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Timing the Discussion of Anti-Obesity Medications during Obesity Treatment

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Current obesity guidelines suggest that sustained weight loss of just 3% to 5% achieved through lifestyle interventions is clinically important.¹ A recent randomized clinical trial demonstrated that 5% weight loss in people with obesity increased insulin sensitivity in fat, muscle, and liver while decreasing plasma concentrations of glucose, insulin, triglycerides, alanine transaminase, and leptin.² Since a lifestyle program emphasizing nutritional changes and increased physical activity is beneficial for people of any weight, such a program has been recommended as the underlying foundation of weight loss interventions. Obesity treatment guidelines state that for individuals with a BMI ≥ 30 kg/m² or BMI ≥ 27 kg/m² having at least one obesity-related co-morbidity who are motivated to lose weight, pharmacotherapy is an optional addition to lifestyle change efforts.¹ However, specific guidelines regarding the time at which anti-obesity medications should be added to a program emphasizing lifestyle changes are singularly lacking.

The current pharmacologic options for overweight and obesity approved by the United States Food and Drug Administration (FDA) for long term use are outlined in Table 1. The FDA has included stopping rules in the package inserts for the anti-obesity medications approved based on early weight loss success. These rules attempt to limit the long-term use of anti-obesity medication to those who will achieve 5% weight loss or greater at one year

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and thus minimize exposure to medications that have risks without attendant clinical benefits. Although there is some variability in the stopping rules, less than 5% weight loss after 12 weeks of full-dose treatment is the general criterion for stopping anti-obesity medications³

These or similar stopping rules have been validated in clinical trials of anti-obesity medications. Among patients receiving naltrexone-ER 32mg/bupropion-ER 360mg, achievement of 5% weight loss at 16 weeks was the best predictor of weight loss after one year of treatment.⁴ In clinical trials comparing lorcaserin to placebo, in conjunction with a program of lifestyle change, 5% weight loss at 12 weeks predicted 5% or more weight loss at one year, both for subjects on lorcaserin and for those on placebo (lifestyle change only).⁵ In this analysis, the predictive value of a week-12 weight loss criterion of 5% was nearly as good for the placebo+lifestyle change patients as for those receiving lorcaserin+lifestyle change; however, subjects given the placebo were less likely than subjects receiving lorcaserin to meet that criterion.⁵ The Look AHEAD trial compared the long-term effects of an intensive lifestyle intervention program with a control condition involving a program of diabetes support and education in subjects with Type 2 diabetes. In the intensive lifestyle change condition, weight losses at one month and two months predicted 12-month weight loss.⁶ Thus, early treatment response to a program emphasizing lifestyle changes may be as informative as the response to pharmacologic interventions.

Time in treatment with a lifestyle program emphasizing nutritional changes and increased physical activity is positively associated with weight loss. Those who stay in treatment for more than six months achieve greater weight loss than those who do not, but the majority of participants discontinue treatment before six months.⁷ There is a tendency for physicians not to discuss weight loss in general and anti-obesity medications in particular, unless the patient brings up the subject. Thus, it is not unusual for patients with obesity to discontinue treatment with a lifestyle program prior to any discussion of a pharmacologic intervention. Therefore, it is crucial to identify the optimal time-point at which non-responders to behavioral weight loss interventions may be treated more aggressively.

Using the equivalent of the medication stopping rules to define the timing to consider adding anti-obesity medication to the foundation of a lifestyle change program may well be appropriate. As an example, not achieving 5% weight loss by 12 weeks of a lifestyle intervention program in patients with a BMI ≥ 30 kg/m² or BMI ≥ 27 kg/m² and having at least one obesity-associated medical complication may be the signal that consideration of the use of anti-obesity medication is indicated. If the weight loss was greater than 5% at 12 weeks, consideration of an anti-obesity medication might be deferred until and unless problems with maintenance develop. Nevertheless, a discussion about this possibility may be appropriate while weight loss is still proceeding so that the patient is aware of the pharmacologic option when needed. Although some individuals can maintain 5% weight loss with a lifestyle program emphasizing nutritional changes and increased physical activity, successful weight maintenance is the exception, since there are physiologic forces predisposing to weight regain. These forces are blunted by obesity medications. Thus, weight loss may be better maintained and even improved with anti-obesity medication.⁸

Whether addressing resistance to weight loss or weight regain, specific criteria for considering medication are needed.

Obesity is a major medical problem. A 5% weight loss can influence health outcomes, and anti-obesity medications could be a useful tool to achieve this goal; yet, they appear to be used sparingly. Only one in fifty patients with obesity receives a prescription for anti-obesity medication.⁹ Lack of recognition of obesity as a chronic condition, and limited coverage by public and private payers are some barriers to prescribing anti-obesity medications.¹⁰ Intensive lifestyle change programs can help many patients to achieve this goal but a large percentage will fail to do so and many of those who achieve it will regain body weight. Although guidelines suggest use of anti-obesity medications for these patients, they offer little specific guidance for individuals or their health care providers regarding the timing for introducing these medications. Discussing the addition of an anti-obesity medication if a lifestyle program fails to produce weight loss or prior to that based on weight loss history, or having that discussion at the time that weight regain occurs may be an appropriate addition to obesity treatment guidelines. Assembling a committee of experts to consider this recommendation seems to be a logical next step. Specific evidence-based recommendations by such a committee and inclusion in obesity treatment guidelines could serve to improve the success of obesity treatment and enhance health outcomes.

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Table 1

Current weight loss medications approved by the United States Food and Drug Administration (FDA) for long term use in conjunction with lifestyle changes, their mechanisms of action, and stopping rules

Medication	Mechanism of action	Recommendation for use
Orlistat (Alli TM , Xenical TM)	Pancreatic lipase inhibitor	None
Locaserin (Belviq TM)	Serotonin 2-C receptor agonist	Discontinue if 5% weight loss is not achieved by 12 weeks of treatment
Phentermine and Topiramate ER (Qsymia TM)	Combination of sympathomimetic phentermine and the anticonvulsant topiramate	Start at phentermine 3.75 mg with topiramate 23 mg/day for 14 days. Increase to 7.5 mg and 46 mg, respectively. If after 12 weeks, 5% weight loss is not achieved, discontinue medication or increase to phentermine 15 mg/ topiramate 96 mg daily. If 5% weight loss is still not achieved after 12 weeks at higher dose, discontinue medication.
Naltrexone HCL and Bupropion HCL (Contrave TM)	Combination of naltrexone, an opioid receptor antagonist and bupropion, a catecholamine reuptake inhibitor	Bupropion 360 mg and naltrexone 32 mg/day titrated four weeks to reach therapeutic dose. Discontinue if 5% weight loss is not achieved in 12 weeks on full therapeutic dose
Liraglutide 3.0 mg, (Saxenda TM)	Glucagon-like peptide-1 analogue	Four week titration period. After 16 weeks, which includes the titration period, discontinue if a weight loss of at least 4% has not been achieved