

Review on obesity management: diet, exercise and pharmacotherapy

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ABSTRACT

Currently, obesity is one of the largest risk factors for cardiometabolic disease in North American adults. Over the past few years, the prevalence of this disease has been steadily increasing. This article is the second article in a three-part series of reviews exploring current clinical guidelines and management strategies used in practice to mitigate the spread of obesity. Guidelines to help physicians manage patients with obesity have been released in Canada and Europe. They outline proper management and treatment for overweight and obese patients. Examples include changes in diet and exercise, behavioural therapy and the administration of antiobesity medications as first-line and second-line treatments. Management of obesity takes on a tiered approach, where first-line therapies include lifestyle changes such as diet and exercise and second-line therapies include the use of antiobesity medications.

BACKGROUND

In this second part of our obesity review series, we will explore the interventions currently used to manage obesity. Interventions include lifestyle changes such as diet, exercise, behavioural therapy and pharmacotherapy.

In the past, pharmacotherapies such as the use of thyroid hormones, dinitrophenol and amphetamines were used to help individuals lose weight.¹ Thyroid hormone increases basal metabolic rate and therefore, thyroid extracts were administered to patients in the early 20th century to help manage obesity.² However, concerns from the medical community highlighted that the thyroid extract's mechanism of action in the body was unknown and that patients appeared to be losing 'functional' body mass such as muscle.¹ This opposition, supported by several clinical studies, eventually resulted in the stoppage of thyroid hormone use in current obesity management. Dinitrophenol, originally used in the manufacture of munitions during World War I, was marketed as a weight-loss agent in the early 20th century.³ Over time, toxicity and death due to dinitrophenol consumption were reported and its use as a weight loss agent halted. Amphetamines also suffered a similar

fate. Originally used to treat attention deficit disorder and psychological illness, clinicians recognised that it also promoted weight loss.⁴ Amphetamines became a main ingredient in the 'Rainbow Pill' for weight loss along with thyroid hormones and laxatives.¹ Rainbow Pills are not prescribed in the clinic; however, they are commercially available on the internet. Current obesity management therapies and pharmacotherapies are outlined below.

DIET AND EXERCISE

The first step to losing weight traditionally includes a change in diet and an increase in exercise.⁵ Past studies have shown that the most effective way to lose a significant amount of weight is a combination of diet, exercise and behavioural changes compared with each of these tools alone. The recommended weekly 150 min of moderate exercise or 75 min of vigorous aerobic exercise is not enough to cause clinically significant weight loss in obese patients without a change in diet.⁶ To maintain weight loss, the American College of Sports Medicine recommends that patients maintain moderate exercise levels of 225–420 min per week (about 60 min of walking a day).⁷ Eating at a calorie deficit of 500–750 calories a day increases weight loss when coupled with physical activity.⁸

Diet

There exist many diets to help promote weight loss. A systematic review conducted in 2014 evaluated the efficiency of four popular weight loss diets (Atkins, South Beach (SB), Weight Watchers (WW) and Zone diets) in promoting weight loss at 12 weeks.⁹ A comparison of multiple studies concluded that modest weight loss was more readily achieved with the Atkins (–2.1 to –4.7 kg), WW (–3.5 to –6.0 kg) and Zone diets (–1.6 to –3.2 kg). Atkins, WW and Zone diets all emphasise a low carbohydrate intake and moderate fat and protein consumption whereas the SB diet focuses on controlling carbohydrates while



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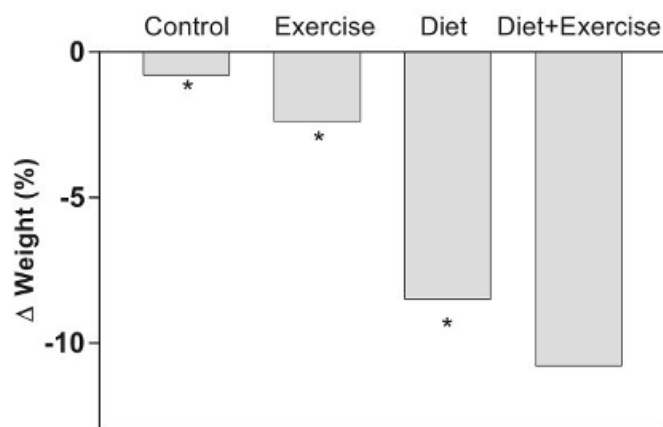


Figure 1 Changes in weight in response to 12 months of diet only, exercise only and the combination of diet and exercise. *A significant difference compared with the diet+exercise arm. Reproduced with permission from Swift *et al.*⁶

consuming lean proteins, monounsaturated or polyunsaturated fats and low-glycaemic index carbohydrates.⁹

