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Semaglutide and Tirzepatide in Type 2 Diabetes and Obesity: Efficacy, Prescribing Safety, and Practical Risk-Mitigation Strategies for Clinical Practice in the UK and Qatar

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Abstract **Review Article**

Semaglutide and tirzepatide have reshaped incretin-based therapy from a predominantly glucose-lowering approach into a broader platform for managing type 2 diabetes, obesity, and selected cardiovascular, kidney, and obesity-related comorbidities. Semaglutide is a GLP-1 receptor agonist, whereas tirzepatide is a dual GIP/GLP-1 receptor agonist, so the two drug families should be discussed together but not treated as pharmacologically identical. In the UK, Ozempic is licensed for adults with insufficiently controlled type 2 diabetes, Wegovy for weight management and cardiovascular risk reduction in selected adults with overweight or obesity, and Mounjaro for type 2 diabetes and weight management. The strongest evidence supports major reductions in glycated haemoglobin and body weight, with semaglutide additionally showing cardiovascular and kidney outcome benefits in selected populations and tirzepatide showing especially strong weight-loss efficacy and emerging benefit in obesity-related comorbidity pathways. Safe use requires careful product selection, gradual titration, attention to co-prescribed insulin or sulfonylureas, counselling on gastrointestinal effects and dehydration, awareness of pancreatitis and gallbladder warnings, reproductive counselling, and clear peri-operative communication. For UK and Qatar practice, a safer prescribing model combines structured baseline assessment, active review during dose escalation, medication reconciliation that detects private prescribing, and bilingual patient education to reduce avoidable harm. [1-6].

Keywords: Semaglutide, Tirzepatide, Glucagon-Like Peptide-1 Receptor Agonists, Diabetes MellitusType 2, Obesity, Obesity Management, Weight Loss, Drug Prescriptions, Drug-Related Side Effects and Adverse Reactions, Medication Reconciliation, Risk Management, Patient Education as Topic.

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INTRODUCTION

GLP-1-based therapies now sit at the intersection of diabetes, obesity, and cardiometabolic medicine. Contemporary review literature describes semaglutide and tirzepatide as among the most effective pharmacological options currently available for lowering body weight and improving glycaemia, and the evidence base has expanded beyond surrogate metabolic endpoints into major cardiovascular and kidney outcomes. [1]

Terminology matters clinically. Ozempic and Wegovy are semaglutide products, but they are not interchangeable from a licensing perspective: Ozempic is used for type 2 diabetes, whereas Wegovy is licensed for weight management and, in selected adults, cardiovascular risk reduction. Mounjaro contains tirzepatide, a long-acting dual GIP/GLP-1 receptor agonist licensed for type 2 diabetes and weight management. [2,3,17]

Pharmacology and current indications

Semaglutide is a GLP-1 receptor agonist, while tirzepatide is a dual GIP/GLP-1 receptor agonist. Both improve glycaemic control and reduce appetite and body weight, but tirzepatide's dual agonism is part of the rationale for its particularly strong effects on weight reduction in comparative studies. [1,3]

In the UK, these medicines are prescription-only and should be supplied through regulated clinical pathways. The MHRA [1]has specifically warned that switching between products without clinical supervision can increase side effects or reduce effectiveness, and that patients should not obtain these medicines from unregulated sources because counterfeit or inappropriately supplied products carry serious health risks. [4]

For obesity care, NICE[2] places semaglutide and tirzepatide within structured weight-management pathways rather than ad hoc prescribing. NICE also advises lower BMI thresholds, reduced by 2.5 kg/m², for several minority ethnic groups because cardiometabolic risk may arise at lower BMI. In Qatar, the Ministry of Public Health obesity guideline provides an appropriate national framework within which local semaglutide- and tirzepatide-based pathways can be aligned. [5,6]

Semaglutide vs Tirzepatide

Semaglutide is a selective glucagon-like peptide-1 receptor agonist (GLP-1RA) with 94% sequence homology to human GLP-1. Modifications, including an -aminoisobutyric acid substitution at position 8 and the addition of a C18 fatty diacid chain, protect it from dipeptidyl peptidase-4 (DPP-4) degradation and facilitate albumin binding, extending its half-life to approximately 165 hours. [7,8]

