Diabetes, Metabolic Syndrome and Obesity

Dovepress

open access to scientific and medical research

Open Access Full Text Article

REVIEW

Novel Anti-obesity Therapies and their Different Effects and Safety Profiles: A Critical Overview

Ozge Telci Caklili[1], Mustafa Cesur[2], Dimitri P Mikhailidis[3], Manfredi Rizzo[4]

[1]Department of Endocrinology and Metabolism, Faculty of Medicine, University of Istanbul, Istanbul, Türkiye; [2]Department of Endocrinology and Metabolism, Ankara Guven University Hospital, Ankara, Türkiye; [3]Department of Clinical Biochemistry and Department of Surgical Biotechnology, Division of Surgery and Interventional Science, Medical School, University College London (UCL), London, UK; [4]School of Medicine, Department of Health Promotion, Mother and Child Care, Internal Medicine and Medical Specialties (Promise), University of Palermo, Palermo, Italy

Correspondence: Manfredi Rizzo, School of Medicine, Promise Department, University of Palermo, Via del Vespro 141, Palermo, 90127, Italy, Tel/Fax +39 091 655-2945, Email manfredi.rizzo@unipa.it

Abstract: Obesity has become an epidemic and a worldwide problem and its treatment is ever-evolving. Apart from diet and exercise, medication and surgery are other options. After disappointing side effects of various obesity drugs, new treatments showed promising results. This review discusses the following anti-obesity drugs: liraglutide, semaglutide, tirzepatide, orlistat, as well as the phentermine/topiramate and bupropion/naltrexone combinations. These drugs have been approved by the Food and Drug Administration (FDA) for weight reduction except for tirzepatide which is still under evaluation. Efficacy and tolerable safety profiles of some of these drugs contribute to the management of obesity and reduce the complications associated with this chronic disease.

Keywords: obesity, drugs, liraglutide, semaglutide, tirzepatide, orlistat, phentermine/topiramate, bupropion/naltrexone

Introduction

Obesity has become an epidemic and a worldwide problem.[1] The prevalence of obesity in adults is estimated to be over 40% and is expected to increase further after the coronavirus disease 2019 (COVID-19) pandemic.[2] There are many risk factors for obesity, from low birth weight to aging, but lifestyle choices have always been the biggest contributor.[3–5]

Obesity has been associated with cardiovascular (CV) diseases, type 2 diabetes, immune dysfunction, and cancer.[6–10] The Global Burden of Disease investigators showed that more than two-thirds of deaths related to high BMI were due to CV disease.[11] Once thought of as an illness of the industrialized countries, it is now known that due to the decreased nutritional value of low-cost food and lack of physical exercise obesity can affect both underdeveloped and developing countries.[12] As obesity pandemic grows further it becomes more costly. It is projected that in 2030 medical costs associated with obesity-related diseases will increase to $48–66 billion/year in the United States.[13]

Although there are several therapeutic options to treat the diseases obesity is related to, agents that can solve the main problem are limited.[14]

Treatment of obesity always starts with lifestyle changes.[14] A healthier diet and a moderate exercise routine are a must in obesity treatment. However although randomized trials have shown >8.% decrease in weight in the first year,[15,16] cumulative data shows that most patients cannot sustain this lifestyle and, more than half of the lost weight was regained within two years.[17]

Anti-obesity drugs are developed to help patients who fail to lose weight with lifestyle measures, but these therapeutic options are limited.

Various drugs were withdrawn from the market due to adverse psychiatric or CV effects.[18] Following the recall of sibutramine from the market, the Food and Drug Administration (FDA) has called for mandatory placebo-controlled CV safety data for new obesity drugs. These mandatory trials showed promising results for obesity treatment. This review will discuss the following drugs; liraglutide, once weekly semaglutide, tirzepatide, orlistat, as well as the phentermine/topiramate and bupropion/naltrexone combinations (Table 1). All but tirzepatide have been approved for weight loss by FDA whereas tirzepatide is still under evaluation at the time of writing.

Received: 23 February 2023
Accepted: 27 May 2023
Published: 14 June 2023

Table 1 Obesity Treatment Options Approved by the Food and Drug Administration (FDA)

Name	Mechanism of Action	Route of Administration	Recommended Dose	Expected Weight Loss, kg
Liraglutide	GLP-1 agonist	Subcutaneous	3 mg once a day	5.7–8
Semaglutide	GLP-1 agonist	Subcutaneous	2.4 mg once a week	9.7–15.3
Tirzepatide*	GLP-1/GIP agonist	Subcutaneous	15 mg once a week	9.5–23.6
Orlistat	Lipase inhibitor	Oral	120 mg three times a day	5.8–10.6
Phentermine-Topiramate	Sympathomimetic amine anorectic/antiepileptic combination	Oral	7.5 mg/46 mg once a day	9.2–12.4
Bupropion-naltrexone	Opioid antagonist/antidepressant combination	Oral	16 mg/180 mg twice a day	3.6–9.3

Note: *Tirzepatide is still under evaluation by the FDA for obesIty treatment approval.
Abbreviations: GLP-1, glucagon-like peptide-1; GIP, glucose-dependent insulinotropic polypeptide.

