



the PRUDENT prescriber

Phil Mohler, M.D.

February 2023

In this edition:

- Do Weight Loss Medicines Work? Should You Prescribe Them? An Update (pg. 1)

Do Weight Loss Medicines Work? Should You Prescribe Them? An Update

I was never a big fan or prescriber of weight loss medicines. Early on I engaged in a few brief misguided trials of phentermine that caused more anxiety for the prescriber than it did weight loss for my patients. This update includes the largest ever systemic review and network meta-analysis of weight lowering drugs, the American Gastroenterological Association's (AGA) practice guidelines for pharmacological interventions for adults with obesity and the Clinical and Economic Review's (ICER) policy recommendations on treatments for obesity management, plus price comparisons.

Shi et al. from West China Hospital Sichuan University offer their systemic review and network meta-analysis summarizing the latest evidence for the benefits and harms of weight lowering drugs (Lancet, Vol 399, January 15, 2022).

Methods:

- This systematic review and network meta-analysis included searches of PubMed, Embase and the Cochrane Library from inception to March 23, 2021, for randomized controlled trials (RCTs) of weight lowering drugs in adults with overweight and obesity.
- The authors identified 143 eligible trials that had enrolled 49,810 participants. Among the participants, the median age was 47 years, the median female proportion was 75%, the median baseline BMI was 35.3 and the median length of follow up was 24 weeks. The authors did not identify country of origin or race of the participants.

- These RCTs compared lifestyle modification and a candidate weight lowering drug with lifestyle modification alone with or without placebo or an alternative active drug. The researchers excluded trials with the crossover design and drug combinations except for one pill combinations like phentermine-topiramate and bupropion-naltrexone.
- The researchers' guideline panel judged the following outcomes as crucial: percentage body weight change from baseline to end of follow up, the proportion of participants reducing their bodyweight by 5% or more, the proportion of participants reporting adverse events leading to treatment discontinuation and weight regain after treatment discontinuation.

Results:

- Phentermine-topiramate (Qsymia), GLP-1 receptor agonists and bupropion-naltrexone were the most effective in lowering weight by greater than 5% or more and 10% or more. (High to moderate certainty evidence).
- Lifestyle modification alone resulted in 266 people per 1000 person years reducing their weight by 5% or more and 106 people per 1000 person years reducing their weight by 10% or more. Treatment with phentermine-topiramate, GLP-1 receptor agonists and bupropion-naltrexone more than doubled people losing weight by 5% or more and 10% or more. (High certainty)
- Phentermine-topiramate, GLP-1 receptor agonists, bupropion-naltrexone and orlistat were associated with increased risk of any adverse event leading to treatment discontinuation. Bupropion-naltrexone and phentermine-topiramate had the worse profile. (Moderate certainty)
- Semaglutide was associated with the largest percentage weight loss of all the drugs and was associated with the greatest likelihood of losing weight by 5% or more and 10% or more. (High certainty)
- Semaglutide consistently outperformed liraglutide and exenatide in weight loss and was comparable in terms of side effects resulting in discontinuation.
- Orlistat is widely used for weight loss worldwide, but possibly ranks no better than lifestyle modification alone in assisting with weight loss.

AGA guidelines: In November 2022 the AGA published their Clinical Practice Guidelines on Pharmacological Interventions for Adults with Obesity in *Gastroenterology* 2022; 163:1198-1225. The guideline includes multiple recommendations.

- In adults with obesity or overweight with weight related complications, who have an inadequate response to lifestyle interventions, the AGA recommends adding pharmacological agents to lifestyle interventions over continuing lifestyle interventions alone. (Strong recommendation, moderate certainty evidence)
- The AGA suggests using the following four drugs all with approval for long term use: semaglutide 2.4 mg, liraglutide 3.0 mg, phentermine - topiramate ER and naltrexone-bupropion ER, all as conditional recommendations with moderate certainty of evidence. They believe that each of the four drugs is likely to result in a high proportion of

patients achieving 5% and 10% total body weight loss. They should not be used in pregnant women.

- The AGA recommends against using Orlistat.
- The AGA suggests use of phentermine and diethylpropion as a conditional recommendation utilizing low certainty evidence.

AGA specific comments on anti-obesity drugs

Drug	Comments
semaglutide	Semaglutide may be prioritized over other approved anti-obesity meds given the magnitude of its net benefit. Both semaglutide and liraglutide have been found to reduce morbidity and mortality in people with type 2 diabetes at risk for cardiovascular disease. Delays gastric emptying with associated nausea and vomiting. Associated with gallbladder disease and pancreatitis. Overall discontinuation rate was 6.4% versus 3.1% for the placebo group.
liraglutide	Less effective than semaglutide. Effects on glucose metabolism. Delays gastric emptying with associated nausea and vomiting. Associated with gallbladder disease and pancreatitis (<0.1%). The incident of nausea and vomiting with liraglutide was 40% and 16%, respectively, and with placebo 15% and 4%, respectively.
phentermine - topiramate ER	Avoid inpatient with history of cardiovascular disease and uncontrolled hypertension. Topiramate is teratogenic. Blood pressure and heart rate should be monitored periodically while taking medications with phentermine. Common side effects include constipation, dizziness, insomnia, paresthesias and dysgeusia.
Naltrexone-bupropion ER	May be considered for the treatment of obesity in patients who are attempting smoking sensation and in patients with depression. It should be avoided in patients with seizure disorder. It should not be used concomitantly with opiate medications. In the first 12 weeks of treatment, blood pressure and heart rate should be monitored periodically. Common side effects include nausea, vomiting, constipation or diarrhea, insomnia, headache, dizziness, and dry mouth.
orlistat	AGA recommends against it. If you are going to take orlistat, need to supplement your diet with fat soluble vitamins A, D E and K taken two hours apart from orlistat.