The Mediterranean diet has also been explored as a potential way to lose weight. A review published in the *American Journal of Medicine* aims to determine the impact of this diet on weight loss and cardiovascular outcomes in patients with obesity.¹⁰ The Mediterranean diet helped patients achieve a similar weight loss when compared with patients consuming a low carbohydrate diet and the diet recommended by the American Diabetes Association (range of mean values: -4.1 to -10.1 kg vs -4.7 to -7.7 kg). Compared with a low-fat diet, participants on the Mediterranean diet lost more weight (range of mean values: -4.1 to -10.1 kg vs 2.9 to -5.0 kg). All diets similarly helped patients improve their blood pressure and lipid levels. Another study evaluating the effects of a calorie-reduced low fat diet versus aerobic exercise versus a combination of both diet and exercise revealed that populations eating a low fat, low-calorie diet and exercising at a moderate-intensity five times a week lost 10% of their body mass while those only dieting or only exercising lost 8.5% and 0.8% body weight, respectively (figure 1).¹¹ A significant weight reduction was also observed between intervention groups comparing diet and exercise with the control, exercise-only and diet-only ($p<0.0001$). This result supports the hypothesis that a combination of diet and exercise is the best way to lose a significant amount of weight.

Exercise

Various studies have evaluated the effect of the recommended level of aerobic exercise on weight loss (~150 min of moderate-intensity activity) without dietary restriction.¹² They conclude that this is an ineffective means of significantly losing weight since less than 5% of body weight was lost during these trials. The Dose Response to Exercise in postmenopausal Women study that evaluated the effect of 72.2 min/week, 135.8 min/week and 191.7 min/week min of physical activity on weight loss revealed

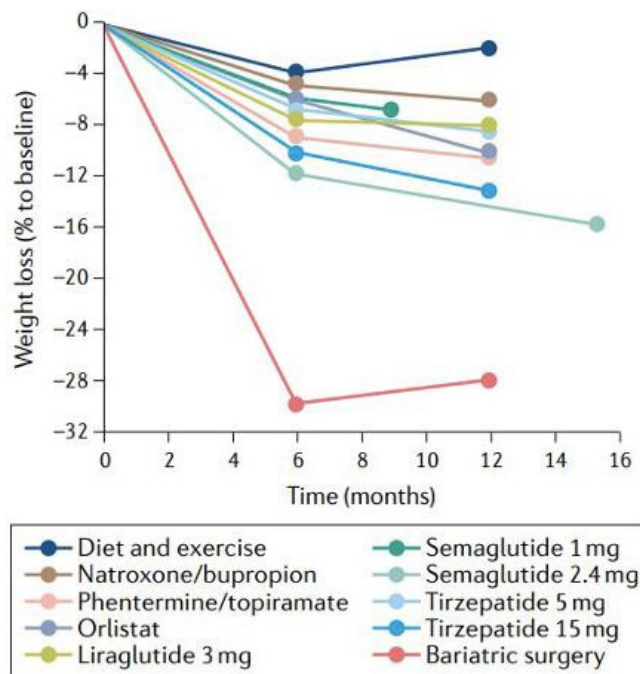


Figure 2 Body weight loss achieved through lifestyle changes, currently approved antiobesity medications and bariatric surgery. Reproduced with permission from Müller *et al.*¹⁴

that in each respective group, women lost 0.5%, 2.5% and 0.7% of their body weight.¹³ This result does not represent a clinically significant deficit in weight, suggesting aerobic exercise is not a sufficient means to lose weight. Furthermore, it is important to note that diet and exercise help patients lose a small amount of weight within the first 6 months of treatment (figure 2).¹⁴ However, their body mass returns to its original weight after 12 months. Aerobic exercise is often prescribed as a common intervention to help patients lose weight. A study evaluating the effects of a 6-month vs 12-month aerobic exercise programme on weight loss and waist circumference measures revealed that both programmes induced moderate changes in weight (-1.6 kg and -1.7 kg, respectively).¹⁵ Thus, to lose a significant amount of weight, a change in diet must also be explored. It is important to note that exercising improves health independent of weight loss. The benefits of exercise include delaying the onset of chronic diseases, strengthening muscles and bones and lengthening lifespan.¹⁶ Therefore, exercise and healthy diet should be promoted by clinicians independent of weight-loss goals, although their weight management can be significant.

BEHAVIOURAL THERAPY INTERVENTIONS

Behavioural therapy is another means physicians use to encourage weight loss. A systematic review and meta-analysis evaluating the effectiveness of behavioural weight loss interventions in primary care settings found that these interventions were only modestly effective at producing weight loss in just over 4500 overweight and

obese patients.¹⁷ The meta-analysis revealed that an average weight loss of 1.36 kg was achieved with behavioural therapy. These data are evidence that therapy should be used as an adjunct to diet and exercise for weight loss and not as a primary method.

Types of behavioural therapy for obesity

Mindfulness

Recently, there has been increasing interest in mindfulness and mindful eating practices as therapeutic methods for obesity management. Mindful eating refers to the maintenance of a non-judgemental awareness while eating.¹⁸ This practice can help obese patients become more sensitive to their hunger and satiety cues, pace of eating and food environments which is essential to learn self-regulation.¹⁸ Previous studies have shown that people who practice mindful eating are more likely to consume smaller portions of energy-dense foods and practice healthier eating habits.¹⁹ Other effects of mindful eating in obese patients include less binge eating or emotional eating leading to weight loss.²⁰

Acceptance-based behavioural therapy

Acceptance-based behavioural therapy (ABBT) incorporates mindfulness to increase awareness of internal and external factors leading to a specific behaviour and accepting them as transient and not fixed character traits.²¹ Overall, ABBT appears to help patients lose weight, increase exercise, reduce cravings, decrease body image concerns and limit the avoidance of weight-related experiences.²¹ A 2012 study reported that post-treatment, patients lost 4.85 lbs and 0.75 body mass index (BMI) points.²¹ Compared with patients receiving standard behavioural treatment (SBT), patients receiving ABBT lost ~13% of their body weight (vs ~7% in SBT).²² Therefore, mindfulness approaches could be useful to help patients change their attitudes towards food and lose weight.