Liraglutide

Liraglutide is a human glucagon-like peptide-1 (GLP-1) analog with an arginine-for-lysine substitution and a C-16 palmitic acid side chain.[19] This modification not only prolongs its absorption time, but also decreases the deactivation rate of the molecule by dipeptidyl peptidase (DPP).[19] Its half-life is approximately 13 h. Its bioavailability after subcutaneous (sc) administration is 55%.[20] As a GLP-1 analog, it increases insulin secretion, decreases glucagon production, delays gastric emptying and decreases appetite.[21] Its effect relies on oral glucose intake.

Once introduced as an antiglycemic agent,[21] liraglutide proved itself as an anti-obesity drug.[22] In the SCALE (Satiety and clinical adiposity – liraglutide evidence in nondiabetic and diabetic individuals) Obesity and Prediabetes Study 3731 patients body mass index (BMI) ≥30 or ≥27 if the patient had treated or untreated dyslipidemia or hypertension were randomized to liraglutide 3 mg/day, sc, plus lifestyle intervention (n=2487) or placebo plus lifestyle intervention (n=1244).[23] After 56 weeks liraglutide plus lifestyle intervention provided a reduction of 8.4±7.3 kg in weight compared with the placebo group (2.8±6.5 kg, $p<0.001$). Sixty-three percent of the patients lost ≥5% of their body weight and 33% lost >10%. As expected, liraglutide reduced prediabetes prevalence compared with placebo. It also affected other metabolic parameters; waist circumference (WC), fasting insulin, both systolic (−4.2 ± 12.2, liraglutide vs −1.5 ± 12.4 mmHg, placebo $p<0.001$) and diastolic blood pressure (−2.6 ± 8.7, liraglutide vs −1.9 ± 8.7 mmHg, placebo $p<0.001$) decreased compared with placebo, and dyslipidemia improved.

As for quality of life, liraglutide treatment provided better scores in physical and mental health questionnaires. Its main side effects were associated with the gastrointestinal system and withdrawal rate was 6.4% compared with 0.7% for the placebo group. Liraglutide was associated with gall-bladder related diseases (including cholelithiasis or cholecystitis) and pancreatitis. Seventy-eight percent of these patients went through surgery and 84% continued their treatment.

The SCALE Sleep Apnea study was completed with 276 patients (liraglutide 3 mg sc, n=134 vs placebo n=142).[24] Withdrawal rate was 12% for liraglutide and 3% for placebo. After 32 weeks patients in the liraglutide group lost 5.7% of their weight whereas the placebo group lost 1.6% ($p<0.0001$). The SCALE weight maintenance study tested the effect of liraglutide on obese patients who have lost >5% of their weight during the run-in period with a 1200–1400 kcal/day low calorie diet.[25] Participants who lost >6% during run-in period lost an additional 6.1% of their weight with liraglutide 3 mg sc, compared with 0.2% of placebo, ($p<0.0001$). It also ameliorated CV risk factors. When liraglutide was tested against an active comparator orlistat, after 20 weeks, liraglutide 3 mg sc provided 7.2 kg weight loss whereas orlistat provided 4.1 kg ($p<0.0001$).[26] Overall withdrawal rate was higher with orlistat compared with liraglutide 3 mg (17 vs 12%).

Liraglutide 1.8 mg sc was also tested in patients (n=9340) with diabetes for nonfatal acute myocardial infarction (AMI), nonfatal stroke, and CV death (MACE) and showed a 13% reduction ($p=0.01$) in the primary composite CV outcome and 22% reduction ($p=0.007$) in CV mortality compared with placebo.[27] Although there is no CV outcome study for 3 mg sc, a post hoc analysis showed no impact on CV risk.[28] This analysis had 5908 participants and with liraglutide

3.0 mg, eight participants had adjudicated events (1.54 events/1000 person years) compared with participants in the comparator group (3.65 events/1000 person-years) with hazard ratio of 0.42 (95% confidence interval (CI): 0.17–1.08). Another study (n=135) showed that in patients with type 2 diabetes liraglutide had better efficacy on cardiometabolic risk factors in obese patients compared with the nonobese.[29]

The SCALE studies have shown that in almost each study (except for the sleep apnea study) more than half of the patients lost >5% of their body weight. These findings were also confirmed in real life studies. An Italian cohort of 93 overweight or obese patients had a mean weight loss of 7.1% with liraglutide 3 mg sc.[30] This study also showed decreased blood pressure and increased heart rate with liraglutide which was also reported in the SCALE Obesity and Prediabetes study. Similarly a Canadian cohort (n=167) showed 7.1% weight loss in more than six months with liraglutide 3 mg sc and lifestyle intervention.[31] A smaller cohort from Switzerland (n=54) reported that liraglutide 3 mg sc and lifestyle intervention results with overall mean weight loss of 12.4% in 10 months.[32] A Korean cohort (n=211) reported an average of 5.85% weight loss with no serious side effects in real life.[33] Compared with orlistat (n=400) in real life liraglutide up to 3 mg sc (n=100) provided 7.7 kg of mean weight loss compared with 3.3 kg for orlistat ($p<0.001$).[34]

