Unit No. 5

USE OF PHARMACOTHERAPY IN OBESITY MANAGEMENT

Dr Tham Kwang Wei

ABSTRACT

Obesity is a chronic disease that is relapsing and progressive due to a disruption in energy homeostasis, rendering people with obesity the challenge of attaining adequate weight loss and/or weight maintenance after successful weight loss. Depending on the presence, type, and severity of the obesity-related comorbidities and complications (ORC), patients may require an amount of weight loss beyond what lifestyle and behavioural modification can attain to improve/treat the ORC. Hence, obesity medications are required to attain clinically meaningful weight loss. After metabolic bariatric surgery (MBS), some patients may not attain their target weight loss or may experience weight regain. Obesity medications may be required to achieve their target weight loss and metabolic control. The use of pharmacotherapy in obesity management remains a vital adjunct to lifestyle and behavioural modifications and even to MBS, particularly in those with multiple or severe ORC and severe stages of obesity. This article discusses the general approach to pharmacotherapy in obesity management, the various obesity medications currently approved, and novel and pipeline medications for obesity treatment.

Keywords: Obesity, obesity medications, pharmacotherapy, weight loss

SFP2025; 51(5): 29-41

INTRODUCTION

TThe global burden of obesity has increased substantially over the last four decades with obesity prevalence still projected to rise. By 2035, 51 percent of the world's population will be estimated to have overweight or obesity, with about 1 in 4 persons having obesity.[1] Obesity is now established as a chronic, progressive disease and often relapsing[2-4] with a complex host of pathogenic and perpetuating factors.[5] These factors, along with the underpinning biologic responses to weight loss, often render people with obesity (PwO) the challenge of attaining adequate and/or maintaining weight loss to improve health,[5-6] often necessitating the use of multiple modalities including pharmacotherapy in obesity management.

DR THAM KWANG WEI
Senior Consultant
Department of Endocrinology
Woodlands Health, Singapore

Despite this clinical need, the use of obesity medications in the United States remains low at an estimated <5 percent among those in whom there is a medical indication. This is clearly much lower than the usage of pharmacotherapy in other chronic diseases like type 2 diabetes.[7,8] In Singapore, people living with overweight and obesity view that weight loss medications are dangerous (65 percent) and only 20 percent feel that medications are effective in weight loss. Coupled with the belief that the responsibility to manage obesity and weight issues (90 percent) lies solely with PwO, this may contribute to PwO not seeking medical attention as they should.[9] Inadequate healthcare coverage for obesity treatments stemming from misconceptions about PwO and about the disease itself results in high out-of-pocket costs and contributes to the poor uptake of obesity pharmacotherapy despite the need for treatment.[10,11] Weight bias and stigma by healthcare professionals from a variety of reasons has resulted in healthcare professionals not adequately addressing obesity in patients.[12]

Over the years, several approved weight loss medications (e.g., fenfluramine, sibutramine, rimonabant, lorcaserin) were withdrawn from the market due to serious adverse events.[11] This may have eroded the confidence in obesity medications in not just the general public but among prescribers. Despite studies proving that weight loss of 5–10 percent improves ORC and cardiovascular risk, the absolute difference may be deemed as insignificant to patients (or even physicians) and might contribute to the low uptake and prescription of obesity medications. Instead, many resort to over-the-counter (OTC) products or unlicensed interventions with undetermined efficacy and safety profile. In recent years, there have been multiple reports of such OTC products being adulterated with obesity medications already withdrawn from the market causing serious side effects to consumers.

To tackle the increasing burden of obesity associated with serious health sequelae, there is clearly a need to address these issues. This paper aims to address the rationale for the use of obesity medications, discuss the currently-approved obesity medications, and the approach physicians can adopt when utilising pharmacotherapy to treat obesity. A brief review of novel and pipeline medications for obesity treatment is also included.

RATIONALE AND CLINICAL REASONING FOR THE USE OF OBESITY MEDICATIONS

Weight Loss Needed for Health Improvement and ORC Control

Lifestyle changes, mainly through instituting a reduction in caloric intake and increased physical activity, and behavioural modification remain the cornerstone in obesity treatment.

Clinically meaningful weight loss of 5–10 percent of initial weight can significantly reduce cardiovascular risk factors and improve obesity-related comorbidities or complications (ORC) such as obstructive sleep apnoea, metabolic dysfunction-associated steatotic liver disease (MASLD; commonly known as fatty liver disease) and the prevention or delay in the development of type 2 diabetes.[13,14] However, some ORC require weight loss beyond 5–10 percent for benefit. For example, improvement in symptomatology and function in osteoarthritis and improvement in ovulation and pregnancy outcomes in female infertility generally require weight loss of ≥10 percent. Weight loss quantum of up to 40 percent may be needed to improve or reverse fibrosis in steatohepatitis. For improvement in the severity of obstructive sleep apnoea (OSA), weight loss of at least 7–11 percent is needed.[15] Reduction in cardiovascular events and mortality is typically seen with greater weight loss (>15 percent). This has been observed after sustained weight loss over 8–15 years after metabolic bariatric surgery.[16,17]

Weight Loss Attainable with Lifestyle and Behavioural Interventions

Intensive lifestyle and behavioural therapy (ILBT) in the most rigorous clinical trials for weight loss can achieve a weight loss of 6.1–8.6 percent[16,18] at one year, which can be maintained at six percent over ten years in the Look AHEAD study.19 However, as in most weight-loss clinical trials involving lifestyle modification, weight regain is inevitable over time. Real-world data from a Canadian multidisciplinary practice using lifestyle and behavioural interventions in routine clinical practice showed that over a follow-up period of 7.5 years, 64 percent of patients lost ≤3 percent of initial weight, with only 32 percent of patients losing significant amounts of weight of ≥7.5 percent.[20] Hence, adjunctive pharmacotherapy is often necessary for clinically meaningful weight loss, especially in patients who require greater amounts of weight loss to treat their ORC. Nonetheless, obesity medications should always be used in addition to best efforts in lifestyle and behavioural modification tailored for the patient and never as a substitute. The effect of obesity medications will then be further enhanced and patients can derive the best benefit of obesity medications as demonstrated repeatedly in clinical trials. In the STEP 3 trial, a mean weight loss of 17.6 percent with once-weekly semaglutide 2.4 mg was seen when used in addition to ILBT (6 percent).[18,21]

Counteracting the Physiologic Adaptive Response to Weight Loss

The negative energy balance created during weight loss evokes a robust physiologic adaptive response effected to restore energy homeostasis. This leads to increased food intake (due to reduced satiety and satiation coupled with increased hunger) and decreased energy expenditure with resultant weight regain.[22,23] Hence, obesity treatment should include therapies that can counteract these adaptive responses for enhanced weight loss and weight maintenance. Obesity medications play a crucial role here as all but one obesity medication act centrally to increase satiety and/or to reduce hunger and food cravings, with the aim being to counteract these adaptive responses via multiple pathways.[10,11]

IN WHOM SHOULD OBESITY MEDICATIONS BE INITIATED?