Meditation

Meditation, a practice involving the use of physical or emotional techniques to achieve a state of calmness and awareness, is also being used to help individuals lose weight. Techniques, such as mindful walking, food

Table 1 Antiobesity medications used in clinical practice

Medication	Dose	Mechanism of action	Side effects	Warnings
Diethylpropion (Tenuate)	75 mg QD	Indirect-acting sympathomimetic agent that acts by releasing norepinephrine from the presynaptic vesicles in the lateral hypothalamus. Stimulates the release of norepinephrine and epinephrine	Nervousness, excitability, insomnia, headache, dry mouth, sweating, nausea, constipation and thirst	Contraindicated for advanced arteriosclerosis, symptomatic CVD, moderate to severe hypertension, hyperthyroidism, glaucoma, patients in an agitated state or those with a history of amphetamine abuse. Warnings include pulmonary hypertension and cardiomyopathy secondary to chronic use of sympathomimetics, and valvular heart disease secondary to use of sympathomimetics with additional anorectic agents
Naltrexone-bupropion (Contrave)	16/180 mg PO QHS	Naltrexone+bupropion, lessens appetite	Constipation, diarrhoea, dizziness, dry mouth, headache, increased blood pressure, increased heart rate, insomnia, liver damage, nausea, vomiting	Contraindicated for people with high blood pressure, dependence on opioids, withdrawal from drugs and alcohol, seizures, history of anorexia or bulimia nervosa, bupropion. Might increase suicidal thoughts or actions.
Orlistat (Xenical)	120 mg PO TID	Reduces amount of fat absorbed	Diarrhoea, gas, leakage of oily stools, stomach pain	Severe liver injury, avoid taking with cyclosporine, must take vitamins daily
Phenterminetopiramate (Qsymia)	7.5/46 mg PO QD	A mix of phentermine, (lessens appetite) and topiramate (treats seizures and headaches). Lessens appetite.	Constipation, dizziness, dry mouth, taste changes, tingling of your hands and feet, trouble sleeping	Contraindicated for glaucoma or hyperthyroidism, do not take if pregnant or breastfeeding
Setmelanotide (Imcivree)	3 mg SC QD	May reduce appetite and increase feeling of fullness, may increase resting metabolism	Injection site reaction, skin darkening, nausea, disturbance in sexual arousal, depression and suicidal ideation, risk of serious adverse reactions in neonates and infants with low birth weight	Only for people with proopiomelanocortin (POMC) deficiency, proprotein convertase subtilisin/kexin type 1 (PCSK1) deficiency, leptin receptor (LEPR) deficiency. Do not use while pregnant or breast feeding.

CVD, cardiovascular disease; PO, per os; QD, once a day; QHS, every bedtime; SC, subcutaneous; TID, three times per day.

Table 2 Sodium-glucose co-transporter 2 (SGLT2) inhibitors for weight

Medication	Dose	Action	Mechanism of weight loss effect	Side effects
Canagliflozin (Invokana)	300 mg QD	Reduce renal tubular glucose reabsorption, to reduce in blood glucose without stimulating insulin release	2.9 kg lost in 12 weeks at a dose of 100 mg ^{1,2}	Urinary tract infection, genital yeast infections, URTI, increased urination, dyslipidaemia, joint pain, nausea, thirst, back pain, constipation, influenza, painful urination. Serious side effects include kidney injury and ketoacidosis.
Dapagliflozin (Farxiga)	10 mg QD		3.4 kg lost in 1 year at a dose of 2.5–20 mg ³	
Empagliflozin (Jardiance)	25 mg QD		2.5 kg lost in 24 weeks on 25 mg ⁴	
Ertugliflozin (Steglatro)	5 or 15 mg QD		3.2 kg lost after 26 weeks on 15 mg ⁵	

QD, once a day; URTI, upper respiratory tract infection.

diaries, self-compassion and breathing exercises, have been shown to affect participants' thoughts and attitudes towards food and, therefore, their weight.²³ A systematic review evaluating the effects of meditation on eating behaviours and weight loss revealed that meditation can have slight benefits in reducing dysfunctional eating patterns such as uncontrolled eating.²⁴ Interestingly, meditation practices encouraged a slight reduction in weight in participants with a BMI >25 kg/m² compared with patients with overweight who did not engage in these techniques.²⁴ However, no difference was observed in participants who had a normal weight. Other studies concluded that meditation techniques reduced participants' calorie intake by 769 calories/day.²³ Thus, coupled with diet and exercise, meditation-oriented behavioural therapy should be explored and optimised as a potential way to help patients improve their eating habits.

