** A decrease in waist circumference
- C:** Improved cardiovascular outcomes

Semaglutide and the Brain

Glucagon-like peptide-1 class drugs show clear protective effects in Parkinson's and Alzheimer's disease clinical trials: A revolution in the making?

Abstract

Question 4: Which of the following drugs on the market for diabetes, showed improvement in cognition and brain shrinkage in a phase II trial in patients with Alzheimer's disease (AD)?

- A:** Exendin-4
- B:** Liraglutide
- C:** Lixisenatide

Discussion

Question 5: Which of the following is **NOT** a disparate system involved in the complex pathologies that underlie Parkinson's disease (PD) and Alzheimer's disease (AD)?

- A:** The acute inflammation response
- B:** Loss of energy utilization
- C:** Loss of synaptic activity
- D:** Impaired autophagy and responses to oxidative stress

Question 6: Is it **TRUE** or **FALSE** that a successful treatment for AD needs to involve a multi-pronged approach that simultaneously improves many different physiological systems and underlying disease mechanisms?

- A:** TRUE
- B:** FALSE

Question 7: Which **ONE** of the following is reduced when activating the GLP-1 or glucose-dependent insulinotropic polypeptide (GIP) receptors in the brain?

- A:** Energy utilization in neurons
- B:** Cell repair and gene expression
- C:** Synaptic activity
- D:** The chronic inflammation response in the brain

Question 8: Which of the following is not **TRUE** about GLP-1?

GLP-1:

- A:** Is a negligible growth factor in the brain
- B:** Can compensate for the loss of insulin signalling
- C:** Can re-sensitize insulin signalling in the brain
- D:** Can improve insulin sensitization in diabetes patients
- E:** Can improve insulin sensitization in patients with AD or PD

Conclusion

Question 9: GLP-1 class drugs that are on the market to treat diabetes showed clear neuroprotective effects in the first clinical trials in AD and PD patients. This is a clear proof of which of the following?

- A:** That this strategy is viable
- B:** That extensive drug discovery research is warranted in this area
- C:** Drugs designed to enter the brain may be more effective than the older drugs that have been designed to treat diabetes

Question 10: Which of the following drugs showed improvements in PD patients?

- A:** Exendin-4
- B:** Liraglutide
- C:** Lixisenatide

THE END

QUESTIONNAIRE

G1(25) Part 4 of 7

Semaglutide – Hype Validation The Great, the Good but keep the Bad in mind

INSTRUCTIONS

- Read through the article and answer the multiple-choice questions provided below.
- **Some questions may have more than one correct answer;** in which case you must mark **all** the correct answers.

Question 1: Which of the following are significant modifiable risk factors for AD?

- A: Alcohol use
- B: T2DM
- C: Cardiovascular factors
- D: Obesity
- E: Depression

Discussion

Question 2: In this study of real-world populations with T2DM, a high-risk group for AD, which of the following showed a lower risk of first-time AD diagnosis or AD-related medication prescriptions?

- A: Insulin
- B: Other non-insulin/non-GLP-1Ras
- C: Semaglutide
- D: Other GLP-1RAs.

Question 3: Clinical studies show semaglutide can do the following. Which **ONE** is **TRUE** of the effect of **other** GLP-1Ras?

- A: Reduce A β -mediated neurotoxicity
- B: Enhance autophagy
- C: Improve brain glucose uptake
- D: Reduce A β plaques and tau tangles
- E: Reduce cognitive impairment in patients with type 2 diabetes mellitus (T2DM)

Question 4: This study showed a reduction associated with semaglutide compared to other GLP-1Ras.

- A: 53%
- B: 40%
- C: 70%

Question 5: Is it **TRUE** that GLP receptors in various organs, can influence multiple intracellular responses that could directly affect AD development or progression in the brain.

- A: YES
- B: NO

Question 6: Sodium-glucose cotransporter 2 inhibitors(SGLT-2) crosses the blood-brain barrier and has neuroprotective effects by increasing which of the following?