Tirzepatide is a first-in-class unimolecular dual agonist targeting both GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) receptors. It is an "imbalanced" agonist, possessing native-like affinity for GIP receptors but 13-fold weaker potency at the GLP-1 receptor. Tirzepatide exhibits biased signalling at the GLP-1 receptor, favouring the cyclic AMP pathway over -arrestin recruitment, which reduces receptor internalisation and may enhance sustained efficacy.[7]

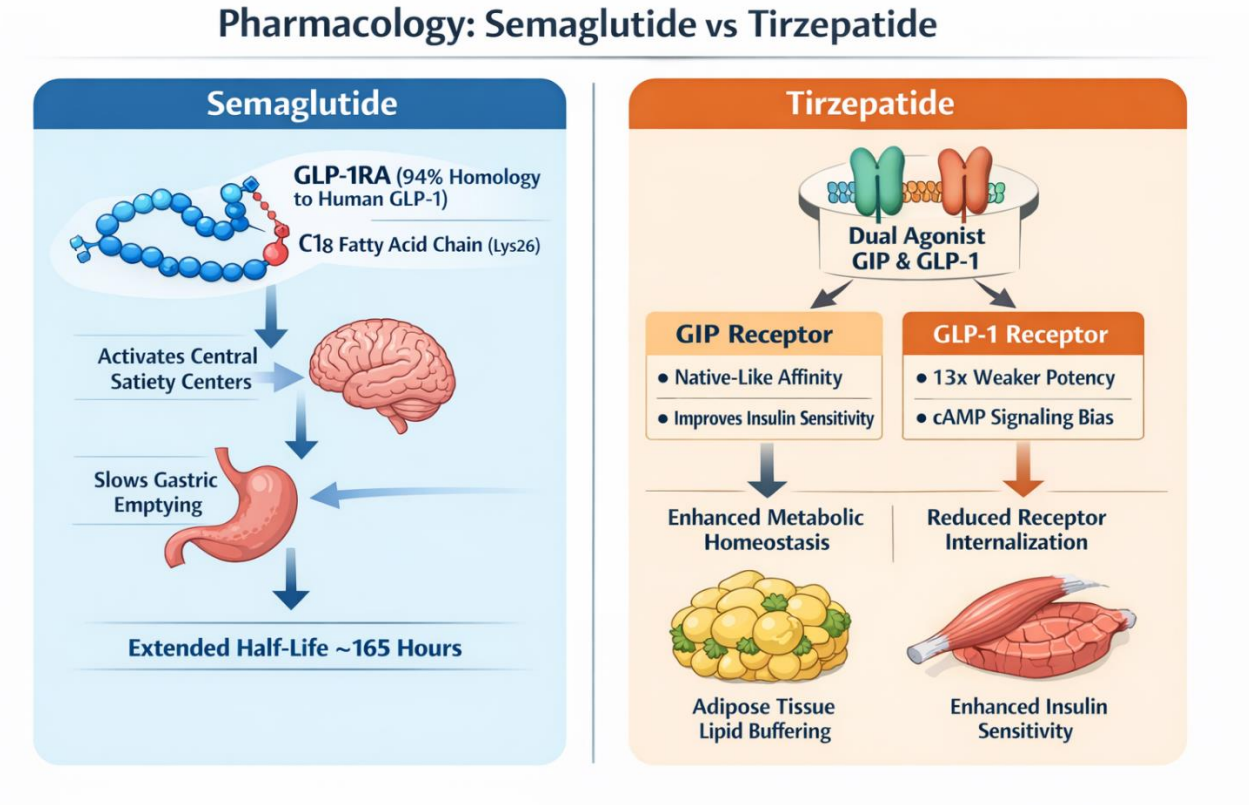

Figure 1: illustration of the pharmacology of Semaglutide and Tirzepatide

Major Clinical Trials

The STEP Program: [9-13]

Semaglutide 2.4 mg in Obesity: The Semaglutide Treatment Effect in People with Obesity (STEP) program evaluated subcutaneous semaglutide 2.4 mg weekly as a primary intervention for weight management. Foundational data from STEP 1 demonstrated that in adults without diabetes, semaglutide achieved a mean weight reduction of 14.9% over 68 weeks, with over 86% of participants reaching a loss. STEP 2 highlighted the "metabolic resistance" inherent in T2DM populations, where the same dose yielded a more modest 9.6% reduction. To address the role of behavioural support, STEP 3 integrated intensive behavioural therapy (IBT) and a low-calorie diet (LCD), resulting in a 16.0% reduction, suggesting that the