In Singapore, the use of obesity medications is recommended for those with a body-mass index (BMI) of ≥30 kg/m^2 or BMI ≥27 kg/m^2 in the presence of at least one ORC.[24] While the BMI cutoff appears to be the indicator for the initiation of obesity medications, a complications-centric approach assessing the severity of obesity or the extent to which obesity has impacted the patients' health should guide physicians on the need for and choice of obesity medication.[14]

Before considering the use of obesity medications, a thorough assessment to gauge the severity of obesity based on the presence and severity of ORC is warranted. The AACE/ACE Adiposity-Based Chronic Disease (ABCD) model and Edmonton Obesity Staging System can be used for this purpose.[15,25] This will guide the decision on the urgency of treatment and, if ORC are present, how much weight loss is needed to ameliorate or prevent progression of the ORC. Therefore, in the presence of ORC, the treatment of overweight and obesity should be prioritised especially if the ORC are either not well-controlled despite maximum medical therapy (severe) or in which treatment of obesity is fundamental to its management, e.g., type 2 diabetes mellitus, dyslipidaemia, steatohepatitis (metabolic dysfunction-associated steatotic hepatitis, MASH) with fibrosis. In these patients, pharmacotherapy should be initiated early as an adjunct to ILBT to treat these moderate to severe ORC and reduce their cardiovascular risks.[15]

WHEN AND WHAT OBESITY MEDICATION TO INITIATE?

When to Initiate?

In the following situations, the initiation of obesity medications should be considered:

1. Concurrent/From the outset: Presence of ORC that are moderate or severe, especially if lifestyle and behavioural interventions alone will not achieve the weight loss required to improve the ORC (e.g., in severe OSA, MASH fibrosis).
2. Sequential: When initial lifestyle interventions implemented result in inadequate weight loss to achieve improvement or resolution of ORC, or greater weight loss is desired to meet patient's goals.
3. Weight regain after lifestyle interventions.
4. Weight regain or inadequate weight loss after bariatric surgery.

There are often differing opinions on the optimal timing of initiation of obesity medications. However, it has been shown that early weight reduction is a key predictor of long-term weight loss success. For this reason, the initiation of adjunctive treatments or intensification of treatment should not be met with inertia.[26]

What to Initiate?

There are currently five obesity medications approved for the adjunctive treatment of obesity in Singapore: Phentermine, approved for short-term use; and orlistat, phentermine, liraglutide 3.0 mg, naltrexone/buproprion ER, and subcutaneous semaglutide 2.4 mg approved for long-term use. Weight loss of 3–13 percent over placebo can be seen with these obesity medications.[10,11,27-29] As in any chronic disease, the ultimate choice of obesity medication needs to take into consideration the cost (affordability) of the medication(s), contraindications for use, weight loss efficacy and additional benefits of the medication (in treating ORC), patient's phenotype (e.g., tendency for cravings, poor satiety), and most importantly, the patient's choice and preference including on mode of administration (e.g., oral vs parenteral).

Orlistat

Orlistat is a gastrointestinal lipase inhibitor administered as 120 mg TDS prior to meals, which reduces intestinal dietary fat absorption by 30 percent. It is one of two medications approved for use in adolescents in Singapore. It is also the most well-studied obesity medication approved with the longest study duration (of four years). Due to its safety record, it is available in some countries over the counter, administered as 60 mg TDS.[27]

Its effect on weight loss is modest albeit significant with weight loss of 3.4 kg (3.1 percent) and 3.6 kg (3.3 percent) over placebo at 12 and 24 months respectively. Of note, in the XENDOS study, which saw a weight loss of 2.7 kg (2.4 percent) over placebo maintained over four years, there was a significant risk reduction of nearly 40 percent in DM development.[30]

Despite having the longest safety profile, its use is often limited by the common undesirable side effects of steatorrhea, faecal urgency, and oil spotting. Long-term use can result in deficiencies in fat-soluble vitamins, hence supplementation with a multivitamin is recommended. Patients should be warned of drug interactions with warfarin, anti-epileptics, cyclosporine, and levothyroxine with proper administration advised.[10,11]

Phentermine

An amphetamine-derivative deemed to have low potential for abuse, phentermine is a sympathomimetic agent that acts centrally in the hypothalamus to stimulate release of norepinephrine. Approved in the US in 1959 for short-term use (≤12 weeks), it is the most commonly prescribed obesity medication in the US. In Singapore, phentermine is available as 15 mg and 30 mg once daily and is approved for short-term use of up to 6–12 months.[24] It should be initiated at the lowest possible dose and increased for efficacy as needed to minimise its side effects.[31,32]

Most studies of phentermine are carried out for 12–28 weeks. At a dosage of 15 mg/day, total weight loss of 6.1 percent (or 4.4 percent above placebo) can be seen while total weight loss of 6.3–8.1 kg (~4-6 kg above placebo) can be expected with 30 mg/day.[11,31] A 36-week study showed that intermittent (alternate month) use of phentermine is as effective as continuous use of phentermine. When used in conjunction with a low-calorie diet (1,000 kcal/day), total weight loss of ~13 kg was seen, although the very high attrition rate of ~40 percent could have augmented its effect.[33]

Common side effects include palpitations, dry mouth, insomnia, and constipation. Phentermine can increase nervousness and should be avoided in those with anxiety disorder. Increases in blood pressure and heart rate observed with phentermine use may have implications for adverse cardiovascular effects in the long term. However, to date, there are no long-term cardiovascular outcome studies for obesity medication used in patients with obesity. Using electronic health record data of a cohort of nearly 14,000 adults who have used phentermine in several US health systems, it was observed that off-label use of phentermine of more than three months in patients with low risk of cardiovascular disease (CVD) was associated with greater weight loss without increased risk of incident CVD or death, up to three years after initiating phentermine.[34] In general, phentermine as monotherapy is still restricted to short-term use with need to closely monitor the blood pressure and heart rates and it is contraindicated in those with uncontrolled hypertension, active cardiovascular disease, and glaucoma.[15,32]

Liraglutide

AAn injectable glucagon-like peptide-1 receptor agonist (GLP1-RA), liraglutide enhances satiety and reduces appetite. Liraglutide is initiated at 0.6 mg daily with weekly dose escalation of 0.6 mg/day as tolerated. It was initially approved for the treatment of T2DM at doses of up to 1.8 mg daily. Used for the treatment of obesity, it can be titrated up to a maximum dose of 3.0 mg daily.[35] In December 2020, the US FDA approved liraglutide for the treatment of obesity in adolescents.

