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USE OF PHARMACOTHERAPY IN OBESITY MANAGEMENT

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ABSTRACT

Obesity is a chronic disease that is relapsing and progressive due in part to energy homeostasis, rendering people with obesity with the challenge of attaining adequate weight loss and/or weight maintenance after successful weight loss. Depending on the presence, types, and severity of the obesity-related comorbidities and complications (ORC), 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 a pivotal adjunct to lifestyle and behavioural modifications and even to bariatric surgery, particularly in those with more severe ORC and severe stages of obesity. This article discusses the general approach to pharmacotherapy in obesity management and the various anti-obesity medications currently approved.

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INTRODUCTION

The global burden of obesity has increased substantially over the past four decades, with obesity prevalence still projected to rise. By 2035, an estimated 51 percent of the world's population will 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 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.

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Despite this need, the use of anti-obesity medications (AOM) in the United States remains low at an estimated at <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 (T2D).[7,8] In Singapore, people living with overweight and obesity are of the opinion that weight loss medications are dangerous (65 percent) and only 20 percent feel that the 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 of healthcare professionals towards PwO 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 AOM, not just by the general public but among prescribers. Despite studies proving that weight loss of 5-10 percent improves comorbidities and complications (ORC) and cardiovascular risk, the absolute difference may be deemed insignificant to patients (or even physicians) and may contribute to the perceived lack of efficacy of AOM. 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 AOM having already been withdrawn from the market after 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 AOM, discuss the currently approved AOM, and the approach physicians can adopt when utilising 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 cornerstones in obesity treatment. Clinically meaningful weight loss of 5-10 percent of initial weight can significantly reduce cardiovascular

risk factors and improve ORC such as obstructive sleep apnoea (OSA), metabolic dysfunction-associated steatotic liver disease (MASLD), and the prevention or delay in the development of T2D.[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 10-40 percent is needed to reduce inflammation and fibrosis in steatohepatitis significantly. For improvement in the severity of 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 over 10 years at 6 percent 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 weight loss to treat their ORC. 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 effects of AOM will then be further enhanced and patients can derive the best benefits of AOM as demonstrated repeatedly in clinical trials. For instance, a mean weight loss of 17.6 percent with once-weekly semaglutide 2.4 mg in addition to ILBT (6 percent) 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 evokes a robust physiologic adaptive response effected to restore the 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 counteract these adaptive responses for enhanced weight loss and weight maintenance. AOM play a crucial role here as all but one AOM act centrally to increase satiety and reduce hunger and food cravings to reduce food intake with the aim of counteracting 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 ≥30 kg/m^2 or BMI ≥27 kg/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 will guide physicians on the need and choice 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 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., T2D, dyslipidaemia, steatohepatitis (NASH) 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 AOM TO INITIATE

When to Initiate?

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

- 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, NASH cirrhosis).
- 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
- Weight regain after lifestyle interventions
- Weight regain or inadequate weight loss after bariatric surgery

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, the initiation of adjunctive treatments or intensification of treatment should not be met with inertia.[26]

What to Initiate?

There are currently six widely-available AOM approved, one for the short term and five for chronic use. At present, orlistat, phentermine, liraglutide 3.0 mg, naltrexone/buproprion ER, and subcutaneous semaglutide 2.4 mg are approved for use as adjunctive treatment of obesity in Singapore. In general, weight loss of 3-13 percent over placebo can be seen with the use of AOM.[10,11,27-29]

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 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 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 of 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 AOM in the US. In Singapore, phentermine is available as 15 mg and 30 mg 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.[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 AOM used in patients with obesity. Analysing 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 >3 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

An 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 T2D at doses of up to 1.8 mg daily. As an AOM, 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 T2D at a maximum of 1.8 mg/day, liraglutide was shown to reduce cardiovascular risk in individuals with T2D 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 diarrhoea.[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.[15,32]

Semaglutide 2.4 mg

Semaglutide is a once-weekly subcutaneous GLP1-RA approved for the long-term treatment of obesity and T2D. 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 T2D[28] with maintenance of the weight loss (12.6 percent above placebo) up to 104 weeks after initiation. In people with T2D, 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, and ileus.[29]

Semaglutide 2.4 mg once weekly is the first AOM 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 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]

Combination Treatments

In Singapore, the fixed combination drugs of phentermine/topiramate-ER is 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 AOM?

AOM 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 biologic reasons as discussed above. As with other chronic diseases like hypertension and T2D, pharmacotherapy should not be planned only for the short-term (1-3 months) but for chronic weight management and 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 AOM is efficacious, long-term use at the lowest and safest possible doses should be considered.

ANTI-OBESITY MEDICATIONS IN 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 T2D. Many analogues of these hormones have either been approved for use in T2D treatment or have undergone phase II and III trials for the treatment of obesity and T2D.

Tirzepatide is a dual agonist of GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) administered as a weekly subcutaneous injection, which was recently approved in Singapore for treatment of T2D in 2023. A 72-week RCT in participants with obesity without T2D showed a weight loss of 20.9 percent with the highest dose (15 mg) of tirzepatide versus 3.1 percent with placebo.[47] Adverse events observed are mostly mild to moderate, transient gastrointestinal symptoms. Other recent phase II RCTs

included that of CagriSema, a once-weekly combination of cagrilintide (an amylin analogue) and semaglutide, and Retatrutide, a single-molecule triple-hormone (GLP1, GIP, glucagon) receptor agonist administered once weekly, which demonstrated an average 2-2.2 percent reduction in HbA_{1c} at 24 weeks and a mean 16-17 percent reduction in body weight at 32-36 weeks (with highest doses) in those with obesity and T2D.[48,49] In people with obesity without T2D, the highest dose of retatrutide resulted in an average 24 percent reduction in body weight after 48 weeks of treatment.[50]

Other compounds such as oxyntomodulin with dual GLP-1 and glucacon receptor agonism, PYY agonists, have shown promising weight loss results in phase 1 and 2 studies.

CONCLUSION

The use of anti-obesity pharmacotherapy is pivotal as an 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. Greater access to AOM may also improve the uptake of AOM in treating obesity as a chronic disease.

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

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]

Anti-obesity pharmacotherapy, indication/use[a]	Mechanism of action, study name, study duration: percent 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, diarrhoea, 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 T2D 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 • 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 or kidney impairment • Narrow-angle glaucoma • Uncontrolled migraine disorder • Generalised 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) • Hypoglycaemia in patients having T2D 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 analog SCALE Obesity & Prediabetes **1 year: 5.6 percent** **3 years: 4.3 percent**	**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 • Diarrhoea • 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 • Hypoglycaemia in patients having T2D 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 Chronic weight management	GLP-1 receptor analog STEP Obesity Adults without T2D **68 weeks: 10.3-12.4%** **104 weeks: 12.6%** Adults with T2D **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 • Diarrhoea • 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 T2D treated with insulin and/or sulfonylureas • Diabetic retinopathy in patients with T2D • Increased heart rate • Dehydration from nausea/vomiting • Injection site reactions • Ileus - Titrate dose based on tolerability (nausea and GI side effects)

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LEARNING POINTS

- **Pharmacotherapy in obesity management plays a crucial role as an adjunct to lifestyle and behavioural modification and 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 ORC) 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, and 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 benefits for treating obesity and its ORC.**