PHARMACOTHERAPY FOR OBESITY MANAGEMENT

There are several different medications available for management of obesity. Guidelines suggest that these therapies can be used if the BMI of a patient is >30 kg/m² or is >27 kg/m² with one weight-related comorbidity.²⁵ Pharmacotherapies available include medical devices, lipase inhibitors, sympathomimetic amine and anorectic agents as well as others (table 1).

Diethylpropion

Diethylpropion, brand name Tenuate, is a sympathomimetic amine and anorectic agent used for short-term weight management.²⁶ Long-term use of this medication can cause serious side effects such as heart problems and high blood pressure.²⁶ It was approved by the US Food and Drug Administration (FDA) in 1959 and is recommended for short-term (less than 12 weeks) obesity treatment. It functions similarly to amphetamines and stimulates the release of high levels of catecholamines, mainly norepinephrine and epinephrine, which act to suppress hunger signals via the central nervous system.²⁷ Diethylpropion is administered daily and is available in immediate-release and the controlled-release tablets.²⁶ Immediate-release tablets are administered orally three

times a day in doses of 25 mg 1 hour before meals and once in mid-evening. Controlled-release tablets are administered orally in doses of 75 mg once a day, typically in mid-morning. Patients on diethylpropion lose an average of 5.9 kg when compared with placebo.²⁸ Common side effects include nervousness, excitability, insomnia, headache, dry mouth, sweating, nausea, constipation and thirst.²⁹ Diethylpropion is contraindicated for patients with advanced arteriosclerosis, symptomatic cardiovascular disease (CVD), moderate to severe hypertension, hyperthyroidism, glaucoma, patients in an agitated state or those with previous amphetamine abuse. Importantly, the short-term use of antiobesity medication can only provide limited benefits to patients, as obesity is a long-term disease. New-generation obesity pharmacotherapies described below are safer for long-term use and can provide greater benefits with regard to weight loss.

Naltrexone/bupropion (Contrave)

Naltrexone/bupropion, brand name Contrave, is a combination drug composed of naltrexone and bupropion. Naltrexone is a mu-opioid receptor antagonist used to treat opioid and alcohol dependence.³⁰ It acts via the cannabinoid-1 receptor to inhibit the effects of beta-endorphin on increasing appetite. Bupropion is a dopamine reuptake inhibitor commonly used in treating depression and as a smoking cessation drug.³⁰ This drug activates pro-opiomelanocortin (POMC) release which acts in the hypothalamus to decrease hunger signals.³¹ Together, naltrexone and bupropion have been proven to be an effective weight management drug.^{32–34} Dosing should be titrated over the course of 4 weeks until a recommended dose of two 8 mg/90 mg tablets two times per day is reached.³⁵ In the COR-I trial, naltrexone/bupropion caused patients to lose approximately 6% of their body weight compared with 1% in the placebo group.³⁶ The side effects of naltrexone/bupropion include constipation, diarrhoea, dizziness, dry mouth, headache, increased blood pressure, increased heart rate, insomnia, liver damage, nausea and vomiting.³⁵ People with high blood pressure, dependence on opioids, withdrawal from drugs and alcohol, seizures, history of anorexia or bulimia

Table 3 Sodium-glucose co-transporter 2 (SGLT2) inhibitors for weight

Medication	Dose	Mechanism of action	Weight loss effect	Side effects
Canagliflozin (Invokana)	300 mg QD	Reduce renal tubular glucose reabsorption, to reduce in blood glucose without stimulating insulin release	2.9 kg lost in 12 weeks at a dose of 100 mg* †	Urinary tract infection, genital yeast infections, URTI, increased urination, dyslipidaemia, joint pain, nausea, thirst, back pain, constipation, influenza, painful urination. Serious side effects include kidney injury and ketoacidosis.
Dapagliflozin (Farxiga)	10 mg QD		3.4 kg lost in 1 year at a dose of 2.5–20 mg‡	
Empagliflozin (Jardiance)	25 mg QD		2.5 kg lost in 24 weeks on 25 mg§	
Ertugliflozin (Steglatro)	5 or 15 mg QD		3.2 kg lost after 26 weeks on 15 mg¶	
*Plodkowski <i>et al.</i> ⁵¹ †Bays <i>et al.</i> ⁶⁴ ‡Huh and Kim. ⁶⁵ §Häring <i>et al.</i> ⁶⁶ ¶Heymsfield <i>et al.</i> ⁶⁷ QD, once a day.				

nervosa and bupropion use are not advised to take this medication. This medication might also increase suicidal thoughts or actions.