Weight loss of 6–8 percent (4–5.6 percent over placebo) at one year is seen[35,36] and this can be maintained up to three years with continued use,[37] with weight loss ≥10 percent occurring in up to 25 percent of individuals on liraglutide 3 mg/day.[35] When used as an adjunct to ILBT or used after a 12-week course of very-low calorie diets, liraglutide can result in total weight loss of up to 12 percent (6 percent over placebo) in one year.[18,38] Such adjunctive treatments are feasible in the primary care setting (total weight loss of 7.5 percent in one year).[39] Increasing liraglutide from

1.8 mg/day to 3.0 mg/day in a person with diabetes will provide additional weight loss without further lowering the HbA1c.[36]

Although an increase in heart rate of 2–3 bpm over placebo is associated with liraglutide, when used in people with T2DM at a maximum of 1.8 mg/day, liraglutide was shown to reduce cardiovascular risk in individuals with T2DM in the LEADER trial.[40] Gastrointestinal side effects (most commonly nausea, vomiting, and diarrhoea) can occur in up to 65 percent of people using liraglutide for weight loss but these are usually mild and improve with time.[35] There is a potential risk of pancreatitis and medullary thyroid cancer though in clinical trials of longer duration, the risk of gallbladder disease was of a greater concern.[37]

In general, when weight loss is <4 percent after 16 weeks from initiation, cessation should be considered. In clinical practice, maximally tolerated doses should be used and monitored for effect for at least 12 weeks before considering stopping the medication.[10]

Naltrexone/Bupropion ER

Commonly known as CONTRAVE, the combination of naltrexone, an opoid antagonist, and bupropion, inhibitor of the neuronal reuptake of dopamine and norepinephrine, was approved for the treatment of obesity by the FDA in 2014 and by the Health Science Authorities in Singapore in January 2022. Formulated as an extended-release tablet, each tablet contains 8 mg naltrexone and 90 mg bupropion, titrated weekly to a maximum dose of 32 mg/360 mg (two tablets twice) daily. Although the exact mechanisms leading to weight loss are not fully understood, the central effect of naltrexone and bupropion on appetite regulatory centre (hypothalamus) and the reward system (mesolimbic dopamine circuit) can lead to appetite suppression and reduction in food cravings.[11,15]

At one year of treatment, weight loss of 4.2–5.2 percent above placebo is seen.[40] The most common side effects associated with naltrexone/bupropion are nausea, constipation, headache, vomiting, dizziness, insomnia, anxiety, dry mouth, and diarrhea.[40,41] The use of naltrexone/bupropion is contraindicated in pregnancy, uncontrolled hypertension, those with a past and current history of seizures (buproprion reduces seizure threshold), bulimia or anorexia nervosa, severe depression, chronic opioid use, and acute alcohol and substance withdrawal. Caution is needed for use in those with a history of depression, anxiety, bipolar disorder, and migraines, with special assessment for suicidal ideation during use. The safety of naltrexone/bupropion has not been studied in those with cardiovascular disease and with its impact on blood pressure and heart rate, patients should be closely monitored for increase in these two parameters after initiation.[15,32]

Semaglutide 2.4 mg

SSemaglutide is a once-weekly subcutaneous GLP1-RA approved for the long-term treatment of obesity and T2DM. At a dose of 2.4 mg weekly, semaglutide can result in placebo-substracted average weight loss of 12.4 percent at 68 weeks in people with obesity without T2DM28 with maintenance of the weight loss (12.6 percent above placebo) up to 104 weeks after initiation. In people with T2DM, a mean total weight loss of ~10 percent at 68 weeks is observed.[43] At present, oral semaglutide (up to 14 mg once daily) is approved only for the treatment of type 2 diabetes mellitus in Singapore although a recent study of oral semaglutide 50 mg once daily in the OASIS 1 study resulted in 15.1 percent weight loss at 68 weeks, with 85 percent of subjects losing ≥5 percent of body weight.44 The side effects of semaglutide are similar to that seen in liraglutide 3.0 mg with caution to monitor for suicidal behaviour, gastroparesis, pancreatitis, and ileus.[29]

Semaglutide 2.4 mg once weekly is the first obesity medication shown to confer cardiovascular benefits in patients with obesity (without diabetes). The SELECT cardiovascular outcome trial followed 17,604 patients who were overweight or obese with established cardiovascular disease and no history of diabetes over a period of five years.[45] Treatment with semaglutide 2.4 mg was associated with a statistically significant 20 percent reduction in major adverse cardiovascular events (MACE), defined as cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke compared with placebo. In a separate RCT, the STEP-HFpEF trial, patients with heart failure with preserved ejection fraction (HFpEF) and obesity who were treated with semaglutide 2.4 mg experienced greater (10.7 percent) weight loss, larger reductions in heart failure symptoms and physical limitations, and greater improvements in exercise function than placebo.[46] In a recent RCT of biopsy-proven metabolic dysfunction-associated steatohepatitis (MASH) and liver fibrosis (ESSENCE trial), 72-week treatment with semaglutide 2.4 mg compared to placebo resulted in greater resolution of MASH (62.9 percent vs 34.1 percent) and improvement in fibrosis (37 percent vs 22.5 percent).[47,48] This was on a background of significant body weight reduction of 10.5 percent with semaglutide compared to 2 percent with placebo, demonstrating a weight-independent effect of semaglutide on MASH and MASH fibrosis.

There is also emerging data on the benefits of semaglutide beyond weight loss including in cognitive impairment (dementia), psoriatic arthritis, and possibly in (substance) addictions, although more rigorous trials are still needed to demonstrate its full clinical efficacy in treating these specific conditions.

Combination Treatments

In Singapore, the fixed combination drugs of phentermine/topiramate-ER is neither available nor approved for use and will not be discussed here. Combination therapy of orlistat, phentermine, and liraglutide and other approved obesity medications has not been well-studied and should not be considered as routine clinical practice.[27]

WHEN TO STOP OBESITY MEDICATIONS?

Obesity medications should be stopped if weight loss of 4–5 percent is not attained after 12–16 weeks on the highest-tolerated dose.[10] Obesity is a chronic disease, with a relapsing nature due to biological reasons as discussed above. As with other chronic diseases like hypertension and T2DM, pharmacotherapy should not be planned only for the short term (1–3 months) but for chronic weight management and/or control of ORC. Just because the parameters are controlled in chronic diseases does not imply that treatment needs to be stopped. The goal of therapy is for the long term, to prevent weight regain or weight maintenance and prevent/manage the ORC. Hence if an obesity medication is efficacious, long-term use at the lowest and safest possible doses should be considered, particularly to maintain the weight loss.

OBESITY MEDICATIONS ON THE HORIZON

A deeper understanding of the role of gut-based and nutrient-stimulated hormones in the regulation of appetite and energy homeostasis, and the metabolism of glucose and lipids, has led to the development of targeted therapeutics in obesity and T2DM. Many analogues of these hormones have either been approved for use in T2DM treatment or have undergone phase II trial or undergoing phase III evaluation for the treatment of obesity and ORC including for MASLD, T2D, OSA, and HFpEF.

