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An Update in Weight Loss Therapies - Including FDA Approved GLP-1 Receptor Agonists

Melissa Yokoyama, Pharm.D and Megan Herink, Pharm.D., Oregon State University Drug Use Research and Management Group

In the past 20 years, the prevalence of obesity in the United States has increased from 30.5% to 41.9% and it is estimated that 1 in 5 children have obesity.[1,2] Obesity is associated with many complications, including cardiovascular disease (CVD), metabolic syndrome, obstructive sleep apnea, type 2 diabetes mellitus (T2DM), osteoarthritis, non-alcoholic fatty liver disease and certain cancers.[1] A comprehensive lifestyle approach, including healthy meal plans, physical activity and behavioral intervention remain the foundation to treating obesity and preventing weight-related complications.[3] For many patients, effectiveness of lifestyle approaches is limited, and pharmacological therapies are needed to achieve weight loss goals. The purpose of this newsletter is to summarize current pharmacologic treatment options for obesity, including the glucagon- like peptide 1 receptor agonist (GLP-1 RA) class.[1,4]

Lifestyle Interventions

A comprehensive lifestyle intervention that combines behavioral, dietary, and physical activity is strongly recommended for all individuals with obesity.[1] Weight loss goals are individualized, and some patients may require larger weight reductions for clinically meaningful benefits. However, a 5-10% weight loss after six months can result in clinically significant benefits on weight associated conditions.[1] There is a dose-response on weight loss with the number and intensity of lifestyle interventions utilized. High-intensity programs have demonstrated 5-10% reductions in weight loss.[5] At one year, lifestyle interventions have also shown to reduce the risk of T2DM.[6] However, intensive lifestyle interventions studied in clinical trials are difficult to replicate in clinical settings.[6] The expense, limited availability, and resources required for implementation contribute to health disparities in access to these interventions.

Pharmacological Therapies for Weight Loss

For patients with obesity (body mass index [BMI] of 30 kg/m^2 or higher) or with a BMI of 27 kg/m^2 or higher with weight-related complications (e.g., hypertension, T2DM, dyslipidemia) who have an inadequate response to lifestyle interventions, guidelines recommend pharmacologic agents **(Tables 1 & 2)**.[3]

The minimal clinically important difference (MCID) for the efficacy of pharmacotherapy in the management of obesity that corresponds to important patient benefits is a mean difference (MD) of 3% total body weight loss (TBWL) between adjunctive pharmacotherapy over lifestyle interventions alone, or an absolute 5% TBWL over baseline.[1] If patients have not lost 5% of their total body weight by 12 weeks of therapy on the maintenance dose, it is generally recommended that medications be discontinued and an alternative medication or treatment be considered.[1]

Table 1: Older Medications for Weight Management[1,3,4]

Drug (Brand name)	Mechanism of Action	%TBWL
Phentermine-topiramate ER (Qysmia)	Sympathomimetic amine-neurostabilizer	MD 8.45% (7.89-9.01%)
Naltrexone-bupropion ER (Contrave)	Opioid antagonist/ dopamine and NE reuptake inhibitor	MD 3.01% (2.47- 3.54%)
Orlistat (Xenical)	Lipase inhibitor	MD 2.78% (2.36 –3.20%)
Phentermine (Adipex)	Sympathomimetic amine	MD 3.63 % (2.97-4.29%)
Diethylpropion (Tenuate)	Sympathomimetic amine	MD 5.36% (3.50– 7.23%)
Abbreviations: ER: extended release; TBWL: total body weight loss, MD: mean difference; NE: norepinephrine		

Phentermine and diethylpropion are FDA-approved for only short-term use (12 weeks). Both medications should be avoided in patients with a history of cardiovascular disease (CVD) or uncontrolled hypertension and are supported by low quality evidence with a limited place in therapy.[1] Despite its FDA approval in 1999, orlistat has limited clinical utility due to its small weight loss benefit and potential for gastrointestinal side effects.[1]

Phentermine-topiramate ER and naltrexone-bupropion ER are FDA-approved for chronic weight loss management.[1] Common side effects include dry mouth, headache, numbness and tingling, and constipation. Topiramate is teratogenic. Women of childbearing potential who take topiramate should be counseled to use effective contraception consistently.[1] Blood pressure and heart rate should be monitored while taking medications with phentermine. The combination of naltrexone-bupropion ER should be avoided in patients with seizure disorders as well as patients taking opioids but may be a consideration in patients with obesity who also need smoking cessation or depression treatment.[1]