Orlistat (Xenical)

Orlistat, also known as Xenical, is a gastric, pancreatic and intestinal lipase inhibitor, preventing the breakdown of fatty acids and triglycerides and consequently, their absorption and metabolism.³⁰ This mechanism reduces the number of calories the patient absorbs through their food, leading to weight loss. Orlistat is administered orally three times a day approximately 1 hour after eating a meal containing 30% fat.³⁷ Each tablet is 120 mg, amounting to a daily dose of 360 mg a day. From baseline to week 68, patients administered Orlistat lost on average 15% of their body weight compared with 1.9% in the placebo group.³⁷ In experimental groups receiving 120 mg of Orlistat, a 9.8% weight loss is observed.³⁸ Side effects include faecal incontinence, oily spotting, fatty stool, constipation, gastrointestinal complications, diarrhoea, gas and stomach pains.³⁰ Orlistat is not recommended for patients with severe liver injury. Cyclosporine and thyroid hormone drugs should not be taken at the same time as Orlistat since they risk reducing its efficiency. Since this medication reduces the absorption of fats and subsequently the absorption of fat soluble vitamins like vitamins A, D, E and K, multivitamins are recommended to avoid deficiency.³⁹

Phentermine/topiramate (Qsymia)

Like naltrexone-bupropion, phentermine/topiramate is a combination of two drugs; phentermine and topiramate that work synergistically to increase the effects of weight loss in obese patients.⁴⁰ Similar to diethylpropion, phentermine reduces hunger signals in the hypothalamus by increasing the secretion of epinephrine.⁴¹ Topiramate is a gamma-aminobutyric acid agonist, glutamate antagonist and carbonic anhydrase inhibitor.⁴² Its mechanism of action is currently

uncertain; however, it exercises its roles by increasing satiety, increasing energy expenditure and reducing caloric intake. Coupled together, these medications can be used at lower doses without compromising its effect on weight loss.³⁰ This medication is used at a recommended dose of one 7.5 mg/46 mg capsule daily taken orally.⁴³ At this dose, patients can lose approximately 13% of their body weight at week 40 compared with 3% in the placebo group.⁴⁴ The side effects of this medication are constipation, dizziness, dry mouth, taste changes, tingling of the hands and feet and trouble sleeping. Topiramate is contraindicated in pregnant patients since it increases the risk of cleft palate in babies.³⁰ Other contraindicated conditions for this drug include uncontrolled hypertension, CVD, chronic kidney disease, glaucoma and hyperthyroidism.

Setmelanotide (Imcivree)

Setmelanotide is a melanocortin-4 (MC4) receptor agonist that treats obesity arising from rare genetic disorders due to POMC, proprotein convertase subtilisin/kexin type 1 (PCSK1) or leptin receptor (LEPR) deficiency.⁴⁵ Since setmelanotide is an analogue to the MC4 receptor ligand alpha-melanocyte stimulating hormone, it functions by binding to the MC4 receptor in the hypothalamus. This regulates hunger, satiety and energy expenditure. It has proven to be effective in patients with Bardet-Biedl syndrome and Alström syndrome.⁴⁶ This drug is specifically used in cases where obesity is caused by a POMC, PCSK1 or LEPR deficiency.⁴⁷ Setmelanotide is administered as a daily 3 mg subcutaneous injection.⁴⁸ In patients with POMC and LEPR deficiency, setmelanotide can help reduce weight by 25% and 12.5% from baseline respectively.⁴⁹ Side effects of this medication include injection site reaction, hyperpigmentation, spontaneous penile erection, depression and suicidal ideation. This medication is contraindicated in women who are pregnant or breast feeding.

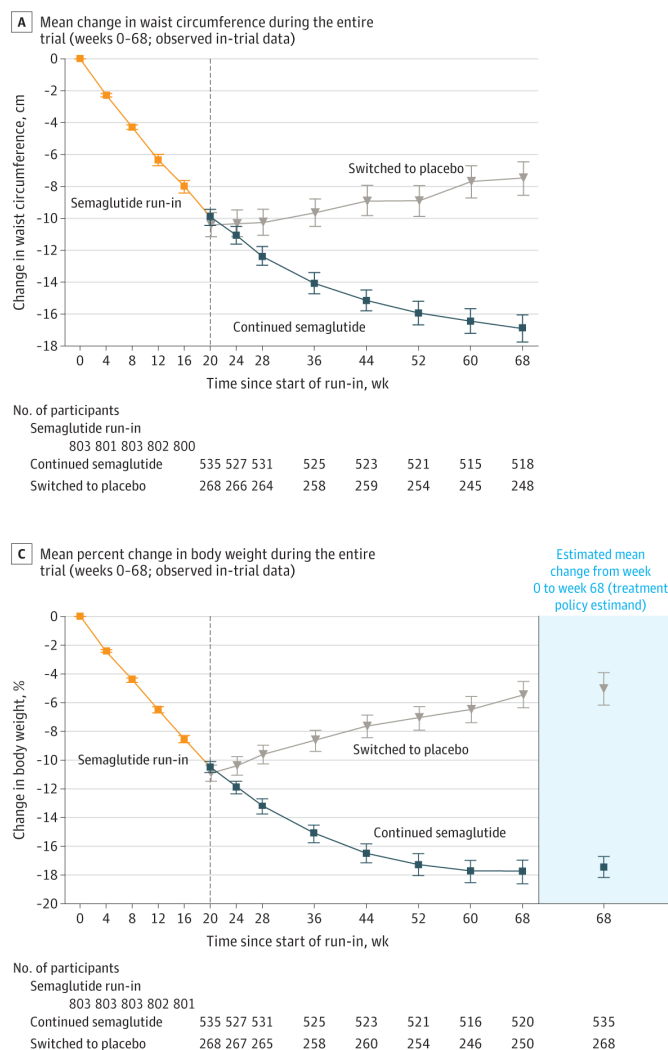


Figure 3 Effect of semaglutide, 2.4 mg once weekly, compared with placebo on efficacy outcomes. Error bars represent 95% CIs for the mean. Participant numbers shown denote those contributing to the mean. The dashed vertical line at week 20 represents the randomisation time point. Reproduced with permission from Rubino *et al.*⁵⁶