Tirzepatide is a dual agonist of GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) administered as a once-weekly subcutaneous injection, which has been approved in Singapore for the treatment of T2DM and also for the chronic treatment of obesity in the USA in 2023. A 72-week RCT in participants with obesity without T2DM (SURMOUNT-1) showed a weight loss of 20.9 percent with the highest dose (15 mg) of tirzepatide versus 3.1 percent with placebo.[49] Most common adverse events observed are mostly mild to moderate and transient gastrointestinal symptoms. In the SURMOUNT series of trials, tirzepatide has not only been shown to be a potent weight loss medication across different patient populations and clinical settings, it has displayed significant benefit in the improvement of ORC such as OSA (SURMOUNT-OSA trial)[50] and in HFpEF (SUMMIT Trial),[51] once again demonstrating the potential therapeutic benefits of novel incretin-based therapies beyond weight loss.

In a 32-week phase 2 trial in adults with T2DM and a BMI ≥27kg/m^2, co-administration of once-weekly subcutaneous cagrilintide 2.4 mg, an amylin analougue, and semaglutide 2.4 mg (CagriSema), was shown to be more efficacious in reducing HbA1c (2.2 percent) compared to semaglutide 2.4 mg (1.9 percent) and cagrilintide (0.9 percent) alone. Mean weight loss at week 32 was also significantly greater with CagriSema (15.6 percent) compared to semaglutide (5.1 percent) and cagrilintide (8.1 percent),[52] with a potential for weight loss exceeding 20 percent if continued longer. A series of phase 3 trials with CagriSema (known as the REDEFINE Programme) will evaluate its impact on weight loss in a larger patient population with overweight and obesity, with or without T2DM, over a longer period of time.

Retatrutide, a single-molecule triple-hormone (GLP1, GIP, glucagon) receptor agonist administered subcutaneously once weekly, demonstrated an average 2–2.2 percent reduction in HbA1c at 24 weeks and a mean 16–17 percent reduction in body weight (with its highest dose, 12 mg) at 32–36 weeks in those with obesity and T2DM.[53] In people with obesity and without T2DM, the highest dose of retatrutide resulted in a mean 24 percent reduction in body weight, with 83 percent of participants achieving a weight loss of 15 percent or more, and 26 percent of participants achieving a weight loss of 30 percent or more after 48 weeks of treatment.[54] Improvements in blood pressure resulted in discontinuation of at least one antihypertensive medication in 30–41 percent of the participants using the higher doses (8 and 12 mg). In a prespecified subgroup analysis of the same cohort of patients at 24 weeks, the higher two doses (8 and 12 mg) of retatrutide produced complete resolution of hepatic steatosis in 79 percent and 86 percent of participants respectively, with a similar percentage of liver fat reduction in the same period.[55] The TRIUMPH Programme, a series of phase 3 trials, will examine retatrutide in chronic weight management, obstructive sleep apnoea, and knee osteoarthritis in people with overweight and obesity.

Survodutide, a GLP-1/glucagon receptor dual-agonist, has shown promising results in people with biopsy-proven MASH and fibrosis stage F1 through F3. After 48 weeks of treatment, 75 percent of participants treated with survodutide experienced resolution of MASH with no worsening of fibrosis compared with 15 percent of patients on placebo. At the highest dose of survodutide (6.0 mg), two-thirds of patients showed evidence of fibrosis regression (based on available biopsy data) within 48 weeks.[56]

AMG133 (maridebart cafraglutide), which combines GLP1 agonism with GIP antagonism, has shown promising results after 12 weeks of a 4-weekly injection regime. Weight loss ranged from 7.2 percent at the lowest dose to 14.5 percent at the highest dose by day 85, with weight maintained even 150 days after the last dose.[57]

Although once-weekly administration of incretin-based therapies is efficacious in the treatment of T2DM and obesity, injections may serve as a barrier to treatment uptake. The once-daily oral formulation of semaglutide, approved for the treatment of T2D, requires strict administration due to the use of an absorption enhancer to enable absorption in the stomach, which may serve to be cumbersome for some patients. Further development of oral and non-peptide formulations will serve to overcome these barriers somewhat and hopefully improve uptake. In a phase 2 trial in overweight and obesity without T2DM, over 36 weeks, Orfloglipron, an oral non-peptide small molecule potent partial agonist of the GLP-1 receptor administered once-daily, resulted in mean weight loss of 9.4 to 14.7 percent

(across the different doses) compared to 2.3 percent with placebo, with nearly 50 percent of participants losing ≥15 percent body weight.[58] Several other oral GLP-1 receptor agnoists are currently under investigation in phase 1 and 2 trials such as GSBR-1290 and ecnoglutide (XW004).

VK2735 is a dual agonist of GLP and GIP receptors currently under investigation. In a 28-day phase 1 multiple ascending dose study, subjects on the oral formulation of VK2735 had dose-dependent body weight reductions, ranging up to 5.3 percent.[59] Oral amycretin, a novel protein-based unimolecular amylin combined with a GLP1-RA, showed promising results with a mean weight loss of 13.1 percent after 12 weeks of treatment on its twice-daily dosage compared with placebo (1.1 percent) in a phase 1 study.[60]

There are many more compounds such as oxyntomodulin with dual GLP-1 and glucacon receptor agonism, and PYY agonists that have either shown promising weight loss results or are still undergoing phase 1 or 2 studies, potentially offering patients with obesity a wider armamentarium of treatment options.

However, with obesity medications now able to result in magnitude of non-surgical weight loss, it must be cautioned that the fundamentals of obesity management comprising of lifestyle and behavioural modification and holistic care remain unchanged. Monitoring for the side effects of medications and the risk of malnutrition and sarcopenia will need to be concurrently carried out by adequately trained healthcare professionals experienced in the management of obesity.

CONCLUSION

The use of obesity medications is pivotal as an adjunct to lifestyle and behavioural therapy to augment the effect of weight loss needed to treat obesity and its ORC. Newer obesity medications can now effect weight loss of up to more than 20 percent with additional benefits on ORC. Despite the clear benefits and efficacy of obesity medication, many barriers remain in the appropriate use of pharmacotherapy in obesity treatment, creating a gap. Proper physician and patient education, and improved access to affordable obesity medication can help to improve uptake of obesity medication and bridge these gaps. Regardless of choice of obesity medication, the management of obesity must be in the context of a chronic disease, under the supervision of trained healthcare professionals of multi-disciplines to concurrently address the multiple facets of obesity.

