Unit No. 6

USE OF PHARMACOTHERAPY IN OBESITY MANAGEMENT

Dr Tham Kwang Wei

ABSTRACT

Obesity is a chronic disease that is often relapsing and progressive due in part to the physiology of energy homeostasis in people with obesity, rendering them with the challenge of attaining adequate weight loss and weight maintenance after successful weight loss. Depending on the presence, types and severity of the obesity-related comorbidities (ORCs), some patients will require an amount of weight loss beyond what lifestyle and behavioural modification can achieve. Even after bariatric surgery, patients may not lose the expected amount of weight or experience weight regain. Anti-obesity medications may be required to support them further. Hence, the use of pharmacotherapy in obesity management remains an important adjunct to lifestyle and behavioural modifications and even to bariatric surgery, particularly in those with more severe ORCs and with a high body mass index. This article discusses the general approach to the use of pharmacotherapy in obesity management and the various anti-obesity medications currently approved.

Keywords: Obesity, anti-obesity medications, pharmacotherapy, weight loss

SFP2021; 47(5) :

INTRODUCTION

The global burden of obesity has grown substantially over the last four decades with obesity prevalence projected to rise. By 2025, about 20 percent of the world's population are estimated to be obese.[1] Obesity is now established as a disease that is chronic, progressive 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 living 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.

THAM KWANG WEI
Senior Consultant Endocrinologist
President
Singapore Association for the Study of Obesity

Despite this need, the use of anti-obesity medications (AOM) in the United States remains low at an estimated at <five 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 the medications are effective in effecting 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 of the disease itself result in high out-of-pocket costs and contribute 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 off the market due to various serious adverse events.[11] This may have eroded the confidence in AOM not just in the general public but among prescribers. Despite studies proving that weight loss of 5-10 percent improves ORCs and cardiovascular risk, the absolute difference may be deemed as insignificant to patients (or even physicians) and may contribute to the low uptake and prescription of AOM. Instead, many resorts to over-the-counter (OTC) products with unproven claims of efficacy and safety. In recent years, there have been multiple reports of such OTC products adulterated with AOM already withdrawn from the market causing serious side-effects to consumers.

In order to tackle the growing burden of obesity which is 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 AOM, discuss the currently approved AOM and the approach physicians can take when deploying pharmacotherapy to treat obesity.

RATIONALE AND CLINICAL REASONING FOR THE USE OF ANTI-OBESITY MEDICATION

Weight loss needed for Health Improvement

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 lead to a significant reduction in cardiovascular

risk factors, improvement in obesity-related comorbidities (ORCs) such as obstructive sleep apnoea, non-alcoholic fatty liver disease and the prevention or delay in the development of type 2 diabetes.[13,14] However, some ORCs 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 ≥ten percent. Weight loss quantum of 10-40 percent is needed to effect a significant reduction of inflammation and 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 amounts of weight loss (>15 percent) and 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 of 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 over ten years at six percent as seen in the Look AHEAD study.[19] However, 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 shows that over a follow-up period of 7.5 years, 64 percent of patients lose ≤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 necessary for clinically meaningful weight loss especially in patients who require greater amounts of weight loss for the treatment of their ORCs. Nonetheless, AOM should always be used in addition to best efforts on lifestyle and behavioural modification tailored for the patient and never as a substitute. The effect of AOM will then be further enhanced and patients can derive the best benefit of AOM as demonstrated repeatedly in clinical trials. Weight loss magnitude of 17.6 percent with once-weekly semaglutide 2.4mg in addition to ILBT was seen in a recent study.[18,21]

Counteracting the Physiologic Adaptive Response to Weight Loss

The negative energy balance created for effective weight loss via calorie restriction evokes a robust physiologic adaptive response effected mostly via the hypothalamus to restore the energy homeostasis. This leads to an increased food intake and decreased energy expenditure with resultant weight regain.[22,23] Hence, obesity treatment should include therapies which counteract these adaptive responses for enhanced weight loss and weight maintenance. AOMs play a crucial role here as all but one AOM acts centrally to increase satiety, reduce hunger and food cravings to reduce food intake with the aim to counteract these adaptive responses via multiple pathways.[10,11]

WHO AND WHY: WHO SHOULD RECEIVE AOM AND WHY ARE WE INITIATING AOM?