Glucagon- Like Peptide 1 Receptor Agonists

Over the past 15 years, GLP-1 RAs have demonstrated beneficial effects on diabetes, renal, CV and weight loss outcomes.[7-10] GLP-1 is an endogenous hormone released by the gastrointestinal (GI) tract in response to the intake of food, resulting in a glucose-dependent release of insulin secretion

(the "incretin" response), delayed gastric emptying, modulation of b-cell proliferation, and improved appetite control, resulting in beneficial effects in glucose levels and body weight.[1]

While all GLP-1 RAs are approved for T2DM, only liraglutide and semaglutide **(Table 2)** are currently FDA-approved for chronic weight management in people with a BMI of 30 kg/m^2 or greater, or 27 kg/m^2 or greater with at least one weight-related comorbid condition.[11,12] The doses approved for chronic weight management are different from doses approved for T2DM. Both medications are not recommended in pregnancy, and contraindicated in patients with a personal or family history of thyroid carcinoma or multiple endocrine neoplasia syndrome type I.[11,12] They are titrated up slowly at weekly intervals to limit GI side effects. The maximum tolerated dose that achieves the goal weight loss should be continued. If at least 5% weight loss of TBWL is not achieved after 12 weeks at maximum tolerated dose, they should be discontinued.

Table 2: FDA Approved GLP-1 RAs for Chronic Weight Management.[1,11,12]

Generic Name	Brand Name	Target Dose	%TBWL[1]
Liraglutide	Saxenda	3 mg SC daily	MD 4.81% (4.23 - 5.39%)
Semaglutide	Wegovy	2.4 mg SC weekly	MD 10.76% (8.73 -12.8%)

Abbreviations: SC: subcutaneous, MD: mean difference, TBWL: total body weight loss

Liraglutide (Saxenda®)

FDA approval of liraglutide for chronic weight management was based on the results of three, 56-week randomized, double-blind, placebo-controlled trials **(Table 3)**, which were all a part of the Satiety and Clinical Adiposity- Liraglutide Evidence in non-diabetic and diabetic individuals (SCALE) program. Trials randomized patients to liraglutide 3 mg daily or placebo, with dosing starting at 0.6 mg and increasing by 0.6 mg weekly to the target dose.[11]

In the SCALE Maintenance Trial, the effects of liraglutide on weight maintenance was evaluated after an initial run-in period.[13] Patients who lost at least 5% of their initial body weight in the 4- to 12-week low calorie diet run-in period were randomized into the trial. Participants lost a mean of 6.3 kg during the run-in period. After 56 weeks, the liraglutide group achieved greater additional mean weight loss of 6.2% compared to 0.2% with placebo.

The SCALE Obesity and Prediabetes trial stratified according to prediabetes status and BMI (≥30 and <30 kg/m^2).[14] After 56 weeks, patients without T2DM treated with liraglutide lost a mean of 8%±6.7% of their body weight compared to 2.6%±5.7% with placebo. Results were similar regardless of prediabetes status but the liraglutide was less effective in patients with a mean BMI >40.[14] More patients in the placebo group developed T2DM than patients in the liraglutide group (6.2% vs. 1.8%).[14]

The SCALE Diabetes trial included patients with obesity and T2DM.[15] A total of 69.2% of patients on liraglutide achieved an HbA1c less than 7% compared to 27.2% in the placebo group, with reductions in HbA1c of 1.3% and 0.3%, respectively (MD -0.93%; 95% CI -1.08 to -0.78%).[15]

Table 3: Liraglutide Clinical Trials.

Study	Study Population	Mean %TBWL vs Placebo	% patients ≥5% & ≥10% TBWL vs Placebo
SCALE Maintenance Trial[13]	Adults with BMI ≥ 30 or ≥27 with ≥1 weight related condition* without T2DM (n=422)	-6.2% ETD: -6.1% (95% CI -7.5 to -4.6)	50.5% vs. 21.8% ARR 29% /NNT 4 26.1% vs. 6.3% ARR 20% /NNT 5
SCALE Obesity and Prediabetes Trial[14]	Adults with BMI ≥ 30 or ≥27 with ≥1 weight-related condition* without T2DM (n=3731)	-8.0% ETD: -5.4% (95% CI −5.8 to −5)	62.3% vs. 27.1% ARR 20% /NNT 5 33.1% vs.10.6% ARR 23% /NNT 5
SCALE Diabetes Trial[15]	Adults with T2DM, BMI ≥27 and HbA1c 7-10% (n=846)	-6.0% ETD: -4.0% (95% CI -5.1 to -2.9)	54.3% vs. 21.4% ARR 33% /NNT 3 25.2% vs. 6.7% RR 19% /NNT 6

* treated or untreated dyslipidemia or hypertension
Abbreviations: ARR: absolute risk reduction; BMI: body mass index; CI: confidence interval; ETD: estimated treatment difference; HbA1c: hemoglobin A1c; NNT: number needed-to-treat; T2DM: type 2 diabetes mellitus; TBWL: total body weight loss.