As with all GLP-1 analogs liraglutide should not be used in patients with a history of pancreatitis and medullary thyroid cancer or multiple endocrine neoplasia or a family history of these conditions.[35,36]

Semaglutide

Semaglutide is another GLP-1 analog used both in type 2 diabetes and obesity.[37] It is available as a once weekly 1 mg sc injection for type 2 diabetes treatment and up to 14 mg once daily oral use. Injectable 2.4 mg is approved for obesity treatment whereas oral semaglutide has not been approved for obesity treatment. Therefore, this review will discuss once-weekly semaglutide for obesity treatment. Starting dose is 0.25 mg and dose is titrated every four weeks until 2.4 mg is reached (approximately 16 weeks). Its half-life is 155–184 h.[38]

The STEP (Semaglutide treatment effect in people) trial program assessed the effects of semaglutide on weight loss. STEP 1 assessed efficacy of semaglutide 2.4 mg sc once a week compared with placebo in a 2:1 ratio.[39] There were 1,961 patients with a BMI ≥30 kg/m² or ≥27 kg/m² with ≥1 weight-related comorbidity and no diabetes. Mean age of the participants was 46 years for semaglutide and 47 years for placebo. After 68 weeks of treatment patients in the treatment group lost 14.9% of their weight whereas the placebo group lost 2.4% ($p<0.001$). Thirty-two percent lost ≥20% of their initial weight. Their weight loss also improved metabolic parameters including WC, blood pressure, fasting glucose, HbA1c and lipid parameters along with quality-of-life assessments. Side effects of semaglutide mostly included transient gastrointestinal discomfort. Three patients had mild acute pancreatitis in the semaglutide group and none in the placebo group. It should be noted that women constituted >70% of the participants; this may have caused an underrepresentation of men.[40]

STEP 2 evaluated the weight loss effect of semaglutide 2.4 mg sc once a week in 1,595 patients who were overweight or obese and with type 2 diabetes and a mean age of 55 years for 68 weeks.[41] In this trial weight loss was 9.6% compared with placebo (3.4%, $p<0.0001$). Side effects were similar to those in the STEP 1 study. The most common gastro-intestinal events were nausea, vomiting, diarrhea, and constipation which were not severe.

Although both STEP 1 and STEP 2 included a lifestyle counseling program, STEP 3 had a more pronounced lifestyle intervention program including eight weeks of low-calorie diet (1,000–1,200 kcal/day) followed by a hypocaloric diet (1,200–1,800 kcal/day) for 60 weeks.[42] The program also included increased physical activity and behavioral strategies. Along with intensive lifestyle intervention weight loss was more prominent with semaglutide 2.4 mg sc once a week than with placebo (16 vs 5.7%).

STEP 4 compared continuing semaglutide therapy with withdrawing it in adults with BMI of ≥30 (or ≥27 with one weight-related comorbidity) and without diabetes.[43] After 20 weeks of semaglutide 2.4 mg sc once a week patients were randomized to either semaglutide 2.4 mg (n=535) or to placebo (n=268). After 48 weeks patients in the semaglutide group lost 7.9% of their weight whereas placebo group gained 6.9% of their weight.

STEP 5 study compared the effect of semaglutide 2.4 mg sc once a week over a more prolonged period of time.[44] In 104 weeks, weight loss was −15.2% in the semaglutide group (n=152) vs −2.6% in the placebo group (n=152),

$p<0.0001$). There were 12 patients with serious adverse effects in the semaglutide group and 18 participants in the placebo group. No participant had acute pancreatitis. There was no reported thyroid cancer in either group.

The semaglutide effects on heart disease and stroke in patients with overweight or obesity (SELECT) study is ongoing and evaluates the impact of semaglutide 2.4 mg sc once a week on CV events in 17,605 participants who are overweight or obese with established CV disease and without diabetes.[45]

Semaglutide 2.4 mg sc once a week (n=126) was compared to liraglutide 3 mg sc once a day (n=127) in the STEP 8 study.[46] Along with lifestyle intervention, the semaglutide arm showed 15.8% weight loss from baseline and liraglutide arm had a 6.4% weight loss in 68 weeks ($p<0.001$). Gastrointestinal disorders were the most frequent advance effects with semaglutide and liraglutide, reported by 84.1% and 82.7% of participants, respectively (placebo: 55.3%); nausea, constipation, and diarrhea were among the most common gastrointestinal disorders.

Contradictions for semaglutide use are the same as for liraglutide and other GLP-1 analogs.

Tirzepatide

Tirzepatide is a relatively new drug from a similar but different class entitled dual co-agonist [acting on GLP-1/GIP (glucose-dependent insulinotropic polypeptide) receptors].[47] The SURMOUNT-1 (Efficacy and safety of tirzepatide once weekly in participants without type 2 diabetes who have obesity or are overweight with weight-related comorbidities: a randomized, double-blind, placebo-controlled trial) study evaluated (for 72 weeks) 2539 adults with a BMI ≥30 or with ≥27 and at least one weight-related complication without diabetes.[48] Along with a moderate lifestyle intervention program participants were given once weekly sc tirzepatide 5, 10, or 15 mg or placebo in a 1:1:1:1 ratio. Weight loss with 15 mg was 20.9% compared with 3.1% for the placebo group ($p<0.001$). Lower doses also decreased body weight significantly; 15.0% with 5 mg, and 19.5% with 10 mg dose ($p<0.001$ compared with placebo). At the time of writing, tirzepatide had received FDA approval for the treatment of type 2 diabetes, but was still in the approval process for the treatment of obesity.