ICER (Institute for Clinical and Economic Review) released (October 20, 2022) their final evidence report assessing the comparative clinical effectiveness and value of semaglutide, liraglutide, phentermine/topiramate and bupropion/naltrexone for the treatment of obesity. ICER is an

independent nonprofit research Institute that produces reports analyzing the evidence on the effectiveness and value of drugs and other medical services. The ICER panel consists of 15 experts with multidisciplinary backgrounds.

- All panelists (15-0) found the evidence is adequate to demonstrate that a net health benefit of semaglutide added to lifestyle modification compared to lifestyle modification alone.
- All panelists (15-0) found the evidence is adequate to demonstrate that a net health benefit of liraglutide added to lifestyle modification compared to lifestyle modification alone.
- The majority of panelists (14-1) found that the evidence is adequate to demonstrate a net health benefit of phentermine/topiramate added to lifestyle modification compared to lifestyle modification alone.
- The majority of panelist (10-5) found that the evidence is adequate to demonstrate a net health benefit of bupropion/naltrexone added to lifestyle modification compared to lifestyle modification alone
- By votes ranging from 10-5 to 15-0, a majority of the panelists found that the evidence is adequate to demonstrate a net health benefit of semaglutide compared to liraglutide, phentermine/topiramate and bupropion/naltrexone.

When considering the long-term value for money the panelists noted that:

- Phentermine/topiramate and bupropion/naltrexone both meet commonly accepted cost effectiveness thresholds when compared to lifestyle modification alone.; Both of these combination therapies are cost saving when prescribed generically.
- When used for weight loss among patients with obesity (and not treatment of diabetes) semaglutide does not meet typical cost-effectiveness thresholds at its current estimated net price, but it is more effective, less burdensome, and more cost-effective than liraglutide.
- At an annual net price of \$13,618, semaglutide exceeds typical cost-effective thresholds. ICER’s health - benefit price benchmark range for semaglutide is between \$7500-\$9800 per year.
- In summary, a majority (11-4) of panelists found that semaglutide added to lifestyle modification represents “low“ long-term value for money.

Cost of one month’s supply of weight loss drugs

Drug Maximum approved dose	Cost of One Month’s Supply Best GoodRx Price (January 2023)
phentermine-topiramate <ul style="list-style-type: none"> • Qsymia (15mg IR/92 mg ER/day) 	\$213
semaglutide <ul style="list-style-type: none"> • Ozempic (2.0 mg) - off label use for weight loss • Wegovy (2.4 mg) - approved for weight loss 	\$878 \$1386

subq/week	
naltrexone/bupropion <ul style="list-style-type: none"> • Contrave (8mg/90mg ext release tabs) 	\$319
orlistat <ul style="list-style-type: none"> • Rx: Xenical 120mg p.o. TID • OTC: Alli 60mg TID 	\$709 \$27



My Take:

- 42% of adults in the United States are obese. Obesity is a disease, and we should treat it as such. There’s no significant prevalence difference between men and women. Minority groups are disproportionately affected. African American women have the highest obesity rates in our nation, and yet are the sub-group least able to afford these medications.
- Guidelines recommend that medications for weight loss are indicated only after lifestyle modification and meal replacement. Specifically, prudent prescribers should consider medications when the patient’s BMI is greater than 30 or with a BMI greater than 27 with a comorbidity.
- We have known for a long time that intensive lifestyle change is the key for weight loss and that weight loss medications are simply an adjunct tool for selected patients.
- There is evidence that weight loss medications are associated with minimal improvement in quality of life. Novo Nordisk currently is conducting a study to attempt to show a causal relationship between semaglutide and reduction in risk of MI, stroke and death.
- Weight loss drugs may reduce the risk of diabetes mellitus, however no more so than lifestyle change programs.
- Prescribers should evaluate weight loss at 12 weeks and if there is not at least a 3% weight loss, the medication should be stopped.
- The dilemma: Although these drugs are approved for chronic use, most patients are adverse to using them long term. The data suggest most patients who stop their weight reduction drug regain their lost weight.

Looking for previous versions of the Prudent Prescriber newsletter? Good news, 10 YEARS of monthly editions are now available on rmhp.org.

Prudent Prescriber
 Authored by Phil Mohler, MD
 Distributed by Rocky Mountain Health Plans, a UnitedHealthcare Company