Table 1. Efficacy, usage, common side effects, contraindications, and precautions to be considered with the obesity medication approved for long-term use.[15,29]

Obesity pharmacotherapy, indication/use[a]	Mechanism of action, study name, study duration: % TBWL greater than placebo or mean kg weight loss over placebo	Dose	Common side effects	Contraindications, cautions, and safety concerns	Monitoring and comments
Orlistat Chronic weight management FDA-approved for children ≥12 years old	Lipase inhibitor XENDOS **1 year: 4.0%** **4 years: 2.6%**	120 mg PO TID (before meals) OTC: 60 mg PO TID (before meals)	• Steatorrhea • Fecal urgency • Incontinence • Flatulence • Oily spotting • Frequent bowel movements • Abdominal pain • Headache	✓ Pregnancy and breastfeeding ✓ Chronic malabsorption syndrome ✓ Cholestasis ✓ Oxalate nephrolithiasis • Rare severe liver injury • Cholelithiasis • Malabsorption of fat-soluble vitamins • Effects on other medications: - Warfarin (enhance) - Anti-epileptics (decrease) - Levothyroxine (decrease) - Cyclosporine (decrease)	**Monitor for:** • Cholelithiasis • Nephrolithiasis - Recommend standard multivitamin (to include vitamins A, D, E, and K) at bedtime or 2 hours after orlistat dose - Eating >30% kcal from fat results in greater GI side effects - Administer levothyroxine and orlistat 4 hours apart
Phentermine Short-term use (<12 weeks) for the management of obesity	NE-releasing agent **2-24 weeks: 3.6 kg**	15–37.5 mg (HCl) PO once daily 15–30 mg (ion-exchange resin complex) PO once daily	• Headache, elevated BP, elevated HR, insomnia, dry mouth, constipation, anxiety • Cardiovascular: palpitation, tachycardia, elevated BP, ischemic events • Central nervous system: overstimulation, restlessness, dizziness, insomnia, euphoria, dysphoria, tremor, headache, psychosis • GI: dryness of the mouth, unpleasant taste, diarrhea, constipation, other GI disturbances • Allergic: urticaria • Endocrine: impotence, changes in libido	• Anxiety disorders (agitated states) • History of heart disease, uncontrolled hypertension • Seizure • MAOIs • Pregnancy and breastfeeding • Hyperthyroidism • Glaucoma • History of drug abuse • Sympathomimetic amines	• Long-term use may lead to pharmacological tolerance, dependence, and withdrawal symptoms

Phentermine/topiramate ER Chronic weight management FDA-approved for adolescents ≥12 years	NE-releasing agent (phentermine) GABA receptor modulation (topiramate) EQUIP CONQUER SEQUEL **1 year: 8.6–9.3% on high dose; 6.6% on treatment dose** **2 years: 8.7% on high dose; 7.5% on treatment dose**	**Starting dose:** 3.75/23 mg PO QD for 2 weeks **Recommended dose:** 7.5/46 mg PO QD **Escalation dose:** 11.25/69 mg PO QD **Maximum dose:** 15/92 mg PO QD	• Headache • Paresthesia • Insomnia • Decreased bicarbonate • Xerostomia • Constipation • Nasopharyngitis • Anxiety • Depression • Cognitive impairment (concentration and memory) • Dizziness • Nausea • Dysgeusia	✓ Pregnancy and breastfeeding (topiramate teratogenicity) ✓ Hyperthyroidism ✓ Acute angle-closure glaucoma ✓ Concomitant MAOI use (within 14 days) • Tachyarrhythmia • Decreased cognition • Seizure disorder • Anxiety and panic attacks • Nephrolithiasis • Hyperchloremic metabolic acidosis • Dose adjustment with hepatic or renal impairment • Concern for abuse potential • Combined use with alcohol or depressant drugs can worsen cognitive impairment	**Monitor for:** • Increased heart rate • Depressive symptomatology or worsening depression especially on maximum dose • Hypokalaemia (especially with HCTZ or furosemide) • Acute myopia and/or ocular pain • Acute kidney stone formation • Hypoglycaemia in patients having T2DM treated with insulin and/or sulfonylureas - Potential for lactic acidosis (hyperchloremic non-anion gap) in combination with metformin - MAOI (allow ≥14 days between discontinuation) - 15 mg/92 mg dose should not be discontinued abruptly (increased risk of seizure); taper over at least 1 week - Healthcare professional should check βHCG before initiating, followed by monthly self-testing at home - Monitor electrolytes and creatinine before and during treatment - Can cause menstrual spotting in women taking birth control pills owing to altered metabolism of estrogen and progestins

Naltrexone ER/bupropion ER Chronic weight management	Opiate antagonist (naltrexone) Reuptake inhibitor of DA and NE (bupropion) COR-I COR-II COR-BMOD **1 year: 4.2–5.2%**	**Titrate dose:** **Week 1:** 1 tab (8/90 mg) PO QAM **Week 2:** 1 tab (8/90 mg) PO BID **Week 3:** 2 tabs (total 16/180 mg) PO QAM and 1 tab 8/90 mg) PO QHS **Week 4:** 2 tabs (total 16/180 mg) PO QHS	• Nausea • Headache • Insomnia • Vomiting • Constipation • Diarrhoea • Dizziness • Anxiety • Xerostomia	✓ Pregnancy and breastfeeding ✓ Uncontrolled hypertension ✓ Seizure disorder ✓ Anorexia nervosa ✓ Bulimia nervosa ✓ Severe depression ✓ Drug or alcohol withdrawal ✓ Concomitant MAOI (within 14 days) ✓ Chronic opioid use • Cardiac arrhythmia • Dose adjustment for liver or kidney impairment • Narrow-angle glaucoma • Uncontrolled migraine disorder • Generalized anxiety disorder • Bipolar disorder • Safety data lacking in patients who have depression • Seizures (bupropion lowers seizure threshold	**Monitor for:** • Increased heart rate and blood pressure • Worsening depression or suicidal ideation • Worsening of migraines • Liver injury (naltrexone) • Hypoglycemia in patients having T2DM treated with insulin and/or sulfonylureas • Seizures (bupropion lowers seizure threshold) - MAOI (allow ≥14 days between discontinuation) - Dose adjustment for patients with renal and hepatic impairment - Avoid taking medication with a high-fat meal - Can cause false positive urine test for amphetamine - Bupropion inhibits CYP2D6
Liraglutide 3.0 mg Chronic weight management FDA-approved for adolescents ≥12 years	GLP-1 receptor analogue SCALE Obesity & Prediabetes **1 year: 5.6%** **3 years: 4.3%**	**Titrate dose weekly by 0.6 mg as tolerated by patient (side effects):** 0.6 mg SC QD→ 1.2 mg SC QD→ 1.8 mg SC QD→ 2.4 mg SC QD→ 3.0 mg SC QD	• Nausea • Vomiting • Diarrhea • Constipation • Headache • Dyspepsia • Increased heart rate	✓ Pregnancy and breastfeeding ✓ Personal or family history of medullary thyroid cancer or MEN2 ✓ Pancreatitis ✓ Acute gallbladder disease • Gastroparesis • Severe renal impairment can result from vomiting and dehydration • Use caution in patients with history of pancreatitis • Use caution in patients with cholelithiasis • Suicidal ideation and behaviour • Injection site reactions	**Monitor for:** • Pancreatitis • Cholelithiasis and cholecystitis • Hypoglycemia in patients having T2DM treated with insulin and/or sulfonylureas • Increased heart rate • Dehydration from nausea/vomiting • Injection site reactions - Titrate dose based on tolerability (nausea and GI side effects)