When tested against an active comparator dulaglutide sc once a week, tirzepatide had better outcomes in both glycemic control and body weight in patients with type 2 diabetes. Patients received tirzepatide sc 5 mg (n=159), 10 mg (n=158), or 15 mg (n=160), or dulaglutide 0.75 mg (n=159). Weight loss was 5.8 kg, 8.5 kg, 10.7 kg and 0.5 kg, respectively (all $p<0.0001$).[49] Nausea was the most common side effect especially with tirzepatide 10 and 15 mg (20% vs 8% with dulaglutide). A meta-analysis compared seven randomized controlled studies (n=12,371) and reported 9.23 kg more weight loss with tirzepatide 15 mg sc weekly compared with semaglutide 2.4 mg sc weekly.[50]

Along with this pronounced weight loss effect of tirzepatide, it is also a promising agent for nonalcoholic fatty liver disease (NAFLD)/nonalcoholic steatohepatitis (NASH).[51]

Orlistat

Orlistat is a pancreatic lipase and gastric lipase inhibitor that can lead to a decrease in fat absorption by as much as 30%.[52] It has a modest weight loss effect which depends mostly on diet.[53] It is an oral treatment (120 mg) taken with each meal or up to one hour later.[54] In the XENDOS study (n=3305) after four years weight loss was higher with orlistat 120 mg three times a day compared with placebo (5.8 vs 3.0 kg; $p<0.001$).[55] It can cause steatorrhea and a decrease in fat soluble vitamins.[56] Patients should be advised against eating foods that are high in fat to prevent high volume diarrhea. A database study showed decreased CV event rates on orlistat treatment compared with persons who did not take this drug.[57] Furthermore, the ATTEMPT study showed that orlistat is useful in multifactorial treatment of CV risk in patients with metabolic syndrome and without diabetes.[58] A total of 1,123 participants were administered hyperlipidemia and hypertension treatment as well as metformin and orlistat for CV risk reduction and two targets were established for LDL cholesterol (LDL-C) (<100 vs <130 mg/dL). After three years, the lower LDL-C threshold showed superior results in CV events (1 vs 13, $p=0.0012$). Mean orlistat dose was 320 mg/day and BMI was significantly reduced in both groups after three years. When same cohort was analyzed for regression of NAFLD, 86% of patients in the low LDL-C threshold group and 74% of patients in the high LDL-C threshold group ($p<0.001$) had better liver enzymes than at baseline.[59]

Phentermine/topiramate

Phentermine is a sympathomimetic that suppresses appetite by increasing norepinephrine and to a lesser extent, dopamine.[60] Topiramate, a gamma-aminobutyric acid (GABA) receptor agonist, decreases appetite and increases satiety.[61] It also increases energy expenditure.[62] The phentermine/topiramate (PHEN/TPM) combination was approved in 2012 for obesity management by the FDA. The combination results with more weight loss compared with its monotherapy components (PHEN/TPM 15/92 mg −11.63 kg vs phentermine 15 mg −7.38 kg, topiramate 92 mg −8.82 kg, $p<0.05$).[63] PHEN/TPM was tested as 3.75/23 mg (low-dose), 7.5/46 mg (mid-dose), and 15/92 mg (high-dose) orally in various studies.[62,64,65] A meta-analysis reports that the average weight loss was 3.55 kg for 3.75/23 mg, 7.27 kg for 7.5/46 mg, and 8.25 kg for 15/92 mg.[66] Patients should be started on a low dose and after 2 weeks this can be increased to mid-dose.[60] If after 12 weeks a 3% loss in baseline body weight is not achieved, the dose can be increased to 11.25/69 mg for 14 days and then to 15/92 mg daily.[60] If there is no weight loss of 5% after 12 weeks on high dose, PHEN/TPM should be discontinued gradually, tapering the dose over at least one week.[60] Adverse effects include dry mouth, psychiatric side effects including depression, anxiety and loss of concentration.[62–65] Studies also reported increased heart rate with PHEN/TPM.[62,64] The CONQUER (Effects of the low-dose, controlled-release, PHEN/TPM combination on weight and associated comorbidities in overweight and obese adults) study showed increase in the mean heart rate with PHEN/TPM 15/92 mg ($p<0.0001$) compared with baseline.[64] In the EQUIP trial, there was also increased heart rate compared with baseline, however, this was not statistically significant [1.2 bpm, ($p=0.0830$ vs placebo)].[62]