All three studies demonstrated a statistically significant reduction in weight compared with placebo after 56 weeks of treatment with liraglutide (**Table 3**). As anticipated, follow-up studies consistently demonstrated weight gain after study medication was stopped, which ranges from 3 to 5%.[1] Therefore, treatment discontinuation needs to be carefully considered in clinical practice and if a clinical response is present, long-term use is expected.

There were more withdrawals due to adverse events with liraglutide compared to placebo (9.8% vs. 4.3%) and the most common adverse effects were GI related, notably nausea (39.3% vs 13.8%), diarrhea (20.9% vs. 9.9%) and constipation (19.4% vs. 8.5%).[1] Most patients reported increased incidence with higher doses and in the first 4-8 weeks of treatment, with decreased reports after week 10.[13-15]

Semaglutide (Wegovy®)

FDA approval of semaglutide for chronic weight management was based off three 68-week, randomized, double-blind, placebo-controlled trials and one 68-week, randomized, double blind, placebo withdrawal trial (**Table 4**), which were a part of the Semaglutide Treatment Effect in People with Obesity (STEP) program.[16-19]

In STEP trials 1-3, semaglutide was titrated to a target dose of 2.4 mg weekly, starting at 0.25 mg weekly for the first 4 weeks, then increased every 4 weeks until week 16.[16,18,19] STEP 4 was a withdrawal trial, evaluating continued semaglutide versus placebo in participants who reached the target 2.4 mg dose in an initial 20-week run-in.[17]

Table 4: Semaglutide Clinical Trials.

Study	Study Population	Mean %TBWL vs Placebo	% patients ≥5% & ≥10% TBWL vs Placebo
STEP 1[19]	Adults with BMI ≥30 or ≥27 with ≥1 condition* without T2DM (n=1961)	-14.9% ETD -12.4% (95% CI -13.4 to -11.5)	86.4% vs. 31.5% ARR 55% /NNT 2 69.1% vs. 12% ARR 41% /NNT 3
STEP 2[16]	Adults with T2DM and BMI ≥27 kg/m^2 with HbA1c 7-10% (n=1210)	-9.6% ETD -6.2% (95% CI -7.3 to -5.2)	68.8% vs. 28.5% ARR 40% /NNT 3 45.6% vs. 8.2% ARR 37% /NNT 3
STEP 3[18]	Adults with BMI ≥30 or ≥27 with ≥1 condition* without T2DM (n=611)	-16.0% ETD -10.3 % (95% CI -12 to -8.6)	86.6% vs. 47.6% ARR 39%/NNT 3 75.3% vs. 27% ARR 48% /NNT 2
STEP 4[17]	Adults with BMI ≥30 or ≥27 with ≥1 condition* without T2DM following run-in period (n=902)	-7.9% ETD -14.8% (95% CI -16 to -13.5)	88.7% vs. 47.6% ARR 41% /NNT 3 79.0% vs. 20.4% ARR 59% /NNT 2

* treated or untreated dyslipidemia, hypertension, obstructive sleep apnea or cardiovascular disease
ARR: absolute risk reduction; BMI: body mass index; ETD: estimated treatment difference, HbA1c: hemoglobin A1c; NNT: number needed to treat, T2DM: type 2 diabetes mellitus.