Semaglutide 2.4 mg 73,169,273-275 Chronic weight management	GLP-1 receptor analogue STEP Obesity Adults without T2DM **68 weeks: 10.3–12.4%** **104 weeks: 12.6%** Adults with T2DM **68 weeks: 6.2%**	**Titrate dose every 4 weeks as tolerated by patient (side effects):** 0.25 mg SC QD→ 0.5 mg SC QD→ 1.0 mg SC QD→ 1.7 mg SC QD→ 2.4 mg SC QD	• Nausea • Vomiting • Diarrhea • Constipation • Headache • Fatigue • Dyspepsia • Dizziness • Abdominal distension • Eructation • Gastroenteritis • Gastroesophageal reflux disease	✓ Pregnancy and breastfeeding ✓ Personal or family history of medullary thyroid cancer or MEN2 ✓ Pancreatitis ✓ Acute gallbladder disease • Gastroparesis • Ileus • Severe renal impairment can result from vomiting and dehydration • Use caution in patients with history of pancreatitis • Use caution in patients with cholelithiasis • Suicidal ideation and behaviour • Injection site reactions	**Monitor for:** • Pancreatitis • Cholelithiasis and cholecystitis • Hypoglycaemia in patients having T2DM treated with insulin and/or sulfonylureas • Diabetic retinopathy in patients with T2DM • Increased heart rate • Dehydration from nausea/vomiting • Injection site reactions • Ileus • Titrate dose based on tolerability (nausea and GI side effects)

Adapted from the AACE/ACE Comprehensive Clinical Practice Guidelines for Medical Care of Patients with Obesity[15] and Obesity in South and Southeast Asia—A new consensus on care and management[29]

REFERENCES

1. World Obesity Federation, World Obesity Atlas 2023. https://data.worldobesity.org/publications/?cat=19. Accessed 1 Sep 2023.
2. Allison DB, Downey M, Atkinson RL, et al. Obesity as a disease: a white paper on evidence and arguments commissioned by the Council of the Obesity Society. Obesity (Silver Spring). 2008 Jun;16(6):1161-77. doi: 10.1038/oby.2008.231. Epub 2008 May 8. PMID: 18464753.
3. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. World Health Organ Tech Rep Ser. 2000;894:i-xii, 1-253. PMID: 11234459.
4. Bray GA, Kim KK, Wilding JPH; World Obesity Federation. Obesity: a chronic relapsing progressive disease process. A position statement of the World Obesity Federation. Obes Rev. 2017 Jul;18(7):715-723. doi: 10.1111/obr.12551. Epub 2017 May 10. PMID: 28489290.
5. Schwartz MW, Seeley RJ, Zeltser LM, et al. Obesity Pathogenesis: An Endocrine Society Scientific Statement. Endocr Rev. 2017 Aug 1;38(4):267-296. doi: 10.1210/er.2017-00111. PMID: 28898979; PMCID: PMC5546881.
6. Heymsfield SB, Wadden TA. Mechanisms, Pathophysiology, and Management of Obesity. N Engl J Med. 2017 Jan 19;376(3):254-266. doi: 10.1056/NEJMra1514009. PMID: 28099824.
7. 7. Zhang S, Manne S, Lin J, Yang J. Characteristics of patients potentially eligible for pharmacotherapy for weight loss in primary care practice in the United States. Obes Sci Pract. 2016 Jun;2(2):104-114. doi: 10.1002/osp4.46. Epub 2016 May 26. PMID: 27840686; PMCID: PMC5089644.
8. Thomas CE, Mauer EA, Shukla AP, Rathi S, Aronne LJ. Low adoption of weight loss medications: A comparison of prescribing patterns of anti-obesity pharmacotherapies and SGLT2s. Obesity (Silver Spring). 2016 Sep;24(9):1955-61. doi: 10.1002/oby.21533. PMID: 27569120; PMCID: PMC5669035.
9. Lee PC, Ganguly S, Tan HC, et al. Attitudes and perceptions of the general public on obesity and its treatment options in Singapore. Obes Res Clin Pract. 2019 Jul-Aug;13(4):404-407. doi: 10.1016/j.orcp.2019.03.007. Epub 2019 Apr 8. PMID: 30975589.
10. Bessesen DH, Van Gaal LF. Progress and challenges in anti-obesity pharmacotherapy. Lancet Diabetes Endocrinol. 2018 Mar;6(3):237-248. doi: 10.1016/S2213-8587(17)30236-X. Epub 2017 Sep 14. PMID: 28919062.
11. Gadde KM, Apolzan JW, Berthoud HR. Pharmacotherapy for Patients with Obesity. Clin Chem. 2018 Jan;64(1):118-129. doi: 10.1373/clinchem.2017.272815. Epub 2017 Oct 20. PMID: 29054924; PMCID: PMC7379842.
12. Rubino F, Puhl RM, Cummings DE, et al. Joint international consensus statement for ending stigma of obesity. Nat Med. 2020 Apr;26(4):485-497. doi: 10.1038/s41591-020-0803-x. Epub 2020 Mar 4. PMID: 32127716; PMCID: PMC7154011.
13. Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med. 2002 Feb 7;346(6):393-403. doi: 10.1056/NEJMoa012512. PMID: 11832527; PMCID: PMC1370926.
14. 14. Wing RR, Lang W, Wadden TA, et al. Benefits of modest weight loss in improving cardiovascular risk factors in overweight and obese individuals with type 2 diabetes. Diabetes Care. 2011 Jul;34(7):1481-6. doi: 10.2337/dc10-2415. Epub 2011 May 18. PMID: 21593294; PMCID: PMC3120182.