Bupropion/naltrexone

Another combination therapy consists of bupropion, a dopamine-reuptake inhibitor used for smoking cessation and naltrexone, an opioid-receptor antagonist for the treatment of alcohol and opioid abuse.[67] This dual treatment has the potential to reduce body weight 4–5%[68–70] however its CV safety is questionable.[71] Due to early release of the interim data, the trial was terminated prematurely. Nissen et al[72] reported that 50% of planned events, occurred in 102 patients (2.3%) in the placebo group and 90 patients (2.0%) in the bupropion-naltrexone group (HR, 0.88; adjusted 99.7%CI: 0.57–1.34) however they concluded that the CV safety of this drug combination is uncertain.[71] This combination therapy can also cause nausea, dizziness and dry mouth.[68]

Conclusion

With the discovery of incretin hormones new obesity drugs have been developed and GLP-1 agonists have shown consistent success. Newer agents which use similar pharmacologic pathways will pave the way for increased weight loss with medication and their results may even be comparable with bariatric surgery. Although sc injections may be less tolerated than oral treatments, both their efficacy and safety profile seem superior to oral treatments. With wider implementation of these drugs, global obesity burden may decrease and type 2 diabetes can be prevented.

Disclosure

The authors declare that this article has been written independently, without any financial or professional help, and only reflects their opinion. Although the authors have given lectures, received honoraria and research support, and participated in conferences, advisory boards, and clinical trials sponsored by many pharmaceutical companies, the industry had no role on this article. DPM has given talks, acted as a consultant or attended conferences sponsored by Amgen and Novo Nordisk. The authors report no other conflicts of interest in this work.

References

1. Hales CM, Carroll MD, Fryar CD, Ogden CL. Prevalence of obesity and severe obesity among adults: United States, 2017–2018. *NCHS Data Brief*. 2020;2020:1.
2. Kapoor N, Kalra S, Al Mahmeed W, et al. The Dual Pandemics of COVID-19 and Obesity: Bidirectional Impact The Dual Pandemics of COVID-19 and Obesity: Bidirectional Impact. *Diabetes Therapy*. 2022;13(10):1723–1736. doi:10.1007/s13300-022-01311-2
3. Martín-Calvo N, Goni L, Tur JA, Martínez JA. Low birth weight and small for gestational age are associated with complications of childhood and adolescence obesity: systematic review and meta-analysis. *Obes Rev*. 2022;23:e13380. doi:10.1111/obr.13380
4. Tam BT, Morais JA, Santosa S. Obesity and ageing: two sides of the same coin. *Obes Rev*. 2020;21(4):e12991. doi:10.1111/obr.12991