[1] Medicine and Healthcare products Regulatory Agency
[2] National Institute for Health and Care Excellence

biological potency of the molecule is the primary driver of weight loss regardless of lifestyle intensity.[9]

The SURMOUNT Program: [14-17]

The SURMOUNT trials were designed to investigate the superior potency of dual GIP/GLP-1 agonism. SURMOUNT-1 reported that tirzepatide 15 mg achieved a mean weight loss of 20.9% at 72 weeks, a magnitude previously associated only with surgical interventions. SURMOUNT-2 confirmed tirzepatide's superior efficacy in T2DM patients, achieving 15.7% weight loss. Notably, SURMOUNT-3 utilised a sequential model where participants first lost weight through IBT before starting medication; those randomised to tirzepatide achieved a total mean weight loss of 26.6%, the highest reported in any major pharmacological trial to date.[10]

Direct Comparative Efficacy: SURPASS-2 [19] and SURMOUNT-5 [18]

Direct head-to-head comparisons have consistently favoured dual agonism. In SURPASS-2, tirzepatide 15 mg was compared to semaglutide 1.0 mg in T2DM patients, with tirzepatide nearly doubling the weight loss (11.2 kg vs. 5.7 kg) and achieving superior reduction. The definitive obesity comparison, SURMOUNT-5, compared the maximum tolerated doses of both agents (Tirzepatide 15 mg vs. Semaglutide 2.4 mg). At 72 weeks, tirzepatide demonstrated clear superiority with a 20.2% weight reduction compared to 13.7% for semaglutide. Network meta-analyses confirm these findings, showing that tirzepatide at maximum dosage ranks as the most effective pharmacological intervention for both adiposity and glycaemic parameters.

Table 1: Summary of Major Clinical Trials (STEP [9-13] and SURMOUNT [14-18])

Trial ID	Population Size (N)	Primary Aim	Key Findings (Mean Weight Loss)	Adjunct Interventions (Non-Pharmacological)
STEP 1	1,961	Efficacy/safety in obesity (no T2D[3])	-14.9% (Sema 2.4mg) vs -2.4% (Placebo)	500-kcal deficit diet; 150 min/wk exercise
STEP 2	1,210	Weight Mx[4] in patients with obesity + T2D	-9.6% (Sema 2.4mg) vs -3.4% (Placebo)	Lifestyle counselling; 500-kcal deficit; 150 min/wk exercise
STEP 3	611	Maximising weight loss via IBT[5] + pharmacotherapy	-16.0% (Sema 2.4mg) vs -5.7% (Placebo)	30 IBT visits; initial 8-wk LCD (1000-1200 kcal/d); physical activity
STEP 4	803	Effect of withdrawal on weight maintenance	-7.9% (Continued Sema) vs +6.9% (Switch to Placebo)	Standard lifestyle intervention (500 kcal deficit)
SURMOUNT1	2,539	Efficacy in adults with obesity (no T2D)	-20.9% (Tirz 15mg) vs -2.4% (Placebo)	500-kcal deficit; regular lifestyle counselling; 150 min/wk exercise
SURMOUNT2	938	Efficacy in adults with obesity + T2D	-15.7% (Tirz 15mg) vs -3.3% (Placebo)	Nutritional advice for 500-kcal deficit; 150 min/wk exercise
SURMOUNT3	806	Sequential IBT followed by Tirzepatide	-26.6% (Total weight loss from study entry)	12-wk IBT lead-in; 500-kcal deficit; 150 min/wk exercise
SURMOUNT5	751	Head-to-head vs Semaglutide 2.4mg	-20.2% (Tirz 15mg) vs -13.7% (Sema 2.4mg)	Standard lifestyle support program

Efficacy in type 2 diabetes

Semaglutide has strong evidence base in type 2 diabetes. In SUSTAIN-6, semaglutide reduced major adverse cardiovascular events in high-risk patients with type 2 diabetes, establishing semaglutide as more than a glucose-lowering therapy alone. [20]