15. Garvey WT, Mechanick JI, Brett EM, et al. AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY COMPREHENSIVE CLINICAL PRACTICE GUIDELINES FOR MEDICAL CARE OF PATIENTS WITH OBESITY. Endocr Pract. 2016 Jul;22 Suppl 3:1-203. doi: 10.4158/EP161365.GL. Epub 2016 May 24. PMID: 27219496.
16. Aminian A, Zajichek A, Arterburn DE, et al. Association of Metabolic Surgery With Major Adverse Cardiovascular Outcomes in Patients With Type 2 Diabetes and Obesity. JAMA. 2019 Sep 2;322(13):1271–82. doi: 10.1001/jama.2019.14231. Epub ahead of print. PMID: 31475297; PMCID: PMC6724187.
17. Sjöström L, Peltonen M, Jacobson P, et al. Bariatric surgery and long-term cardiovascular events. JAMA. 2012 Jan 4;307(1):56-65. doi: 10.1001/jama.2011.1914. PMID: 22215166.
18. Wadden TA, Walsh OA, Berkowitz RI, et al. Intensive Behavioral Therapy for Obesity Combined with Liraglutide 3.0 mg: A Randomized Controlled Trial. Obesity (Silver Spring). 2019 Jan;27(1):75-86. doi: 10.1002/oby.22359. Epub 2018 Nov 13. PMID: 30421856; PMCID: PMC6800068.
19. Look AHEAD Research Group. Eight-year weight losses with an intensive lifestyle intervention: the look AHEAD study. Obesity (Silver Spring). 2014 Jan;22(1):5-13. doi: 10.1002/oby.20662. PMID: 24307184; PMCID: PMC3904491.
20. Kuk JL, Wharton S. Differences in weight change trajectory patterns in a publicly funded adult weight management centre. Obes Sci Pract. 2016 Mar 23;2(2):215-223. doi: 10.1002/osp4.35. PMID: 29071099; PMCID: PMC5523699.
21. Wadden TA, Bailey TS, Billings LK, et al. Effect of Subcutaneous Semaglutide vs Placebo as an Adjunct to Intensive Behavioral Therapy on Body Weight in Adults With Overweight or Obesity: The STEP 3 Randomized Clinical Trial. JAMA. 2021 Feb 24:e211831. doi: 10.1001/jama.2021.1831. Epub ahead of print. PMID: 33625476; PMCID: PMC7905697.
22. Sumithran P, Proietto J. The defence of body weight: a physiological basis for weight regain after weight loss. Clin Sci (Lond). 2013 Feb;124(4):231-41. doi: 10.1042/CS20120223. PMID: 23126426.
23. Fothergill E, Guo J, Howard L, et al. Persistent metabolic adaptation 6 years after "The Biggest Loser" competition. Obesity (Silver Spring). 2016 Aug;24(8):1612-9. doi: 10.1002/oby.21538. Epub 2016 May 2. PMID: 27136388; PMCID: PMC4989512.
24. Lee YS, Biddle S, Chan MF, et al. Health Promotion Board-Ministry of Health Clinical Practice Guidelines: Obesity. Singapore Med J. 2016 Jun;57(6):292-300. doi: 10.11622/smedj.2016103. PMID: 27353244; PMCID: PMC4971447.
25. Padwal RS, Pajewski NM, Allison DB, Sharma AM. Using the Edmonton obesity staging system to predict mortality in a population-representative cohort of people with overweight and obesity. CMAJ. 2011 Oct 4;183(14):E1059-66. doi: 10.1503/cmaj.110387. Epub 2011 Aug 15. PMID: 21844111; PMCID: PMC3185097.
26. Kheniser K, Saxon DR, Kashyap SR. Long-term weight loss strategies for obesity. J Clin Endocrinol Metab. 2021 Feb 17:dgab091. doi: 10.1210/clinem/dgab091. Epub ahead of print. PMID: 33595666.
27. Yanovski SZ, Yanovski JA. Long-term drug treatment for obesity: a systematic and clinical review. JAMA. 2014 Jan 1;311(1):74-86. doi: 10.1001/jama.2013.281361. PMID: 24231879; PMCID: PMC3928674.
28. Wilding JPH, Batterham RL, Calanna S, et al. Once-Weekly Semaglutide in Adults with Overweight or Obesity. N Engl J Med. 2021 Mar 18;384(11):989-1002. doi: 10.1056/NEJMoa2032183. Epub 2021 Feb 10. PMID: 33567185.
29. Tham KW, Abdul Ghani R, Cua SC, et al. Obesity in South and Southeast Asia-A new consensus on care and management. Obes Rev. 2023 Feb;24(2):e13520. doi: 10.1111/obr.13520. Epub 2022 Dec 1. PMID: 36453081; PMCID: PMC10078503.
30. Torgerson JS, Hauptman J, Boldrin MN, Sjöström L. XENical in the prevention of diabetes in obese subjects (XENDOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. Diabetes Care. 2004 Jan;27(1):155-61. doi: 10.2337/diacare.27.1.155. Erratum in: Diabetes Care. 2004 Mar;27(3):856. PMID: 14693982.
31. Haddock CK, Poston WS, Dill PL, Foreyt JP, Ericsson M. Pharmacotherapy for obesity: a quantitative analysis of four decades of published randomized clinical trials. Int J Obes Relat Metab Disord. 2002 Feb;26(2):262-73. doi: 10.1038/sj.ijo.0801889. PMID: 11850760.
32. Apovian CM, Aronne LJ, Bessesen DH, et al. Pharmacological management of obesity: an endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2015 Feb;100(2):342-62. doi: 10.1210/jc.2014-3415. Epub 2015 Jan 15. Erratum in: J Clin Endocrinol Metab. 2015 May;100(5):2135-6. doi: 10.1210/jc.2015-1782. PMID: 25590212.