5. Chao AM, Quigley KM, Wadden TA. Dietary interventions for obesity: clinical and mechanistic findings. *J Clin Invest*. 2021;131(1). doi:10.1172/JCI140065
6. Muennig P, Lubetkin E, Jia H, Franks P. Gender and the burden of disease attributable to obesity. *Am J Public Health*. 2006;96:1662–1668. doi:10.2105/AJPH.2005.068874
7. Ortega FB, Lavie CJ, Blair SN. Obesity and cardiovascular disease. *Circ Res*. 2016;118:1752–1770. doi:10.1161/CIRCRESAHA.115.306883
8. Al-Goblan AS, Al-Alfi MA, Khan MZ. Mechanism linking diabetes mellitus and obesity. *Diabetes Metab Syndr Obes*. 2014;2014:587–591. doi:10.2147/DMSO.S67400
9. De Heredia FP, Gómez-Martínez S, Marcos A. Obesity, inflammation and the immune system. *Proc Nutr Soc*. 2012;71:332–338. doi:10.1017/S0029665112000092
10. Calle EE, Thun MJ. Obesity and cancer. *Oncogene*. 2004;23:6365–6378. doi:10.1038/sj.onc.1207751
11. GBD 2015 Obesity Collaborators. Health effects of overweight and obesity in 195 countries over 25 years. *N Engl J Med*. 2017;377(1):13–27. doi:10.1056/NEJMoa1614362
12. Popkin BM, Adair LS, Ng SW. Global nutrition transition and the pandemic of obesity in developing countries. *Nutr Rev*. 2012;70(1):3–21. doi:10.1111/j.1753-4887.2011.00456.x
13. Wang YC, McPherson K, Marsh T, Gortmaker SL, Brown M. Health and economic burden of the projected obesity trends in the USA and the UK. *Lancet*. 2011;378(9793):815–825. doi:10.1016/S0140-6736(11)60814-3
14. Gadde KM, Martin CK, Berthoud HR, Heymsfield SB. Obesity: pathophysiology and management. *J Am Coll Cardiol*. 2018;71(1):69–84. doi:10.1016/j.jacc.2017.11.011
15. Look AHEAD Research Group. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. *N Engl J Med*. 2013;369(2):145–154. doi:10.1056/NEJMoa1212914
16. Elhayany A, Lustman A, Abel R, Attal-Singer J, Vinker S. A low carbohydrate Mediterranean diet improves cardiovascular risk factors and diabetes control among overweight patients with type 2 diabetes mellitus: a 1-year prospective randomized intervention study. *Diabetes Obes Metab*. 2010;12(3):204–209. doi:10.1111/j.1463-1326.2009.01151.x
17. Hall KD, Kahan S. Maintenance of lost weight. *Med Clin North Am*. 2018;102:183–197. doi:10.1016/j.mcna.2017.08.012
18. Onakpoya IJ, Heneghan CJ, Aronson JK. Post-marketing withdrawal of anti-obesity medicinal products because of adverse drug reactions: a systematic review. *BMC Med*. 2016;14:1–11. doi:10.1186/s12916-015-0545-7
19. Lin CH, Shao L, Zhang YM, et al. An evaluation of liraglutide including its efficacy and safety for the treatment of obesity. *Expert Opin Pharmacother*. 2020;21:275–285. doi:10.1080/14656566.2019.1695779
20. Kela R, Khunti K, Davies MJ. Liraglutide for type 2 diabetes mellitus. *Expert Opin Biol Ther*. 2011;11:951–959. doi:10.1517/14712598.2011.583641
21. Gallwitz B. Glucagon-like peptide-1 analogues for Type 2 diabetes mellitus: current and emerging agents. *Drugs*. 2011;71:1675–1688. doi:10.2165/11592810-000000000-00000
22. Madsbad S, Schmitz O, Ranstam J, Jakobsen G, Matthews DR. Improved glycemic control with no weight increase in patients with type 2 diabetes after once-daily treatment with the long-acting glucagon-like peptide 1 analog liraglutide (NN2211): a 12-week, double-blind, randomized, controlled trial. *Diabetes Care*. 2004;27:1335–1342. doi:10.2337/diacare.27.6.1335
23. Pi-Sunyer X, Astrup A, Fujioka K, et al. A randomized, controlled trial of 3.0 mg of liraglutide in weight management. *N Engl J Med*. 2015;373:11–22. doi:10.1056/NEJMoa1411892
24. Blackman A, Foster GD, Zammit G, et al. Effect of liraglutide 3.0 mg in individuals with obesity and moderate or severe obstructive sleep apnea: the SCALE Sleep Apnea randomized clinical trial. *Int J Obes*. 2016;40:1310–1319. doi:10.1038/ijo.2016.52
25. Wadden TA, Hollander P, Klein S, et al. Weight maintenance and additional weight loss with liraglutide after low-calorie-diet-induced weight loss: the SCALE Maintenance randomized study. *Int J Obes*. 2013;37:1443–1451. doi:10.1038/ijo.2013.120
26. Astrup A, Rössner S, Van Gaal L, et al. Effects of liraglutide in the treatment of obesity: a randomised, double-blind, placebo-controlled study. *Lancet*. 2009;374:1606–1616. doi:10.1016/S0140-6736(09)61375-1
27. Marso SP, Daniels GH, Brown-Frandsen K, et al; LEADER Steering Committee; LEADER Trial Investigators. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2016;375:311–322. doi:10.1056/NEJMoa1603827
28. Davies MJ, Aronne LJ, Caterson ID, Thomsen AB, Jacobsen PB, Marso SP. Liraglutide and cardiovascular outcomes in adults with overweight or obesity: a post hoc analysis from SCALE randomized controlled trials. *Diabetes Obes Metab*. 2018;20:734–739. doi:10.1111/dom.13125
29. Nikolic D, Patti AM, Giglio RV, et al. Liraglutide improved cardiometabolic parameters more in obese than in non-obese patients with type 2 diabetes: a real-world 18-month prospective study. *Diabetes Ther*. 2022;13:453–464. doi:10.1007/s13300-022-01217-z
30. Ferrari F, Fierabracci P, Salvetti G, et al. Weight loss effect of liraglutide in real-life: the experience of a single Italian obesity center. *J Endocrinol Invest*. 2020;43:1779–1785. doi:10.1007/s40618-020-01334-1
31. Wharton S, Liu A, Pakseresht A, et al. Real-world clinical effectiveness of liraglutide 3.0 mg for weight management in Canada. *Obesity*. 2019;27:917–924. doi:10.1002/oby.22462
32. Santini S, Vionnet N, Pasquier J, et al. Marked weight loss on liraglutide 3.0 mg: real-life experience of a Swiss cohort with obesity. *Obesity*. 2023;31:31. doi:10.1002/OBY.23596
33. Park JH, Kim JY, Choi JH, et al. Effectiveness of liraglutide 3 mg for the treatment of obesity in a real-world setting without intensive lifestyle intervention. *Int J Obes*. 2021;45:776–786. doi:10.1038/s41366-021-00739-z
34. Gorgojo-Martínez JJ, Basagoiti-Carreño B, Sanz-Velasco A, Serrano-Moreno C, Almodóvar-Ruiz F. Effectiveness and tolerability of orlistat and liraglutide in patients with obesity in a real-world setting: the XENSOR study. *Int J Clin Pract*. 2019;73. doi:10.1111/IJCP.13399
35. Gallo M. Thyroid safety in patients treated with liraglutide. *J Endocrinol Invest*. 2013;36:140–145. doi:10.1007/BF03346749
36. Bjerre Knudsen L, Madsen LW, Andersen S, et al. Glucagon-like peptide-1 receptor agonists activate rodent thyroid C-cells causing calcitonin release and C-cell proliferation. *Endocrinology*. 2010;151(4):1473–1486. doi:10.1210/en.2009-1272
37. Elsayed NA, Aleppo G, Aroda VR, et al. 9. pharmacologic approaches to glycemic treatment: standards of care in diabetes-2023. *Diabetes Care*. 2023;46:S140–57. doi:10.2337/dc23-S009
38. Lau J, Bloch P, Schäffer L, et al. Discovery of the once-weekly Glucagon-Like Peptide-1 (GLP-1) analogue semaglutide. *J Med Chem*. 2015;58:7370–7380. doi:10.1021/acs.jmedchem.5b00726