In Singapore, the use of AOM is recommended for those with a body-mass index (BMI) of ≥30kg/m^2 or BMI ≥27kg/m^2 in the presence of at least one ORC.[24] While the BMI cut-off appears to be the indicator for the initiation of AOM, a complications-centric approach assessing the severity of obesity or the extent to which obesity has impacted the patients' health may serve their clinical needs better and guide physicians in the use of AOM.[14]

Before considering the use of AOM, a thorough assessment to stage 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 ORCs are present, how much weight loss is needed to ameliorate or prevent progression of the ORC. Therefore, in the presence of ORCs, the treatment of overweight and obesity should be prioritised especially if the ORCs 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 (NASH) with fibrosis. In these patients, pharmacotherapy should be initiated early as an adjunct to ILBT to treat these moderate to severe ORCs and reduce their cardiovascular risks.[15]

WHEN AND WHAT: WHEN TO INITIATE AOM AND WHAT TO USE?

When to Initiate?

In the following situations, initiation of AOM should be considered:

1. From the outset: Presence of ORCs which are moderate or severe especially if lifestyle and behavioural interventions alone will not achieve the weight loss required to improve the ORCs (e.g., in severe OSA, NASH cirrhosis).
2. When lifestyle interventions result in weight loss and more weight loss is required, especially in those with ORCs and/or very high BMI.
3. Weight loss with lifestyle intervention but unable to maintain weight loss.
4. After frequent unsuccessful weight loss attempts with lifestyle interventions.
5. After bariatric surgery when there is weight regain or inadequate weight loss.

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

What to Use?

There are currently five commonly used AOM approved, one for short-term and four for chronic use. In Singapore, only orlistat, phentermine and liraglutide are approved and available for use as adjunctive treatment of obesity. In general, weight loss of 3-9 percent over placebo can be seen with the use of AOM.[10,11,27]

Table 1 lists the efficacy, usage, common side effects, contraindications and precautions to be considered with the AOM approved for long-term use.[15]

WEIGHT-LOSS MEDICATIONS APPROVED BY THE FDA FOR LONG-TERM TREATMENT OF OBESITY

Anti-obesity Medication (Trade Name) Year of FDA Approval	Mechanism of Action, Study Name, Study Duration: % TBWL Greater Than Placebo	Dose	Common Side Effects	Contraindications, Cautions, and Safety Concerns ✓ Contraindication • Warning, Safety Concern	Monitoring and Comments

Orlistat
(Xenical™)
(Alli™) – OTC
1999
	Lipase inhibitor
	XENDOS
	1 yr: 4.0%
	4 yr: 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)
				  • Antiepileptics (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
					- FDA-approved for children ≥12 years old
					- Administer levothyroxine and orlistat 4 hours apart

Phentermine/ Topiramate ER (Qsymia®) 2012	NE-releasing agent (phentermine) GABA receptor modulation (topiramate) EQUIP CONQUER SEQUEL **1 yr: 8.6%-9.3% on high dose; 6.6% on treatment dose** **2 yr: 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) • Tachyarrhythmias • Decreased cognition • Seizure disorder • Anxiety and panic attacks • Nephrolithiasis • Hyperchloremic metabolic acidosis • Dose adjustment with hepatic and 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 • Hypokalemia (especially with HCTZ or furosemide) • Acute myopia and/or ocular pain • Acute kidney stone formation • Hypoglycemia 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 - Health care 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 due to altered metabolism of estrogen and progestins
Naltrexone ER/ Bupropion ER (Contrave®) 2014	Opiate antagonist (naltrexone) Reuptake inhibitor of DA and NE (bupropion) COR-I COR-II COR-BMOD **1 yr: 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 • Diarrhea • 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 and 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 and 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 mg (Saxenda®) 2014	GLP-1 analog SCALE Obesity & Prediabetes **1 yr: 5.6%**	**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 behavior • 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)

Abbreviations: BID = twice daily; DA = dopamine; FDA = US Food and Drug Administration; GI = gastrointestinal; HCTZ = hydrochlorothiazide; MAOI = monoxidase inhibitor; MEN2 = multiple endocrine neoplasia type 2; NE = norepinephrine; OTC = over-the-counter medication; % TBWL = percent total body weight loss from baseline over that observed in the placebo group; PO = oral; QAM = every morning; QD = daily; QHS = every bedtime; SC = subcutaneous; SNRI = serotonin–norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TID = 3 times a day; T2DM = type 2 diabetes mellitus.