Sodium-glucose co-transporter 2 inhibitors

Sodium-glucose co-transporter 2 inhibitors are also common weight loss medications (table 2). These drugs have been approved by the FDA for treatment of type II diabetes and can be taken in conjunction with metformin to control insulin levels.⁵⁰ Recently, studies have shown that SGLT2 is also cause weight loss and can be used as antiobesity drugs.⁵⁰ These drugs share a mechanism of action where they reduce renal tubular glucose absorption and subsequently reduce blood glucose without stimulating insulin production. This reduces the amount of glucose the body absorbs, and consequently, the number of calories absorbed.⁵⁰ So far, there exists four main SGLT2s being used in the clinic: canagliflozin (Invokana), dapagliflozin (Farxiga), empagliflozin (Jardiance) and ertugliflozin (Steglatro).⁵¹ On average, regular use of SGLT2 is results in an approximate 3 kg of weight loss.⁵¹ Common side effects include urinary tract

infections, genital yeast infections, increased urination, dyslipidaemia, thirst and painful urination.⁵² More rare side effects include kidney injury and ketoacidosis.

GLP-1 agonists

Glucose-like protein 1 (GLP-1) receptor agonists are also effective for weight loss (table 3). These agents mimic GLP-1 and targeted areas of the brain that regulate appetite and food intake. In the body, GLP-1 is secreted from the intestines in response to the intake of fats and carbohydrates.⁵³ It increases insulin secretion by stimulating pancreatic B-cells and inhibits glucagon secretion from pancreatic A-cells. This peptide also acts on the hypothalamus to increase satiety, the stomach to reduce gastric emptying, skeletal muscles to increase glucose deposit and the heart.⁵⁴ GLP-1 receptor agonists were initially developed to mitigate diabetes mellitus but have since been used for obesity due to their weight loss properties.⁴⁰ Common GLP-1 medications used for obesity are dulaglutide (Trulicity), liraglutide (Saxenda), lisenatide (Adlyxin) and semaglutide (Wegovy or Ozempic).⁵³ These medications are typically administered through daily or weekly subcutaneous injection. Each of these medications is associated with gastrointestinal side effects including nausea, diarrhoea, vomiting, decreased appetite, abdominal pain and indigestion.⁵⁵ Other side effects include fatigue, injection site reaction, headaches and nasopharyngitis. The risks of using these drugs include developing acute pancreatitis and pancreatic carcinoma, an increased risk of bile duct and gallbladder disease and diabetic ketoacidosis.⁵³

A study published in *JAMA* in 2021 evaluated the effect of continuous use of 2.4 mg semaglutide on weight loss in overweight and obese patients.⁵⁶ A total of 803 participants were treated with semaglutide. Those who achieved a mean of 10.6% body weight reduction in the first 20 weeks were randomised to either continue treatment or switch to a placebo. Patients on the medication lost an average of 7.6% more weight while the placebo group gained 6.9% (figure 3). In total, patients lost approximately 18% of their body weight when treated with 2.4 mg of semaglutide for 68 weeks. Furthermore, their waist circumference measures decreased by 17 cm. At 68 weeks, participants who switched to a placebo observed an overall reduction of 8 cm in their waist circumference and approximately 5% reduction in body mass. Therefore, long-term use of semaglutide is an efficient way to reduce weight and might be moderately useful over shorter periods of time.

A novel GLP-1 receptor agonist called tirzepatide (Mounjaro) was approved by the FDA in 2022 as a medication for type II diabetes (table 4).⁵⁷ Importantly, a clinical trial published in the *New England Journal of Medicine* aimed to evaluate tirzepatide as a potential antiobesity medication.⁵⁸ In this study, 2539 adults with a BMI of >30 or >27 with one weight-related comorbidity were administered weekly injections of Mounjaro for a period of 72 weeks. Patients were randomised into 1:1:1:1 ratio

Table 4 Glucose-like peptide 1 (GLP-1) receptor agonists for weight

Medication	Dose	Mechanism of action	Weight loss effects	Common side effects
Dulaglutide (Trulicity)	0.75 mg–4.5 mg/0.5 mL SC weekly		4 kg lost at 26 weeks at 3 mg*	Nausea, diarrhoea, vomiting, abdominal pain, decreased appetite, indigestion, fatigue
Liraglutide (Saxenda)	3 mg SC QD		8.4 kg lost at 56 weeks at 3 mg†	Nausea, diarrhoea, constipation, abdominal pain, headache, increased heart rate
Lixisenatide (Adlyxyn)	20 µg SC QD	Mimics glucagon-like peptide-1 (GLP-1) that targets areas of the brain that regulate appetite and food intake	2.0 kg loss at 26 weeks at 20 µg‡	Nausea, vomiting, headache, injection site, reaction, dizziness, diarrhoea, dyspnoea, constipation
Semaglutide (Wegovy)	0.5 mg SC weekly		4.4 kg after 12 weeks at 1.7 and 2.4 mg§	Nausea, diarrhoea, vomiting, constipation, abdominal pain, headache, fatigue