Tirzepatide has also shown very strong glycaemic and weight efficacy in diabetes. In SURPASS-2, tirzepatide was superior to semaglutide 1 mg once weekly for both HbA1c reduction and body-weight reduction at 40 weeks. These findings support the clinical view that both agents are highly effective for glycaemic control, but tirzepatide may offer greater average weight reduction than semaglutide at the doses directly compared in that study. [19]

Efficacy in obesity and weight maintenance

Semaglutide 2.4 mg has transformed pharmacological obesity treatment. In STEP 1, adults with overweight or obesity without diabetes achieved a mean weight reduction of about 14.9% at 68 weeks with semaglutide 2.4 mg, compared with 2.4% with placebo [10]. In STEP 4, patients who continued semaglutide after a run-in period continued to lose weight, whereas those switched to placebo regained weight. [13]

[3] T2D : Type 2 Diabetes Mellitus
[4] Mx: Management
[5] IBT: intensive Behavioural therapy

The STEP 1 extension showed that stopping semaglutide was followed by substantial regain of lost weight over time, supporting the view that obesity pharmacotherapy often behaves more like chronic disease treatment than a short-course intervention. [10]

Tirzepatide has produced similarly important advances in obesity medicine. SURMOUNT-1 showed large and sustained weight reduction over 72 weeks in adults with obesity or overweight. In later head-to-head evidence, tirzepatide also produced greater mean weight loss than semaglutide 2.4 mg in obesity, reinforcing the impression that tirzepatide may be the more potent weight-loss agent on average, although clinical choice still depends on indication, tolerability, availability, and patient-specific factors. [14,15,18]

Cardiovascular, kidney, and expanding indications

The semaglutide evidence base extends beyond body weight and glycaemia. In SELECT, semaglutide reduced major adverse cardiovascular events in adults with overweight or obesity and established cardiovascular disease who did not have diabetes. In FLOW, semaglutide reduced a composite of clinically important kidney outcomes and cardiovascular death in patients with type 2 diabetes and chronic kidney disease. [21,22]

Semaglutide has also shown benefit in obesity-related heart failure with preserved ejection fraction, with improvements in heart-failure symptoms, physical limitations, exercise capacity, and body weight. Tirzepatide is likewise moving beyond diabetes and general obesity, with evidence of benefit in obesity-related obstructive sleep apnoea and in obesity-related heart failure with preserved ejection fraction. Together, these studies suggest that semaglutide and tirzepatide are increasingly being positioned as broader cardiometabolic therapeutics. [23-24]

Prescribing principles

Safe prescribing begins with selecting the correct product for the correct indication. In UK practice, Ozempic should be prescribed as a diabetes medicine, Wegovy as an obesity and cardiovascular-risk medicine according to its licence, and Mounjaro according to its diabetes or weight-management licence. Product-specific prescribing is important because similar-sounding incretin medicines have different indications, maintenance doses, and counselling points. [2,3,25]

Baseline assessment should be structured. NICE (National Institute of Health and Care Excellence, UK) guideline materials for tirzepatide recommends confirming eligibility, reviewing the patient's motivation to engage with diet and physical-activity support, documenting medical history and concomitant medicines, recording baseline measures, and setting a treatment goal. In day-to-day practice, the baseline safety review should also include prior pancreatitis, gallbladder disease, major visual history including diabetic retinopathy, renal risk from dehydration, pregnancy intention, contraception, and the possibility that the patient is already using a privately sourced incretin medicine that does not appear on the routine prescribing record. [4,26]

Dose escalation should be deliberate rather than hurried. Ozempic is initiated at 0.25 mg weekly and up-titrated at intervals of at least 4 weeks; Wegovy uses a 16-week escalation schedule to improve tolerability; and tirzepatide starts at 2.5 mg weekly before stepwise increases in 2.5 mg increments at intervals of at least 4 weeks to the highest tolerated maintenance dose. [2,3,25]

Active review during titration is a key safety strategy. NICE follow-up material for tirzepatide recommends regular review during escalation with documentation of adverse effects, injection-use difficulties, weight, BMI, pregnancy plans, and need for further support. If adverse effects occur, dose escalation may be delayed and down-titration considered. [26]