33. Munro JF, MacCuish AC, Wilson EM, Duncan LJ. Comparison of continuous and intermittent anorectic therapy in obesity. Br Med J. 1968 Feb 10;1(5588):352-4. doi: 10.1136/bmj.1.5588.352. PMID: 15508204; PMCID: PMC1984840.
34. Lewis KH, Fischer H, Ard J, et al. Safety and Effectiveness of Longer-Term Phentermine Use: Clinical Outcomes from an Electronic Health Record Cohort. Obesity (Silver Spring). 2019 Apr;27(4):591-602. doi: 10.1002/oby.22430. PMID: 30900410.
35. Pi-Sunyer X, Astrup A, Fujioka K, et al. A Randomized, Controlled Trial of 3.0 mg of Liraglutide in Weight Management. N Engl J Med. 2015 Jul 2;373(1):11-22. doi: 10.1056/NEJMoa1411892. PMID: 26132939.
36. Davies MJ, Bergenstal R, Bode B, et al. Efficacy of Liraglutide for Weight Loss Among Patients With Type 2 Diabetes: The SCALE Diabetes Randomized Clinical Trial. JAMA. 2015 Aug 18;314(7):687-99. doi: 10.1001/jama.2015.9676. Erratum in: JAMA. 2016 Jan 5;315(1):90. PMID: 26284720.
37. le Roux CW, Astrup A, Fujioka K, et al. 3 years of liraglutide versus placebo for type 2 diabetes risk reduction and weight management in individuals with prediabetes: a randomised, double-blind trial. Lancet. 2017 Apr 8;389(10077):1399-1409. doi: 10.1016/S0140-6736(17)30069-7. Epub 2017 Feb 23. Erratum in: Lancet. 2017 Apr 8;389(10077):1398. PMID: 28237263.
38. Wadden TA, Hollander P, Klein S, et al. Weight maintenance and additional weight loss with liraglutide after low-calorie-diet-induced weight loss: the SCALE Maintenance randomized study. Int J Obes (Lond). 2013 Nov;37(11):1443-51. doi: 10.1038/ijo.2013.120. Epub 2013 Jul 1. Erratum in: Int J Obes (Lond). 2013 Nov;37(11):1514. Erratum in: Int J Obes (Lond). 2015 Jan;39(1):187. PMID: 23812094.
39. Wadden TA, Tronieri JS, Sugimoto D, et al. Liraglutide 3.0 mg and Intensive Behavioral Therapy (IBT) for Obesity in Primary Care: The SCALE IBT Randomized Controlled Trial. Obesity (Silver Spring). 2020 Mar;28(3):529-536. doi: 10.1002/oby.22726. PMID: 32090517; PMCID: PMC7065111.
40. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2016 Jul 28;375(4):311-22. doi: 10.1056/NEJMoa1603827. Epub 2016 Jun 13. PMID: 27295427; PMCID: PMC4985288.
41. Apovian CM, Aronne L, Rubino D, et al. A randomized, phase 3 trial of naltrexone SR/bupropion SR on weight and obesity-related risk factors (COR-II). Obesity (Silver Spring). 2013 May;21(5):935-43. doi: 10.1002/oby.20309. PMID: 23408728; PMCID: PMC3739931.
42. Wadden TA, et al. COR-BMOD Obesity (Silver Spring) 2011;19:110-20
43. Davies M, Færch L, Jeppesen OK, et al. Semaglutide 2·4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): a randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial. Lancet. 2021 Mar 13;397(10278):971-984. doi: 10.1016/S0140-6736(21)00213-0. Epub 2021 Mar 2. PMID: 33667417.
44. Knop FK, Aroda VR, do Vale RD, et al. Oral semaglutide 50 mg taken once per day in adults with overweight or obesity (OASIS 1): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2023 Aug 26;402(10403):705-719. doi: 10.1016/S0140-6736(23)01185-6. Epub 2023 Jun 26. PMID: 37385278.
45. Lincoff AM, Brown-Frandsen K, Colhoun HM, et al. Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes. N Engl J Med. 2023 Dec 14;389(24):2221-2232. doi: 10.1056/NEJMoa2307563. Epub 2023 Nov 11. PMID: 37952131.
46. Kosiborod MN, Abildstrøm SZ, Borlaug BA, et al. Semaglutide in Patients with Heart Failure with Preserved Ejection Fraction and Obesity. N Engl J Med. 2023 Sep 21;389(12):1069-1084. doi: 10.1056/NEJMoa2306963. Epub 2023 Aug 25. PMID: 37622681.
47. Newsome PN, Sanyal AJ, Engebretsen KA, et al. Semaglutide 2.4 mg in Participants With Metabolic Dysfunction-Associated Steatohepatitis: Baseline Characteristics and Design of the Phase 3 ESSENCE Trial. Aliment Pharmacol Ther. 2024 Dec;60(11-12):1525-1533. doi: 10.1111/apt.18331. Epub 2024 Oct 16. PMID: 39412509; PMCID: PMC11599791.
48. Newsome PN, Sanyal AJ, Engebretsen KA, et al. Semaglutide 2.4 mg in Participants With Metabolic Dysfunction-Associated Steatohepatitis: Baseline Characteristics and Design of the Phase 3 ESSENCE Trial. Aliment Pharmacol Ther. 2024 Dec;60(11-12):1525-1533. doi: 10.1111/apt.18331. Epub 2024 Oct 16. PMID: 39412509; PMCID: PMC11599791.
49. Jastreboff AM, Aronne LJ, Ahmad NN, et al. Tirzepatide Once Weekly for the Treatment of Obesity. N Engl J Med. 2022 Jul 21;387(3):205-216. doi: 10.1056/NEJMoa2206038. Epub 2022 Jun 4. PMID: 35658024.
50. Malhotra A, Grunstein RR, Fietze I, et al. Tirzepatide for the Treatment of Obstructive Sleep Apnea and Obesity. N Engl J Med. 2024 Oct 3;391(13):1193-1205. doi: 10.1056/NEJMoa2404881. Epub 2024 Jun 21. Erratum in: N Engl J Med. 2024 Oct 17;391(15):1464. doi: 10.1056/NEJMx240005. PMID: 38912654; PMCID: PMC11598664.
51. Packer M, Zile MR, Kramer CM, et al. Tirzepatide for Heart Failure with Preserved Ejection Fraction and Obesity. N Engl J Med. 2024 Nov 16. doi: 10.1056/NEJMoa2410027. Epub ahead of print. PMID: 39555826.
52. Frias JP, Deenadayalan S, Erichsen L, et al. Efficacy and safety of co-administered once-weekly cagrilintide 2·4 mg with once-weekly semaglutide 2·4 mg in type 2 diabetes: a multicentre, randomised, double-blind, active-controlled, phase 2 trial. Lancet. 2023 Aug 26;402(10403):720-730. doi: 10.1016/S0140-6736(23)01163-7. Epub 2023 Jun 23. PMID: 37364590.
53. Rosenstock J, Frias J, Jastreboff AM, et al. Retatrutide, a GIP, GLP-1 and glucagon receptor agonist, for people with type 2 diabetes: a randomised, double-blind, placebo and active-controlled, parallel-group, phase 2 trial conducted in the USA. Lancet. 2023 Aug 12;402(10401):529-544. doi: 10.1016/S0140-6736(23)01053-X. Epub 2023 Jun 26. PMID: 37385280.
54. Jastreboff AM, Kaplan LM, Frías JP, et al. Triple-Hormone-Receptor Agonist Retatrutide for Obesity - A Phase 2 Trial. N Engl J Med. 2023 Aug 10;389(6):514-526. doi: 10.1056/NEJMoa2301972. Epub 2023 Jun 26. PMID: 37366315.
55. Sanyal AJ, Kaplan LM, Frias JP, et al. Triple hormone receptor agonist retatrutide for metabolic dysfunction-associated steatotic liver disease: a randomized phase 2a trial. Nat Med. 2024 Jul;30(7):2037-2048. doi: 10.1038/s41591-024-03018-2. Epub 2024 Jun 10. PMID: 38858523; PMCID: PMC11271400.
56. Sanyal AJ, Bedossa P, Fraessdorf M, et al. A Phase 2 Randomized Trial of Survodutide in MASH and Fibrosis. N Engl J Med. 2024 Jul 25;391(4):311-319. doi: 10.1056/NEJMoa2401755. Epub 2024 Jun 7. PMID: 38847460.
57. Greenhill C. Phase 1 results for AMG 133. Nat Rev Endocrinol. 2024 Apr;20(4):193. doi: 10.1038/s41574-024-00967-z. PMID: 38388678.
58. Wharton S, Blevins T, Connery L, et al. Daily Oral GLP-1 Receptor Agonist Orforglipron for Adults with Obesity. N Engl J Med. 2023 Sep 7;389(10):877-888. doi: 10.1056/NEJMoa2302392. Epub 2023 Jun 23. PMID: 37351564.
59. https://vikingtherapeutics.com/pipeline/metabolic-disease-program/vk2735/
60. Gasiorek A. Safety, tolerability and weight reduction findings of oral amycretin: a novel amylin and glucagon-like peptide-1 receptor co-agonist, in a first-in-human study. Presented at the 60th European Association for the Study of Diabetes Annual Meeting September 2024

LEARNING POINTS

- **Pharmacotherapy in obesity management plays a crucial role as an adjunct to lifestyle and behavioural modification and metabolic bariatric surgery.**
- **Assessment of the stage/severity of obesity is a necessary initial step as more severe stages of obesity (usually in the presence of ORC) will warrant more urgent treatment with consideration of obesity medication at the outset.**
- **There are now safe and effective obesity medications approved for long-term use in obesity management with more in the pipelines. Understanding the indications, efficacy, and side-effect profile of each obesity medication along with patient phenotype and risk profile will help to match the most suitable treatment to the patient. This will improve compliance to the treatment and harness the best benefits for treating obesity and its ORC.**