- A: Neuroinflammation
- B: Oxidative stress
- C: Mitochondrial dysfunction
- D: Brain-derived neurotrophic factors

Question 7: This and prior research suggests may offer neuroprotective effects via pathways like neuroinflammation and mitochondrial function beyond insulin resistance improvement.

- A: Semaglutide
- B: SGLT2i
- C: Dipeptidyl Peptidase IV (DPP IV) Inhibitors

Question 8: Findings from this study support the idea that semaglutide could help delay or prevent the onset of AD by mitigating modifiable risk factors. Semaglutide was shown to improve cardiovascular health in patients with which of the following significant modifiable risk factors?

- A: Smoking
- B: Obesity
- C: Alcohol drinking
- D: Depression
- E: T2DM

Question 9: Is it **TRUE** that in an analysis by obesity status conducted among T2DM patients prescribed with Semaglutide, a consistent decrease in first-time AD diagnosis regardless of obesity status was found?

- A: TRUE
- B: FALSE

Question 10: Which of the following should **NOT** be done in future research?

- A:** Explore the effect of semaglutide in mild cognitive impairment, other dementias, and neurodegenerative diseases
- B:** Investigate other GLP-1RAs like tirzepatide and combination therapies with other antidiabetic medications
- C:** Include studies to shed light on the mechanisms of the potential benefits of semaglutide in preventing or delaying the onset of AD
- D:** Ignore causal effects of AD through randomized trials

THE END

QUESTIONNAIRE

G1(25) Part 5 of 7

Semaglutide – Hype Validation the Great, the Good but keep the Bad in mind

INSTRUCTIONS

- Read through the article and answer the multiple-choice questions provided below.
- Some questions may have more than one correct answer; in which case you must mark all the correct answers.

Association of semaglutide with reduced incidence and relapse of cannabis use disorder in real-world populations: a retrospective cohort study

Introduction

Question 1: In the United States between 2008 and 2019, there was an increase of in the number of adults with cannabis use disorder (CUD)?

- A: 22.6 to 45.0 million
- B: 3.4 to 4.1 million
- C: 3.6 to 9.8 million

Question 2: Is it **TRUE** or **FALSE** that nearly a quarter of cannabis users who meet the DSM-5 (the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition) criteria for CUD have a severe disorder that interferes with their everyday lives?

- A: TRUE
- B: FALSE

Question 3: Which **ONE** of the following is **NOT TRUE** about managing the treatment of CUD?

- A: Tapering marijuana use
- B: Providing support to combat withdrawal symptoms alongside behavioural interventions
- C: Focusing exclusively on behavioural therapies
- D: To urgently develop medications that can help treat CUD

Discussion

Question 4: Although the majority of cannabis users do not proceed to develop CUD, there is a risk of approximately for young users to develop CUD?

- A: 10%
- B: 20%
- C: 30%
- D: 40%

Question 5: Is it **TRUE** that the results in this study show that semaglutide was associated with a lower risk for both incident and relapse of CUD compared to non-GLP-1 RA anti-obesity and anti-diabetes medications?

- A: YES
- B: NO

Exploring the Potential Impact of GLP-1 Receptor Agonists on Substance Use, Compulsive Behaviour, and Libido: Insights from Social Media Using a Mixed-Methods Approach

Introduction

Question 6: Which **ONE** of the following is **NOT TRUE** about Glucagon-like peptide-1 (GLP-1)?

- A: It is a multifaceted incretin hormone
- B: It plays a minor role in glucose homeostasis and metabolic regulation
- C: Its primary function is to stimulate insulin secretion in a glucose-dependent manner
- D: It helps to reduce blood glucose levels

Question 7: Is GLP-1 involved in various independent central and peripheral pathways related to appetite regulation?

- A: YES
- B: NO

Question 8: Which of the following is **NOT** a result of the impact of the release of dopamine in the nucleus accumbens by GLP-1 RAs at the central nervous system level?

- A: Modulating the rewarding effects of substance abuse
- B: Influencing drug-seeking behaviour
- C: Increasing responsiveness to drug cues
- D: Probably alleviating the withdrawal symptoms' experience

Discussion

Question 9: Which of the following are classified as recreational drugs?