39. Wilding JPH, Batterham RL, Calanna S, et al. Once-weekly semaglutide in adults with overweight or obesity. *N Engl J Med*. 2021;384:989–1002. doi:10.1056/NEJMoa2032183
40. Jensterle M, Rizzo M, Janež A. Semaglutide in obesity: unmet needs in men. *Diabetes Ther*. 2023;14:461–465. doi:10.1007/s13300-022-01360-7
41. Davies M, Færch L, Jeppesen OK, et al. Semaglutide 2·4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): a randomised, double-blind, double-dummy, placebo-controlled, Phase 3 trial. *Lancet*. 2021;397:971–984. doi:10.1016/S0140-6736(21)00213-0
42. Wadden TA, Bailey TS, Billings LK, et al. Effect of subcutaneous semaglutide vs placebo as an adjunct to intensive behavioral therapy on body weight in adults with overweight or obesity: the STEP 3 randomized clinical trial. *JAMA*. 2021;325:1403–1413. doi:10.1001/jama.2021.1831
43. Rubino D, Abrahamsson N, Davies M, et al. Effect of continued weekly subcutaneous semaglutide vs placebo on weight loss maintenance in adults with overweight or obesity: the STEP 4 randomized clinical trial. *JAMA*. 2021;325:1414–1425. doi:10.1001/jama.2021.3224
44. Garvey WT, Batterham RL, Bhatta M, et al. Two-year effects of semaglutide in adults with overweight or obesity: the STEP 5 trial. *Nat Med*. 2022;28:2083–2091. doi:10.1038/s41591-022-02026-4
45. Ryan DH, Lingvay I, Colhoun HM, et al. Semaglutide effects on cardiovascular outcomes in people with overweight or obesity (SELECT) rationale and design. *Am Heart J*. 2020;229:61–69. doi:10.1016/j.ahj.2020.07.008
46. Rubino DM, Greenway FL, Khalid U, et al. Effect of weekly subcutaneous semaglutide vs daily liraglutide on body weight in adults with overweight or obesity without diabetes: the STEP 8 randomized clinical trial. *JAMA*. 2022;327:138–150. doi:10.1001/jama.2021.23619
47. Min T, Bain SC. The role of tirzepatide, dual GIP and GLP-1 receptor agonist, in the management of type 2 diabetes: the SURPASS clinical trials. *Diabetes Ther*. 2021;12:143. doi:10.1007/s13300-020-00981-0
48. Jastreboff AM, Aronne LJ, Ahmad NN, et al. Tirzepatide once weekly for the treatment of obesity. *N Engl J Med*. 2022;387:205–216. doi:10.1056/NEJMoa2206038
49. Inagaki N, Takeuchi M, Oura T, Imaoka T, Seino Y. Efficacy and safety of tirzepatide monotherapy compared with dulaglutide in Japanese patients with type 2 diabetes (SURPASS J-mono): a double-blind, multicentre, randomised, phase 3 trial. *Lancet Diabetes Endocrinol*. 2022;10:623–633. doi:10.1016/S2213-8587(22)00188-7
50. Alkhezi OS, Alahmed AA, Alfayez OM, Alzuman OA, Almutairi AR, Almohammed OA. Comparative effectiveness of glucagon-like peptide-1 receptor agonists for the management of obesity in adults without diabetes: a network meta-analysis of randomized clinical trials. *Obes Rev*. 2023;24(3):e13543. doi:10.1111/obr.13543
51. Muzurović EM, Volčanšek Š, Tomšić KZ, et al. Glucagon-like peptide-1 receptor agonists and dual glucose-dependent insulinotropic polypeptide/glucagon-like peptide-1 receptor agonists in the treatment of obesity/metabolic syndrome, prediabetes/diabetes and non-alcoholic fatty liver disease-current evidence. *J Cardiovasc Pharmacol Ther*. 2022;27:10742484221146371. doi:10.1177/10742484221146371
52. Heck AM, Yanovski JA, Calis KA. Orlistat, a new lipase inhibitor for the management of obesity. *Pharmacother J Hum Pharmacol Drug Ther*. 2000;20:270–279. doi:10.1592/phco.20.4.270.34882
53. Drew BS, Dixon AF, Dixon JB, Drew andrew F, Dixon John B, Dixon BS. Obesity management: update on orlistat. *Vasc Health Risk Manag*. 2007;3:817–821.
54. Sjöström L, Rissanen A, Andersen T, et al. Randomised placebo-controlled trial of orlistat for weight loss and prevention of weight regain in obese patients. *Lancet*. 1998;352:167–172. doi:10.1016/S0140-6736(97)11509-4
55. Torgerson JS, Hauptman J, Boldrin MN, Sj¨ostr¨om L, Sj¨ostr S, Sj¨ostr¨om S XENical in the Prevention of Diabetes in Obese Subjects (XENDOS) Study A randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients; 2004. Available from: http://diabetesjournals.org/care/article-pdf/27/1/155/563509/zdc00104000155.pdf. Accessed February 9, 2023.