FDA indication for all medications: BMI >30 kg/m^2 or BMI ≥27kg/m^2 with significant comorbidity.

After 3 to 4 months of treatment with antiobesity medication:

- **For naltrexone ER/bupropion ER and lorcaserin:**
  If the patient has not lost at least 5% of their baseline body weight at 12 weeks on the maintenance dose, the medication should be discontinued.
- **For phentermine/topiramate ER:**
  Continue medication if the patient has lost >5% body weight after 12 weeks on recommended dose (7.5 mg/42 mg); if the patient has not lost at least 3% of body weight after being on the recommended dose for 12 weeks then the medication should be discontinued, or the patient can be transitioned to maximum dose (15 mg/92 mg); if patient has not lost at least 5% after 12 additional weeks on the maximum dose, the medication should be discontinued.
- **For liraglutide 3 mg:**
  If the patient has not lost at least 4% of body weight 16 weeks after initiation, the medication should be discontinued.

References:
1–4 and package inserts for each medication

1. Wyatt HR. Update on treatment strategies for obesity. *J Clin Endocrinol Metab*. 2013;98(4):1299-1306.
2. Garvey WT, Garber AJ, Mechanick JI, Bray GA, Dagogo-Jack S, Einhorn D, et al. American Association of Clinical Endocrinologists and American College of Endocrinology position statement on the 2014 advanced framework for a new diagnosis of obesity as a chronic disease. *Endocr Pract*. 2014;20(9):977-989.
3. Yanovski SZ, Yanovski JA. Long-term drug treatment for obesity: a systematic and clinical review. *JAMA*. 2014;311(1):74-86.
4. Fujioka K. Current and emerging medications for overweight and obesity in people with comorbidities. *Diabetes Obes Metab*. 2015;17(11):1021-1032.

Adapted from the AACE/ACE Comprehensive Clinical Practice Guidelines for Medical Care of Patients with Obesity[14]

Orlistat

Approved for long-term use, orlistat is a gastrointestinal lipase inhibitor administered as 120mg 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 the US (only one approved in Singapore to-date). It is also the most well-studied AOM 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 60mg TDS.[27]

Its effect on weight loss is modest albeit significant with weight loss of 3.4kg (3.1 percent) and 3.6kg (3.3 percent) over placebo at 12 and 24 months respectively. Of note, in the XENDOS study, which saw a weight loss of 2.7kg (2.4 percent) over placebo maintained over four years, there was a significant risk reduction of nearly 40 percent in DM development.[28]

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 of low potential for abuse, phentermine is a sympathomimetic agent which 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 AOM in the US. In Singapore, phentermine is available as 15mg and 30mg once daily dosages 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.[30]

Most studies of phentermine are carried out for 12– 28 weeks. At a dosage of 15mg/day, total weight loss of 6.1 percent (or 4.4 percent above placebo) can be seen while total weight loss of 6.3 – 8.1kg (~4-6kg above placebo) can be expected with 30mg/day.[11,29] 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 (1000kcal/day), total weight loss of ~13kg was seen although the very high attrition rate of ~40 percent could have augmented its effect.[30]

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 AOM used in patients with obesity. Hence, phentermine as monotherapy is still restricted to short-term use with need to closely monitor the blood pressure and heart rates. It is contraindicated in those with uncontrolled hypertension, active cardiovascular disease and glaucoma.[15,31]

Liraglutide

An injectable glucagon-like peptide-1 receptor agonist, liraglutide enhances satiety and reduces appetite. Liraglutide is initiated at 0.6mg daily with weekly dose escalation of 0.6mg/day as tolerated. It was initially approved for the treatment of T2DM at doses of up to 1.8mg daily. As an AOM, it can be titrated up to a maximum dose of 3.0mg daily.[32] In December 2020, the US FDA approved liraglutide for the treatment of obesity in adolescents.