- A: Alcohol
- B: Cannabinoids
- C: Nicotine
- D: Psychostimulants
- E: Caffeine

Question 10: The beneficial effect of GLP-1 RAs on which of the following could be hypothesized as being significant factors contributing to reduced drug consumption levels?

- A: Lifestyle changes
- B: Psychopathological aspects
- C: The significant weight loss-related improvement in one's appearance

Question 11: Recent findings showed preliminary evidence of the potential benefit of semaglutide in CUD in distinct populations with which of the following?

- A: Obesity
- B: Type 1 diabetes
- C: Type 2 diabetes

Question 12: Is it **TRUE** that current clinical evidence shows promising results in both female and male fertility levels, due to weight loss and/or direct actions on the reproductive system?

- A: YES
- B: NO

Question 13: Particular attention should be paid to all the following groups at risk of GLP1-RAs abuse, except (choose one)?

- A: Pregnant/lactating women
- B: All individuals taking psychostimulants
- C: Eating-disordered individuals
- D: The elderly
- E: People with reduced muscle mass levels

Semaglutide and Tirzepatide reduce alcohol consumption in individuals with obesity

Question 14: Which **ONE** of the following is **NOT TRUE** about Alcohol Use Disorder (AUD)?

- A: It is a multi-faceted chronic relapsing brain disorder
- B: It contributes greatly to global mortality
- C: It remains one of the most undertreated conditions
- D: The FDA-approved treatments have been highly successful in treating AUD
- E: 50% of individuals diagnosed with AUD achieve remission during extended follow-up periods

Discussion

Question 15: Participants endorsing Semaglutide and Tirzepatide use reported which of the following?

- A: Fewer drinks as measured by the Timeline Followback Assessment (TLFB)
- B: More binge episodes
- C: Less stimulating and less sedative effects of alcohol than before starting their medication

Question 16: Which **ONE** of the following is a result of reduced blood alcohol content (BAC)?

- A: An increase in a feeling of fullness
- B: Reduced alcohol consumption
- C: Increased levels of acetaldehyde
- D: A decreased sedative and stimulating effect

Semaglutide – Safety, efficacy, misuse and cost-effectiveness

Is There a Risk for Semaglutide Misuse? Focus on the Food and Drug Administration's FDA Adverse Events Reporting System (FAERS) Pharmacovigilance Dataset

Introduction

Question 17: Agents that impact the brain satiety centres' function may provide effective, non-invasive treatment of obesity for individuals with and without diabetes. Which of the following was shown to be the most effective?

- A: Placebo
- B: Basal insulin
- C: Dulaglutide
- D: Tirzepatide
- E: Semaglutide

Discussion

Question 18: Is it **TRUE** or **FALSE** that semaglutide is considered to possess an overall favourable risk/benefit profile for patients with T2DM given the low risk of severe adverse events and its beneficial metabolic and cardiovascular actions?

- A: TRUE
- B: FALSE

Question 19: Exenatide, administered weekly in combination with nicotine replacement therapy, had which of the following results?

- A: Improved smoking abstinence
- B: Reduced craving and withdrawal symptoms
- C: Decreased weight gain among abstainers

Question 20: Preclinical studies suggest that exenatide can do all the following, **EXCEPT**?

- A:** Normalize dopaminergic function
- B:** Have a substantial therapeutic utility in diseases where neuroinflammation may play a significant role
- C:** Can be successfully employed to alleviate the motor symptoms of PD patients
- D:** Negatively affect the signalling of the brain-derived neurotrophic factor (BDNF)
- E:** Introduce the possibility of long-lasting behavioural effects driven by the long-term structural brain and neural modifications

THE END

QUESTIONNAIRE

G1(25) Part 6 of 7

Semaglutide – Hype Validation The Great, the Good but keep the Bad in mind

INSTRUCTIONS

- Read through the article and answer the multiple-choice questions provided below.
- Some questions may have more than one correct answer; in which case you must mark all the correct answers.

