naltrexone/bupropion, orlistat, and fixed-combination phentermine/topiramate) results in greater weight reduction than a CLI alone. This SR and meta-analysis also included data on the weight-loss medication lorcaserin. However, in February 2020, the FDA requested the withdrawal of the weight-loss drug lorcaserin (Belviq, Belviq XR) from the U.S. market citing potential risk of cancer outweighing the benefits of use.[153] The meta-analysis reported that after a minimum follow-up of 12 months, each of the four medications was associated with a greater reduction in total body weight compared to placebo. Further, a greater proportion of patients in the medication group achieved at least 5% or 10% weight loss from baseline compared to placebo, which is considered to be clinically significant.[152]

Based on the meta-analysis, patients who received fixed-combination phentermine/topiramate had the highest probability of achieving a 5% or 10% weight loss, followed by liraglutide, fixed-combination naltrexone/bupropion, and orlistat.[152] The mean weight loss of these agents compared to placebo followed the same pattern and is also shown in Table 1 below.

Table 1. Weight Loss and Adverse Event Outcomes with Medications for Long-term Weight Loss* [152]

Medication for weight loss	Mean weight loss versus placebo	≥5% weight loss (OR)	≥10% weight loss (OR)	Discontinuation due to an adverse event (OR)
Phentermine/topiramate	-8.80 kg	9.22	11.40	2.29
Liraglutide	-5.24 kg	5.54	4.99	2.95
Naltrexone/bupropion	-4.95 kg	3.96	4.19	2.64
Orlistat	-2.63 kg	2.70	2.42	1.84

* lorcaserin is not included in this table as it was requested to be removed from the U.S. market in February 2020.[153] Data for lorcaserin: MD -3.25 kg; OR ≥5%: 3.10; OR ≥10%: 3.20; OR discontinuation due to adverse event: 1.34.

Abbreviations: OR: odds ratio

Pharmacotherapy may produce significant weight loss in conjunction with CLI; however, treatment individualization is critically important due to the potential for adverse effects. As reported in the SR by Khera et al. (2016), all of the weight loss medications evaluated were associated with a statistically significant risk of medication discontinuation due to adverse events when compared to placebo.[152] Liraglutide had the highest odds of treatment discontinuation, followed by fixed-combination naltrexone/bupropion, fixed-combination phentermine/topiramate, then orlistat (see Table 1).[152] As noted in the 2018 USPSTF systematic review,[2] trials of weight loss medications often had very selective inclusion and exclusion criteria. Included patients who volunteer for participation in research may have higher levels of adherence than community-dwelling patients. Patients may be excluded from participation due to medical conditions that are often present in the patient populations intended for management by this CPG. The Work Group considered the applicability of these results to the general patient population as well as the potential harms from the weight loss medications. In addition, certain pharmacotherapies may be inappropriate for patients with conditions such as HTN, hyperthyroidism, valvular heart disease, nephrolithiasis, glaucoma, cholestasis, seizure disorder, drug misuse disorder potential, pregnancy, or are breastfeeding. Patients should be informed of the risks and adverse effects of each medication to properly incorporate patient preference in the medication selection (see Appendix H for additional information on pharmacotherapy considerations). It is also appropriate to carefully evaluate medication lists to eliminate or reduce agents that cause weight gain as a side effect (see Sidebar 2).