There was a significant decrease in weight loss from baseline with semaglutide compared to placebo (**Table 4**). In the STEP 1 trial, 84.1% of patients with prediabetes reverted to normoglycemia compared to 47.8% on placebo. A decrease in systolic blood pressure was observed with semaglutide compared to placebo (-6.16 mm Hg vs. -1.06 mm Hg).[19] In the STEP 2 trial, patients with T2DM randomized to semaglutide experienced a mean weight loss of 9.6 kg compared to 3.5 kg with placebo.[16] Furthermore, 67.5% of patients on 2.4 mg of semaglutide achieved an HbA1c less than 6.5% compared to 15.5%.[16] In STEP 3, semaglutide was combined with an intensive behavioral therapy program. STEP 3 resulted in a significant weight reduction compared to placebo (16% vs. 5.7%), and efficacy was consistent with previous studies including less intensive "usual advice".[8]

In the STEP 4 withdrawal trial, patients without T2DM on semaglutide had a mean 10.6% weight loss from baseline during a 20-week run-in period. Following the run-in-period, the mean weight loss with semaglutide was 7.9% compared to a weight gain of 6.9% when patients who were switched to placebo.[17]

Like liraglutide, there was a higher rate of withdrawals due to adverse events (5.7% vs. 3.0%) and GI side effects with semaglutide compared to placebo, including nausea (44% vs. 16%), diarrhea (30% vs. 16%) and vomiting (24% vs. 6%). Most of these adverse events were classified as mild to moderate and decreased or resolved over time. Like liraglutide, there is a significant regain of weight following treatment discontinuation of semaglutide and slow dose titration is important to ensure GI tolerability. The STEP 1 extension study found that patients on average gained two-thirds of prior weight loss after a year of discontinuation.[20]

Phase 3 clinical trials evaluating oral semaglutide for the treatment of obesity are underway and FDA review is expected later this year.

Tirzepatide (Mounjaro®)

Tirzepatide is a once weekly subcutaneous injectable with activity at both GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) incretin hormone receptors.[21] While not yet FDA approved, a published phase 3 trial found a mean 20.9% weight reduction with the highest dose of tirzepatide (15 mg) compared to 3.1% with placebo in patients with obesity and without diabetes. There was also a greater reduction in systolic blood pressure (-7.2 mm Hg versus -1.0 mm Hg) and triglycerides (-24.8% versus -5.6%) compared to placebo.[21] A dose-response was observed in both weight reduction and GI side effects. FDA review for possible fast-track approval is currently underway.

Current Policies

Obesity was first recognized as a disease in 2013. Under the Medicaid Drug Rebate Program, weight-loss drugs can be excluded from mandatory coverage, and coverage varies between states. Currently, treatment coverage for obesity through the Oregon Health Plan (OHP) is limited to intensive counseling on nutrition and physical activity with the exceptions below. Intensive counseling visits are covered for an initial 6 months and can be continued for 6 months if there is evidence of continued weight loss. However, access to these covered services can be a barrier for patients. Bariatric surgery is also covered for adults with BMI ≥ 40 kg/m^2 or BMI ≥ 30 kg/m^2 with T2DM or at least 2 other serious obesity-related comorbidities and in adolescents ≥ 13 years old with obesity or significant comorbid conditions. Pharmacological treatments and devices used specifically for weight loss are not currently covered under the OHP Prioritized List of health services, except for specific cases in children and youth under the age of 21 years through the Early and Periodic Screening, Diagnostic and Treatment (EPSDT) Program. OHP members with T2DM with or without obesity may also be treated with GLP-1 RAs with prior authorization.

Conclusion

Pharmacological therapy is recommended for patients with obesity (BMI ≥ 30 kg/m^2) or with a BMI of 27 kg/m^2 or greater with weight-related complications who have an inadequate response to lifestyle interventions alone. Newer agents have shown a significant weight loss benefit. Magnitude of efficacy comes with more GI side effects that will need to be considered with each patient and thoughtfully managed with dose titration and education. It remains unclear on optimal duration of risks versus benefits of long-term chronic therapy. Long-term studies are currently underway that will clarify benefit of FDA-approved medications for obesity on long-term clinical outcomes, such as maintenance of weight loss, quality of life, non-alcoholic fatty liver disease, cardiovascular morbidity, and all-cause mortality.

Comprehensive lifestyle interventions currently remain the foundation to treating obesity in individuals on the OHP. With the landscape of obesity treatment rapidly changing, OHP will begin reviewing coverage policies and guidelines in 2024 for possible coverage changes to provide access to cost-effectiveness treatments in Oregon Medicaid.

Peer Reviewed By: Rita Parsiani, PharmD, BC-ADM, CDCE, Clinical Pharmacist, Harold Schnitzer Diabetes Health Center, Oregon Health & Science University and Jonathan Q Purnell, MD, FTOS, Professor of Medicine, Director, The Center for Preventive Cardiology, Knight Cardiovascular Institute, Division of Endocrinology, Diabetes, and Clinical Nutrition Oregon Health & Science University

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