Safety profile and literature-based risk mitigation

Gastrointestinal adverse effects are the dominant early tolerability issue. Product information for semaglutide and tirzepatide identifies nausea, vomiting, diarrhoea, constipation, and abdominal discomfort as common adverse effects, especially during early treatment and dose escalation. The most evidence-based mitigation strategy is slow up-titration, smaller meals, adequate hydration, and early review if symptoms become persistent or severe. [2,3,25,26]

Dehydration can worsen renal function. Product information for both semaglutide and tirzepatide warns that gastrointestinal adverse reactions may lead to dehydration and deterioration in renal function, including acute kidney injury. Patients should therefore receive clear written advice to maintain fluid intake and to seek review promptly if prolonged vomiting, diarrhoea, or reduced oral intake develops. [2,3,26]

Pancreatitis remains an important warning. Product information advises caution in those with a history of pancreatitis, immediate discontinuation if pancreatitis is suspected, and non-restart if pancreatitis is confirmed. The MHRA has additionally strengthened class warnings on acute pancreatitis, including severe presentations. [2,3,27]

Gallbladder and biliary events also deserve attention, especially during substantial weight loss. Tirzepatide meta-analytic data and product information support vigilance for gallbladder or biliary disease and cholelithiasis. A practical mitigation strategy is to warn patients about right upper-quadrant pain, fever, jaundice, or persistent post-prandial abdominal pain and to investigate early when symptoms arise. [3,28]

Hypoglycaemia risk is mainly a co-prescribing problem rather than a property of semaglutide or tirzepatide alone. When these medicines are used alongside insulin or sulfonylureas, the risk of hypoglycaemia increases and the doses of those agents may need review or reduction. The safest approach is planned, stepwise adjustment rather than abrupt change, with home glucose monitoring or CGM[6] support where appropriate. [2,3,25]

Pregnancy and reproductive counselling are essential. These medicines should not be used during pregnancy or while breastfeeding. Semaglutide should be stopped before planned pregnancy, and tirzepatide should also be stopped before conception. Tirzepatide can reduce exposure to oral contraceptives, so non-oral contraception or additional barrier protection is advised after treatment initiation and after dose escalation. [3,25]

Visual safety requires attention, particularly in people with diabetes. Semaglutide product information warns that patients with diabetic retinopathy, especially those using insulin, may need closer monitoring because worsening diabetic retinopathy complications were observed in the cardiovascular outcomes trial. Sudden or substantial visual deterioration should prompt urgent clinical assessment. [2,7,29]

Peri-operative safety has become a major practical issue because these medicines delay gastric emptying. Product information and UK safety messaging stress that patients should inform peri-operative teams that they are taking semaglutide or tirzepatide, and management should be individualised rather than based on unsupervised stopping by the patient. [4,25,30]

Both semaglutide and tirzepatide carry an FDA[7] boxed warning regarding the risk of thyroid C-cell tumors, a concern primarily derived from observations of dose-dependent tumor development in rodent studies. Consequently, these agents are absolutely contraindicated in individuals with a personal or family history of medullary thyroid carcinoma (MTC) or Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Clinical management necessitates vigilant monitoring for acute pancreatitis, and healthcare providers must instruct patients to immediately discontinue treatment if symptoms such as persistent severe abdominal pain (potentially radiating to the back) occur. [1,2,3,19]

Boxed Warnings & Contraindications [1,2,3,19]

- **Thyroid C-cell Tumor Risk:** Both agents carry an FDA **boxed warning** due to a potential risk for medullary thyroid carcinoma (MTC), based on rodent studies.
- **Absolute Contraindications:** Not to be used in patients with a personal or family history of **MTC** or **Multiple Endocrine Neoplasia syndrome type 2 (MEN 2)**.
- **Pancreatitis:** Prescribers should check for a history of pancreatitis; treatment should be discontinued immediately if acute pancreatitis is suspected (e.g., persistent severe abdominal pain).