Efficacy and safety of subcutaneous semaglutide in adults with overweight or obese: a subgroup meta-analysis of randomized controlled trials

Introduction

Question 1: Is it **TRUE** that a comprehensive network meta-analysis of pharmacotherapy compared with lifestyle modification only, demonstrated phentermine-topiramate and GLP-1 RAs achieved the best effects on weight loss for adults?

- A: YES
- B: NO

Question 2: In a comparison of the following drugs, which ONE shows a superior capability of weight-lowering with a similar low risk of adverse events?

- A: Exenatide
- B: Semaglutide
- C: Dulaglutide
- D: Liraglutide

Question 3: Which of the following was the most common adverse effect of semaglutide?

- A: Hypoglycaemia
- B: Excessive weight loss in the first 3 months of treatment
- C: An improvement in the quality of life in adults with overweight or obese
- D: Gastrointestinal disorders

Question 4: Lifestyle interventions were the foundation of all obesity treatments according to most of the recommendations and guidelines. Which of the following are **TRUE** about participants with no lifestyle interventions?

- A: They achieved more on the weight loss goal of 5%
- B: They had a greater improvement in triglyceride (TG) level
- C: They had the benefit of optimizing lipid metabolism
- D: They had a higher incidence of hypoglycaemia

Effectiveness of Oral versus Injectable Semaglutide in Adults with Type 2 Diabetes: Results from a Retrospective Observational Study in Croatia

Introduction

Question 5: Diabetes is certainly one of the fastest-growing global health issues of the 21st century. According to the International Diabetes Federation, it is estimated that about people worldwide have impaired glucose tolerance.

- A: 783 million
- B: 937 million
- C: 541 million

Question 6: Long-acting GLP-1 receptor agonists (GLP-1RAs) have been shown to be an effective treatment for patients with type 2 diabetes. Which of the following is **NOT TRUE** about the remarkable clinical benefits of GLP-1 RAs?

- A: Maintaining glycemic control and protecting against hypoglycaemia
- B: Achieving moderate weight loss
- C: Lowering blood pressure and improving lipid profiles
- D: A reduced risk of major cardiovascular events (MACE), cardiovascular death, non-fatal myocardial infarction
- E: Reduced risk of non-fatal ischemic stroke in patients with T2D

Discussion

Question 7: Is it **TRUE** or **FALSE** that the oral formulations of semaglutide have been shown to be significantly more effective in achieving a hemoglobin A1C (HbA1c) reduction and weight loss than the injectable formulations?

- A: TRUE
- B: FALSE

Conclusions

Question 8: The oral formulation and the injectable formulation of semaglutide show almost equal effects. Which of the following is an advantage of the oral formulation?

- A: It must be taken on an empty stomach
- B: There is no injection burden

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A Real-World Study of the Effectiveness and Safety of Semaglutide for Weight Loss

Introduction

Question 9: Is it **TRUE** or **FALSE** that people with obesity should receive personalized care from a multidisciplinary team?

- A: TRUE
- B: FALSE

Question 10: Semaglutide has been approved by both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for which of the following?

- A: Chronic weight management in patients with either a BMI greater than 30 kg/m² or a BMI greater than 27 kg/m², regardless of weight-related conditions
- B: Type 2 diabetes mellitus (DM)

Question 11: Semaglutide has become the first anti-obesity medication (AOM) that results in a greater than average weight loss over that attributable to lifestyle interventions?

- A: 5%
- B: 12.5%,
- C: 15%
- D: 10%

Question 12: Out of 40 participants, discontinued semaglutide due to adverse events?

- A: 65%
- B: 2.5%
- C: 55%
- D: 7.5%

Discussion

Question 13: Which of the following were found in a real-world cohort study in the United States on the effects of semaglutide?

- A: An early improvement in glycemic markers
- B: An improvement in numerous cardiovascular risk factors
- C: A significant decrease in C-reactive protein

Question 14: Future research efforts should aim to achieve which of the following?

- A: Evaluate the potential synergistic effect of combining semaglutide with other AOMs and different lifestyle interventions
- B: Explore its use as neo-adjuvant or adjuvant therapy along with bariatric surgery
- C: Disregard distinct obesity phenotypes and the evaluation of the use of semaglutide in patient subgroups with different main comorbidities

Conclusions

Question 15: The advent of semaglutide could represent a paradigm shift in obesity care to achieve which of the following?

