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USE OF PHARMACOTHERAPY IN OBESITY MANAGEMENT

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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, burdening 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 complications (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 pharmacotherapy in obesity management and the various anti-obesity medications currently approved.

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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 will be estimated to be obese.[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, tend to burden people living with obesity (PwO) with 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 (T2DM).[7,8] In Singapore, a local survey revealed that people living with overweight and obesity view that weight loss medications were dangerous (65 percent) and only 20 percent felt that medications were effective in weight loss. Coupled with the belief that the responsibility to manage obesity and weight issues lies solely with PwO (90 percent), 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 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 various 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 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 resort 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.

To tackle the growing 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, and to 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 significantly reduce cardiovascular risk factors and improve obesity-related complications (ORCs) such as obstructive sleep apnoea, non-alcoholic fatty liver disease, and the prevention or delay in the development of T2DM.[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 ≥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 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 6 percent over 10 years 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 showed 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 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. 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.[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 that counteract these adaptive responses for enhanced weight loss and weight maintenance. AOMs 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 may better serve their clinical needs and guide physicians in the use of AOM.[14]

Before considering the use of AOM, 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 the 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., T2DM, 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 that 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, the initiation of adjunctive treatments or intensification of treatment should not be met with inertia.[26]

What to Use?

There are currently six commonly-used AOM approved globally, one for short-term and five for chronic use. In Singapore, orlistat, phentermine, naltrexone/buproprion, and liraglutide are currently approved 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]

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.[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 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.[30]

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.[11,29] 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 (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.[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 a 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 (subcutaneous) glucagon-like peptide-1 receptor agonist (GLP-1 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. As an AOM, it can be titrated up to a maximum dose of 3.0 mg daily.[32] In December 2020, the US Food and Drug Administration (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[32,33] and this can be maintained up to three years with continued use,[34] with weight loss of ≥10 percent occurring in up to 25 percent of individuals on liraglutide 3 mg/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 (6 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 1.8 mg/day to 3.0 mg/day in a person with diabetes will provide additional weight loss without further lowering the HbA1c.[33]

Although an increase in heart rate of 2-3 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 events 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, the risk of gall bladder disease was of a greater concern.[34]

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

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]

After one year of treatment, weight loss of 4.2-5.2 percent above placebo is seen.[15,38,39] The most common side effects experienced are nausea, constipation, headache, vomiting, dizziness, insomnia, anxiety, dry mouth, and diarrhoea.[38,39] The use of naltrexone/bupropion is contraindicated in pregnancy, uncontrolled hypertension, those with a past and current history of seizures, 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, and naltrexone being associated with hepatotoxicity, patients should be closely monitored.[15,31]

In Singapore, the fixed combination of phentermine/topiramate-ER is not approved for use and will thus not be discussed here. Combination therapy with orlistat, phentermine, and liraglutide and other approved AOM has not been well-studied and should not be considered as routine clinical practice.[27]

IN THE HORIZON

In recent years, two novel incretin-based therapies have been approved for the treatment of T2DM and obesity. Semaglutide, a GLP-1 RA available both as a once-weekly injection and an oral tablet, has been approved for the treatment of T2DM in Singapore since June 2021. HbA1c reductions of 1.3-1.9 percent and 1.0-1.4 percent are seen with the use of subcutaneous (SC) and oral semaglutide respectively with corresponding weight loss in the range of 4.5-6 kg in SC and 3-5 kg in oral semaglutide use.[40] For obesity treatment, SC semaglutide once-weekly in doses of up to 2.4 mg/week (higher than those used for T2DM treatment) resulted in weight loss of about 12-14 percent over placebo (total weight loss 17-18 percent) in the STEP clinical trials,[21,41,42] and its use has been approved by the FDA in 2021. Side-effects are similar to those seen in liraglutide.

Tirzepatide, a once-weekly dual receptor agonist of glucose-dependent insulinotropic polypeptide (GIP) receptor and GLP-1, was approved by the FDA in May 2022 for the treatment of T2DM. At its highest dose of 15 mg once-weekly, tirzapetide can achieve HbA1c reductions between 2.07 percent and 2.59 percent with weight loss of up to 12.9 kg in the SURPASS clinical trials.[43-45] In the SURMOUNT-1 clinical trial designed to study the efficacy of tirzapetide on weight loss in people without diabetes, a mean weight loss of 22.5 percent was achieved after 52 weeks of treatment on the highest dose.[46]

Many other compounds such as oxyntomodulin with dual GLP-1 and glucacon receptor agonism,[47] combination semaglutide, and amylin analogues, [48] have shown promising weight loss results in phase 1 and 2 studies.

WHEN TO STOP TREATMENT?

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 biological reasons as discussed above. As with other chronic diseases like hypertension and T2DM, pharmacotherapy principles should not be planned only for the short term (1-3 months). Just because the parameters are controlled in a chronic disease, does not imply that treatment needs to be stopped. The goal of therapy is for the long term, for weight maintenance, and to prevent weight regain with the ultimate aim of preventing/managing 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. Adequate physician and patient education is one of the keys to bridging these gaps.

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LEARNING POINTS

- **Weight loss requires a multifaceted approach, as isolated dietary control or exercise is unlikely to 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 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, 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 benefit for treating obesity and its ORCs.**