Current Clinical Practice Guidelines and Recommendations

- ADA 2024 (American Diabetes Association): GLP-1 RAs and tirzepatide are recommended for T2D and obesity, especially when weight loss or cardiorenal protection is a priority; metformin remains first-line unless weight or organ protection is prioritized. [31,32]
- EASD/ESC[8]: Prioritize agents with proven CV benefit (semaglutide, liraglutide, dulaglutide, tirzepatide) in T2D with ASCVD or high risk. [31]
- NICE/WHO[9]: Endorse GLP-1 RAs for obesity and T2D with comorbidities; recommend multidisciplinary support and long-term therapy. [31]

Suggested strategies to improve safety of prescribing and administration in the UK and Qatar

First, prescribing systems should be product-specific and indication-linked. Electronic prescribing should make it clear whether the clinician is selecting Ozempic for type 2 diabetes, Wegovy for obesity or cardiovascular-risk reduction, or Mounjaro for type 2 diabetes or weight management. This reduces avoidable confusion between similar weekly injectable medicines. [2,3,25]

Second, services should use a standardised baseline assessment bundle. This should include body weight, BMI, blood pressure, glycaemic status, medication reconciliation, pregnancy and contraception review, pancreatitis and gallbladder history, major visual history, and a check for private or duplicated prescribing. This approach is consistent with NICE initiation

[6] Continuous glucose monitoring
[7] Food and Drug Administration
[8] a collaboration between the European Association for the Study of Diabetes (EASD) and the European Society of Cardiology (ESC) to manage diabetes, pre-diabetes, and cardiovascular diseases (CVD) as a single entity
[9] National Institute of Health and Care Excellence, UK / World Health Organisation

materials and with MHRA concerns about medicines obtained outside regulated pathways. [4,26]

Third, services should implement structured titration follow-up, ideally at roughly 4-week intervals during dose escalation, in addition to reviewing compliance and preventing start-stop medicine self-administration [33]. In both the UK and Qatar, pharmacist-, nurse-, or clinician-led follow-up during the titration phase is likely to be safer than issuing several months of treatment without active review. [26]

Fourth, every initiation in a patient using insulin or a sulfonylurea should trigger a written co-prescribing plan covering glucose monitoring, dose review, and sick-day advice [10]. This is one of the most practical ways to reduce avoidable hypoglycaemia and unsafe medication changes. [2,3,25]

Fifth, red-flag counselling should be standardised. Patients should receive clear verbal and written advice on severe abdominal pain, persistent vomiting, dehydration, right upper-quadrant pain, jaundice, worsening vision, pregnancy planning, and the need to tell surgical and anaesthetic teams that they are taking semaglutide or tirzepatide. [2-4,25-27]

Sixth, patient education should be bilingual where relevant. In the UK, multilingual counselling helps diverse populations; in Qatar, English-Arabic instructions are especially practical. The core content should cover weekly dosing, injection technique, storage, sharps disposal, missed doses, expected early gastrointestinal symptoms, hydration advice, and when not to escalate the dose. [2,3,6,25]

Practical safety summary table

Table 2: Key prescribing and safety issues with practical mitigation steps for routine clinical use. Citations are retained in each row for editing

Safety domain	Why it matters	Suggested mitigation	Key refs
Product selection	Ozempic, Wegovy, and Mounjaro are not interchangeable products.	Link prescribing to indication and product name in the electronic record.	[2,3,25]
Dose escalation	Rapid escalation increases gastrointestinal intolerance and drop-out.	Use scheduled stepwise titration and delay escalation if adverse effects occur.	[2,3,25,26]
GI adverse effects	Nausea, vomiting, diarrhoea, and constipation are common early problems.	Counsel on small meals, hydration, slower eating, and early review for persistent symptoms.	[2,3,25,26]
Renal risk	Vomiting and dehydration can precipitate renal deterioration.	Give written hydration advice and review urgently if intake is poor or vomiting continues.	[2,3,25]
Pancreatitis	Severe abdominal pain requires urgent assessment.	Stop treatment if pancreatitis is suspected and do not restart if confirmed.	[2,3,27]
Gallbladder disease	Rapid weight loss and treatment may be associated with biliary events.	Warn about RUQ pain, jaundice, fever, and investigate promptly.	[3,19]
Co-prescribed insulin/SU	Hypoglycaemia risk rises when combined with insulin or sulfonylureas.	Use a planned glucose-monitoring and dose-adjustment plan.	[2,3,25]
Pregnancy/ contraception	These medicines are unsuitable in pregnancy; tirzepatide affects oral contraception exposure.	Provide pregnancy counselling and contraception prompts at initiation and review.	[3,25]
Visual symptoms	Semaglutide may require closer monitoring in diabetic retinopathy.	Advise urgent review for sudden visual deterioration.	[2,7]
Peri-operative care	Delayed gastric emptying may affect anaesthetic planning.	Ensure patients tell surgical and anaesthetic teams they are using the medicine.	[2-4,25]