*Frias *et al.*⁶⁸†Pi-Sunyer *et al.*⁶⁹‡Rosenstock *et al.*⁷⁰§Ghush *et al.*⁷¹

QD, once a day; SC, subcutaneous.

to doses of 5 mg, 10 mg, 15 mg or placebo. The mean percentage of change in weight at week 72 was –15.0% with 5 mg doses, –19.5% with 10 mg doses, –20.9% with 15 mg doses and –3.1% with placebo injections (figure 4). This study suggests that tirzepatide could be useful as a future antiobesity medication. Furthermore, it suggests that GLP-1 receptor agonists are highly effective for weight loss and at its highest dosages cause a greater than 20% reduction weight loss with use over 72 weeks.

Common antiobesity drugs differ in the per cent of weight lost they induce compared with baseline¹⁴

(figure 2). The mean weight loss achieved with approved antiobesity medications is limited to 3%–7% after 6–12 months of treatment. Very few patients manage to achieve a body mass reduction of 10%–15% relative to placebo. GLP-1 receptor agonists semaglutide and tirzepatide appear to be significantly more efficient than other classes of medications. Semaglutide at 2.4 mg and tirzepatide at doses of 10 g and 15 mg can help patients reduce their body weight by more than 10%. Overall, this indicates that GLP-1 receptor agonists cause more weight loss in obese patients than other classes of medications.

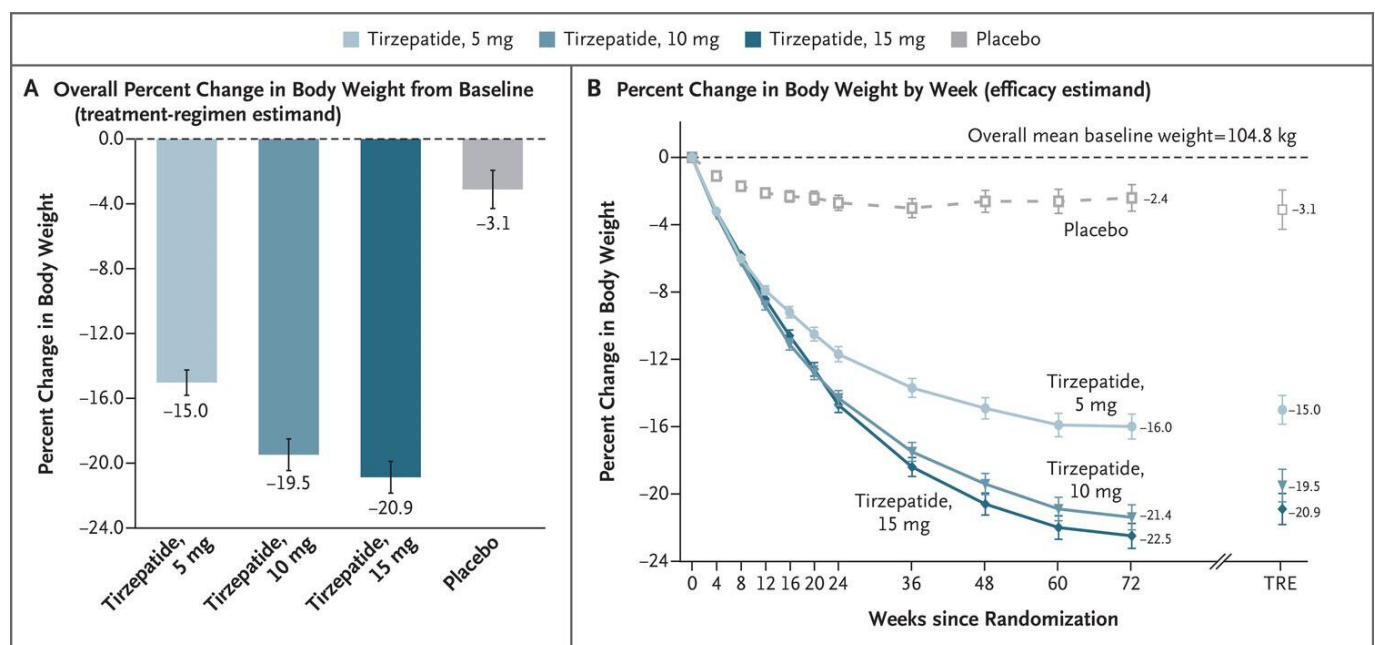


Figure 4 (A) The per cent change in body weight from baseline to week 72, derived from an analysis of covariance model for the treatment-regimen estimand (TRE). (B) The per cent change in body weight according to weeks since randomisation, derived from a mixed model for repeated measures analysis for the efficacy estimand; week 72 estimates for the treatment-regimen estimand are also shown. Reproduced with permission from Jastreboff *et al.*⁵⁸