Weight loss of 6-8 percent (4-5.4 percent over placebo) at one year is seen[32,33] and this can be maintained up to three years with continued use[34], with weight loss ≥10 percent occurring in up to 25 percent of individuals on liraglutide 3mg/day.[33] 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 (six percent over placebo) in one year.[18,35] Such adjunctive treatments are feasible in the primary care setting (total weight loss of 7.5 percent in one year).[36] Increasing liraglutide from 1.8mg/day to 3.0mg/day in a person with diabetes will provide additional weight loss without further lowering the HbA1c.[33]

Although an increase in heart rate of 2-3bpm over placebo is associated with liraglutide, when used in people with T2DM at a maximum of 1.8mg/day, liraglutide was shown to reduce cardiovascular risk in individuals with T2DM in the LEADER trial.[37] 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.[32] There is a potential risk of pancreatitis and medullary thyroid cancer though in clinical trials of longer duration, risk of gallbladder disease was of a greater concern.[34]

In general, when weight loss is <four 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]

In Singapore, the fixed combination drugs of phentermine/topiramate-ER and Naltrexone/bupropion are not available nor approved for use and will not be discussed here. Combination therapy of orlistat, phentermine and liraglutide and other approved AOM has not been well-studied and should not be considered as routine clinical practice.[27]

When to Stop?

The lowest effective dose should be considered and all

AOM should be stopped if weight loss of 4-5 percent is not attained in 12-16 weeks on the highest-tolerated dose.[10] Obesity is a chronic disease, with a relapsing nature due to biologic reasons as discussed above. As with other chronic disease like hypertension and T2DM, the principles of pharmacotherapy should not be planned only for the short-term (1-3 months). Just because the parameters are controlled in chronic disease, 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 ORCs. Hence if the AOM is efficacious, long-term use at the lowest and safest possible doses should be considered.

CONCLUSION

Pharmacotherapy is often needed in adjunct to lifestyle and behavioural therapy to augment the effect of weight loss needed to treat obesity and its ORCs. Despite the clear benefit and efficacy of AOM, many barriers remain in adopting pharmacotherapy in obesity treatment, creating a gap in obesity treatment. Proper physician and patient education is one of the keys to bridging these gaps.

REFERENCE

1. GBD 2015 Obesity Collaborators, Afshin A, et al. Health Effects of Overweight and Obesity in 195 Countries over 25 Years. N Engl J Med. 2017 Jul 6;377(1):13-27. doi: 10.1056/NEJMoa1614362. Epub 2017 Jun 12. PMID: 28604169; PMCID: PMC5477817.
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, 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. Zhang S et al. 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 et al. Low adoption of weight loss medications: A comparison of prescribing patterns of antiobesity pharmacotherapies and SGLT2s. Obesity (Silver Spring). 2016 Sep;24(9):1955-61. doi: 10.1002/oby.21533. PMID: 27569120; PMCID: PMC5669035.
9. Lee PC 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 Fet 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 et al; Diabetes Prevention Program Research Group. 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. Wing RR et al; Look AHEAD Research Group. 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 et al; Reviewers of the AACE/ACE Obesity Clinical Practice Guidelines. 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 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 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 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 et al; STEP 3 Investigators. 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 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 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 et al. 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. Torgerson JS et al. 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.
29. Haddock CK et al. 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.
30. 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.
31. Apovian CM et al; Endocrine Society. 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. PMID: 25590212.
32. Pi-Sunyer X et al; SCALE Obesity and Prediabetes NN8022-1839 Study Group. 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.
33. Davies MJ et al; NN8022-1922 Study Group. 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.
34. le Roux CW et al; SCALE Obesity Prediabetes NN8022-1839 Study Group. 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.
35. Wadden TA et al; NN8022-1923 Investigators. 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.
36. Wadden TA 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.
37. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, et al; LEADER Steering Committee; LEADER Trial Investigators. 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.

LEARNING POINTS

- **Pharmacotherapy in obesity management play a crucial role as an adjunct to lifestyle and behavioural modification as well as to bariatric surgery.**
- **Assessment of the stage / severity of obesity prior to considering anti-obesity medication (AOM) is crucial as more severe stages of obesity (usually in the presence of ORCs) will warrant more urgent treatment with consideration of AOM at the outset.**
- **There are now safe and effective AOM approved for long-term use in obesity management. Understanding the indications, efficacy, side-effect profile of each AOM will help to match the most suitable treatment to the patient. This will improve compliance to the treatment and harness the best benefit for treating obesity and its ORCs.**