- A: To encompass the widespread long-term use of pharmacotherapy across lifestyle interventions
- B: To employ a personalized treat-to-target approach, similar to the contemporary management of type 2 DM
- C: To prevent and treat weight-related complications

THE END

QUESTIONNAIRE

G1(25) Part 7 of 7

Semaglutide – Hype Validation the Great, the Good but keep the Bad in mind

INSTRUCTIONS

- Read through the article and answer the multiple-choice questions provided below.
- Some questions may have more than one correct answer; in which case you must mark **all** the correct answers.

What Are the Bad Side Effects of Ozempic?

Semaglutide

Adverse effects

Question 1: Is it **TRUE** or **FALSE** that there is a risk of hypoglycaemia significantly increasing with escalating doses of semaglutide and when it is administered with other anti-hyperglycaemic medications?

- A: TRUE
- B: FALSE

Question 2: Which of the following is the most prevalent gastrointestinal adverse effect of Ozempic?

- A: Vomiting
- B: Abdominal pain
- C: Decreased appetite
- D: Nausea
- E: Dyspepsia

Question 3: Semaglutide can result in acute kidney injury. Which of the following is **NOT** associated with a high risk of kidney injury?

- A: Nausea
- B: Vomiting
- C: Diarrhoea
- D: Dehydration
- E: Constipation

Question 4: GLP-1 receptor agonists directly stimulate GLP-1 receptors in pancreatic islet beta cells and exocrine duct cells. This process may lead to all the following EXCEPT

- A: Hyperplasia
- B: Decreased pancreatic weight
- C: Duct occlusion
- D: Back pressure
- E: Acute or chronic inflammation

Question 5: During the initial phases of drug development, animal studies involving semaglutide revealed the development of thyroid C-cell tumours. Which of the following groups may face an elevated risk for C-cell tumours?

- A: Individuals with a personal or family history of medullary thyroid carcinoma (MTC)
- B: Those diagnosed with multiple endocrine neoplasia type 2 (MEN 2) syndrome

Question 6: If semaglutide is used alongside which of the following it can result in a notable risk of hypoglycaemia?

- A: Orally administered medications
- B: Other blood-glucose-lowering agents
- C: Other GLP-1 receptor agonists or tirzepatide

Question 7: Which of the following medications have the potential to diminish the therapeutic effects of semaglutide?

- A: Beta-blockers
- B: Thiazide diuretics
- C: Salicylates
- D: Furosemide
- E: Selective serotonin reuptake inhibitors

Question 8: Which of the following is **NOT TRUE** about precautions that should be taken when using semaglutide?

- A: It is advisable to avoid the use of semaglutide in individuals with a history of suicidal attempts or current suicidal ideation
- B: It is an indisputable fact that semaglutide does not impede the absorption of other medications
- C: If the multiple-dose injection pen (Ozempic®) is shared among individuals there is a risk of transmitting infections
- D: Semaglutide is contraindicated in patients with type 1 diabetes
- E: The use of semaglutide in combination with other weight loss medications should be avoided

Question 9: Is there an increased risk of gastrointestinal complications for patients with a history of bariatric surgery when using semaglutide?

- A: YES
- B: NO

How does Ozempic affect the face?

Question 10: Ozempic can cause rapid weight loss that is often more pronounced on the face. Facial fat serves as which of the following?

- A:** Protection for facial aesthetics and elasticity
- B:** To cushion the skin

THE END



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ANSWER SHEET

G1(25)

Semaglutide – Hype Validation The Great, the Good but keep the Bad in mind

*Time spent on activity											hour											min																					
PART 1											PART 2											PART 3											PART 4										
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ANSWER SHEET

G1(25)

*Time spent on activity												hour					min						
You can complete any one, or all the parts of this activity.																							
PART 5										PART 6					PART 7								
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How relevant was the content of this activity to your scope of practice? <div> Not at all Somewhat Mostly Extremely </div>												11											
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