Other factors influencing prescribing

1 -Cost Effectiveness, Health Economics, and Access

[10]
- Check glucose more often when unwell.
- Do not make abrupt insulin changes on your own.
- Maintain fluids and watch for dehydration.
- Seek urgent review if severe or persistent abdominal pain develops.
- Contact the clinical team if oral intake is poor, recurrent vomiting occurs, or glucose readings.

- ICER (Institute for Clinical and Economic Review, USA) analysis: Both semaglutide and tirzepatide are highly cost-effective at conventional thresholds ($53,400–$69,300 per QALY), but high prices limit affordability and access; <1% of eligible US adults can be treated before exceeding budget thresholds. [34]
- Insurance coverage: NHS (National Health Service, UK) access is limited due to budget impact, similar to the U.S. situation [35]. Variable; more likely for T2D than obesity; access is a major barrier in many regions, including Qatar and the Middle East [36]. Private-sector uptake is rising sharply, especially among women aged 30–49, with significant socioeconomic disparities. [36].

2- Weight Maintenance and Regain

- Semaglutide: Discontinuation leads to substantial weight regain (STEP 4: 68% of lost weight regained after 1 year off-treatment). [10,13]
- Tirzepatide: SURMOUNT-4 showed 89.5% maintained ≥80% of weight loss at 88 weeks with continued therapy; discontinuation led to reversal of cardiometabolic improvements.[17]
- Meta-analyses: Weight regain after stopping GLP-1 RAs is rapid, with return to baseline within 1.5–2 years; ongoing therapy is required for sustained benefit. [37]

3- Discontinuation and Adherence

- Real-world data: 42–54% discontinue within 1 year; higher rates in non-diabetic populations and outside academic centers. [33]
- Predictors of discontinuation: Older age, GI side effects, lower income, less weight loss, and lack of insurance coverage. [33]
- Reinitiation: Weight regain is a strong motivator for restarting therapy. [33]

CONCLUSION

Semaglutide and tirzepatide are among the most important therapeutic advances in modern diabetes and obesity care. The strongest evidence supports major improvements in HbA1c and body weight, clinically meaningful cardiovascular and kidney benefit with semaglutide in selected populations, and increasingly broad obesity-related benefits with tirzepatide. [1,7-15, 38,39]

Their rapid uptake, however, makes safe prescribing just as important as efficacy. The literature and regulatory guidance support a safety model built on correct product selection, structured baseline assessment, gradual titration, careful handling of insulin and sulfonylureas, proactive counselling on gastrointestinal effects, dehydration, pancreatitis, gallbladder disease, visual symptoms, peri-operative communication, and pregnancy-specific safeguards. Those principles are directly applicable in UK practice and can be adapted in Qatar through local guideline alignment, formulary governance, and taking into account patient sensitive factors including cultural factors [2-6,16-19]., and it is in the authors' opinion that patients and their society's biopsychological and socioeconomic factors should be taken into account when designing a patient family-centered care (PFCC) clinical guideline. Keeping in mind the short- and long-term therapeutic outcomes within the larger picture of the patients in their community.

Topical clinical trials notable for future discussion:

- FOCUS: Long-term effects of semaglutide on diabetic retinopathy (2026).
- SOUL: MACE prevention with oral semaglutide in T2D with CVD/CKD.
- SURPASS-CVOT: Cardiovascular outcomes with tirzepatide vs dulaglutide (completed 2025).
- Registries: Postmarketing surveillance for rare adverse events, long-term outcomes, and special populations.

Future Directions

The horizon of metabolic medicine includes triple hormone agonists like retatrutide (GLP-1/GIP/Glucagon), which has shown weight loss approaching 28% [1,40]. Research is also focusing on preservation of lean mass through combination with activin receptor blockers and the development of non-peptidyl oral agents like orforglipron to improve equity and global access. [1,41]

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