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

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. Obesity is now established as a disease that is chronic, progressive and often relapsing with a complex host of pathogenic and perpetuating factors. 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, often necessitating the use of multiple modalities including pharmacotherapy in obesity management.

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. 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. 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.

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. 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.

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 affect 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. 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.

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. 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. 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.

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. 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.

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/m² or BMI ≥27kg/m² in the presence of at least one ORC. 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.

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. 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.

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.

**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.

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

<table>
<thead>
<tr>
<th>Orientation</th>
<th>Medication</th>
<th>Year of FDA Approval</th>
<th>Mechanism of Action</th>
<th>Study Name</th>
<th>Safety Proportion: % TMBL Greater Than Placebo</th>
<th>Dose</th>
<th>Common Side Effects</th>
<th>Common Contraindications, Cautions, and Safety Concerns</th>
<th>Monitoring and Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orlistat</td>
<td>Aerobically stable lipase inhibitor</td>
<td>1999</td>
<td>Increased fecal fat loss</td>
<td>Large, placebo-controlled</td>
<td>136 mg or 112 mg PO TID (before meals)</td>
<td>Steatorrhea, fecal urgency, malabsorption of lipids and fat-soluble vitamins, weight loss</td>
<td>Monitor weight loss, stools, and serum lipids</td>
<td>Palmar and plantar xerosis, cholecystitis, pancreatitis</td>
<td>Cholelithiasis, biliary obstruction</td>
</tr>
<tr>
<td>Phentermine</td>
<td>Norepinephrine releasing agent</td>
<td>2012</td>
<td>Weight loss</td>
<td>Large, placebo-controlled</td>
<td>37.5-75 mg PO TID for 3 weeks</td>
<td>Weight loss, increased heart rate, decreased appetite, improved mood</td>
<td>Monitor weight loss, heart rate, blood pressure</td>
<td>Hypertension, palpitations, orthostatic hypotension, dysrhythmias</td>
<td>Increased heart rate, bradycardia, cardiovascular death</td>
</tr>
<tr>
<td>Liraglutide 3 mg</td>
<td>GLP-1 analog</td>
<td>2014</td>
<td>Weight loss</td>
<td>Large, placebo-controlled</td>
<td>3 mg SC weekly, titrated over 4 weeks</td>
<td>Weight loss, increased glucose, nausea, diarrhea, vomiting</td>
<td>Monitor weight loss, glucose, blood pressure</td>
<td>Hypoglycemia, pancreatitis, cholecystitis, pancreatitis</td>
<td>Pancreatic cancer, acute pancreatitis, severe mal-feeding, alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevation</td>
</tr>
</tbody>
</table>

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

**FSA for all medications:** BMI ≥ 30 kg/m² or BMI ≥ 27 kg/m² with significant comorbidity.

**After 4 months of treatment with unsuccesful weight loss:**
- For orlistat: Discontinue if patient has not lost at least 1% of their initial body weight after 12 weeks on the maintenance dose, the medication should be discontinued.
- For phentermine/Topiramate ER: Continue medication if the patient has lost at least 5% body weight after 12 weeks on the recommended dose (7.5 mg/45 mg); if the patient has not lost at least 5% of body weight after 10 days of the recommended dose for 12 weeks then the medication should be discontinued. Additional medications or a change in baseline diet and activity levels and a comprehensive counseling program should be considered. If the patient has not lost at least 3% body weight after 12 weeks on the maximum dose, the medication should be discontinued.

**References:**

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.2,27

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.13,29 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.33 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 seen32,33 and this can be maintained up to three years with continued use34, with weight loss ≥10 percent occurring in up to 25 percent of individuals on liraglutide 3mg/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 (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.\textsuperscript{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 (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 (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 (1-3 months).

CONCLUSION

Pharmacotherapy is often needed in adjunct to lifestyle and behaviour 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


**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.