56. Ballinger A. Orlistat in the treatment of obesity. *Expert Opin Pharmacother*. 2005;1:841–847. doi:10.1517/14656566614841
57. Ardissino M, Vincent M, Hines O, et al. Long-term cardiovascular outcomes after orlistat therapy in patients with obesity: a nationwide, propensity-score matched cohort study. *Eur Heart J Cardiovasc Pharmacother*. 2022;8:179–186. doi:10.1093/ehjcvp/pvaa133
58. Athyros VG, Ganotakis E, Kolovou GD, et al. Assessing the treatment effect in metabolic syndrome without perceptible diabetes (ATTEMPT): a prospective-randomized study in middle aged men and women. *Curr Vasc Pharmacol*. 2011;9:647–657. doi:10.2174/157016111797484080
59. Athyros VG, Giouleme O, Ganotakis ES, et al. Safety and impact on cardiovascular events of long-term multifactorial treatment in patients with metabolic syndrome and abnormal liver function tests: a post hoc analysis of the randomised ATTEMPT study. *Arch Med Sci*. 2011;7:796. doi:10.5114/aoms.2011.25554
60. Smith SM, Meyer M, Trinkley KE. Phentermine/Topiramate for the treatment of obesity new drug approvals. *Ann Pharmacother I*. 2013;47. doi:10.1345/aph.1R501
61. Ben-Menachem E, Axelsen M, Johanson EH, Stagge A, Smith U. Predictors of weight loss in adults with topiramate-treated epilepsy. *Obes Res*. 2003;11:556–562. doi:10.1038/oby.2003.78
62. Allison DB, Gadde KM, Garvey WT, et al. Controlled-release phentermine/topiramate in severely obese adults: a randomized controlled trial (EQUIP). *Obesity*. 2012;20:330–342. doi:10.1038/oby.2011.330
63. Aronne LJ, Wadden TA, Peterson C, Winslow D, Odeh S, Gadde KM. Evaluation of phentermine and topiramate versus phentermine/topiramate extended-release in obese adults. *Obesity*. 2013;21(11):2163–2171. doi:10.1002/oby.20584
64. Gadde KM, Allison DB, Ryan DH, et al. Effects of low-dose, controlled-release, phentermine plus topiramate combination on weight and associated comorbidities in overweight and obese adults (CONQUER): a randomised, placebo-controlled, phase 3 trial. *Lancet*. 2011;377:1341–1352. doi:10.1016/S0140-6736(11)60205-5
65. Garvey WT, Ryan DH, Look M, et al. Two-year sustained weight loss and metabolic benefits with controlled-release phentermine/topiramate in obese and overweight adults (SEQUEL): a randomized, placebo-controlled, phase 3 extension study. *Am J Clin Nutr*. 2012;95:297–308. doi:10.3945/ajcn.111.024927
66. Lei XG, Ruan JQ, Lai C, Sun Z, Yang X. Efficacy and safety of phentermine/topiramate in adults with overweight or obesity: a systematic review and meta-analysis. *Obesity*. 2021;29:985–994. doi:10.1002/oby.23152
67. Caixàs A, Albert L, Capel I, Rigla M. Naltrexone sustained-release/bupropion sustained-release for the management of obesity: review of the data to date. *Drug Des Devel Ther*. 2014;1419–1427. doi:10.2147/DDDT.S55587
68. Greenway FL, Fujioka K, Plodkowski RA, et al. Effect of naltrexone plus bupropion on weight loss in overweight and obese adults (COR-I): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2010;376:595–605. doi:10.1016/S0140-6736(10)60888-4

69. Wadden TA, Foreyt JP, Foster GD, et al. Weight loss with naltrexone SR/bupropion SR combination therapy as an adjunct to behavior modification: the COR-BMOD trial. *Obesity*. 2011;19:110–120. doi:10.1038/oby.2010.147
70. Apovian CM, Aronne L, Rubino D, et al. A randomized, phase 3 trial of naltrexone SR/bupropion SR on weight and obesity-related risk factors (COR-II). *Obesity*. 2013;21:935–943. doi:10.1002/oby.20309
71. Sharfstein JM, Psaty BM. Evaluation of the cardiovascular risk of naltrexone-bupropion: a study interrupted. *JAMA*. 2016;315:984–986. doi:10.1001/jama.2016.1461
72. Nissen SE, Wolski KE, Prcela L, et al. Effect of naltrexone-bupropion on major adverse cardiovascular events in overweight and obese patients with cardiovascular risk factors: a randomized clinical trial. *JAMA*. 2016;315:990–1004. doi:10.1001/jama.2016.1558