Physicians may use a prescribing algorithm to help determine which antiobesity medication to prescribe (online supplemental appendix 1).³⁰ First, patients must meet the eligibility criteria to receive pharmacotherapy for obesity which is having a BMI of $>30\text{ kg/m}^2$ or $>27\text{ kg/m}^2$ with one weight-related comorbidity. In adjunct to pharmacotherapy, lifestyle interventions such as diet and exercise should be recommended. Physicians should consider a patient's comorbidities to prescribe the correct medication. For instance, a patient who suffers from hypertension should be prescribed orlistat as a first-line therapy. If the first-line therapy does not provide significant results, second-line or third-line therapies should be explored. In this case, these therapies include phentermine/topiramate and liraglutide. Patients with depression and anxiety should be prescribed orlistat, then naltrexone and if appropriate liraglutide may be used. Drug use should be followed up every 3 months.

The future of antiobesity pharmacotherapy

Several promising new drugs have been undergoing clinical trials for approval as antiobesity medications. Phase I trials of a molecule called BI 456906, a dual glucagon receptor/glucagon-like peptide-1 receptor agonist, are currently underway. Preliminary studies show a 12.3% decrease in body weight at 16 weeks of treatment as well as adequate tolerability by patients.⁵⁹ A recent phase II trial of the drug orforglipron, an oral GLP-1 receptor agonist, reports that at week 26, patients administered the agonist lost 8.6%–12.6% of their body weight compared with 2% in the placebo group.⁶⁰ By week 36, this reduction had jumped to –14.7% in the treatment group and –2.3% in the placebo group.⁶⁰ Cardiometabolic measures were also vastly improved in the treatment group. The weight loss effects of orforglipron are significant, and importantly, comparable to existing weight-loss medications. Another antiobesity medication on the rise is retratrutide, a triple hormone receptor agonist also in phase II trials. Retratrutide agonises the glucagon-like peptide 1, and glucagon receptors and is administered subcutaneously like semaglutide.⁶¹ Studies reveal that this drug has a dose-dependent weight loss effect, with patients who received 8 mg injections losing 17.3% of their body weight at 24 weeks compared with –1.6% in the placebo group.⁶¹ This weight reduction exceeds that of orforglipron, semaglutide and tirzepatide. Should it be approved for marketing, retratrutide could significantly change the pharmacological landscape of antiobesity medications. Coadministration of semaglutide and cagrilintide (CagriSema) to patients with obesity has also shown promising results, as the dual administration of these drugs increases weight loss to –15.6% at week 32 compared with –5.1% for semaglutide alone and –8.1% for cagrilintide alone. It is clear that novel antiobesity medications with dual receptor

agonist actions or dual administration are superior to currently used pharmacotherapies and could be the future of obesity management.

CONCLUSION

Obesity is a complex, multifactorial and chronic disease. The rise of obesity is in part related to the consumption of agricultural subsidies, the increasing availability of energy-dense foods and the reduction of physical activity.⁶² To mitigate the spread of this disease, physicians should assess the presence of overweight and obesity at every patient encounter.²⁵ Recommendations include using BMI and waist circumference to diagnose overweight and obesity. Healthcare workers should be aware that a BMI $>25\text{ kg/m}^2$ is associated with an increased risk of comorbidities including diabetes and CVD. In addition, BMI $>30\text{ kg/m}^2$ is associated with an increase in the rate of weight-related comorbidities, CVD and mortality. Clinical management of overweight and obesity should involve lifestyle intervention for 6 months including referral to a dietitian as well as increased physical activity.²⁵ Pharmacotherapy should be considered as an adjunct to diet and exercise if the patient has a BMI $>30\text{ kg/m}^2$ or $>27\text{ kg/m}^2$ with comorbidities.⁶³

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REFERENCES

- 1 Bray GA, Purnell JQ. An historical review of steps and missteps in the discovery of anti-obesity drugs. In: *Endotext*. South Dartmouth (MA): MDText.com, Inc, 2000-2024. Available: <https://www.ncbi.nlm.nih.gov/books/NBK581942/>

- 2 Kaptein EM, Beale E, Chan LS. Thyroid hormone therapy for obesity and nonthyroidal illnesses: a systematic review. *J Clin Endocrinol Metab* 2009;94:3663–75.
- 3 Grundlingh J, Dargan PI, El-Zanfaly M, et al. 2,4-dinitrophenol (DNP): a weight loss agent with significant acute toxicity and risk of death. *J Med Toxicol* 2011;7:205–12.
- 4 Lesses MF, Myerson A. Human Autonomic Pharmacology. *N Engl J Med* 1938;218:119–24.
- 5 Chao AM, Quigley KM, Wadden TA. Dietary interventions for obesity: clinical and mechanistic findings. *J Clin Invest* 2021;131:e140065.
- 6 Swift DL, McGee JE, Earnest CP, et al. The Effects of Exercise and Physical Activity on Weight Loss and Maintenance. *Prog Cardiovasc Dis* 2018;61:206–13.
- 7 Donnelly JE, Blair SN, Jakicic JM, et al. Appropriate Physical Activity Intervention Strategies for Weight Loss and Prevention of Weight Regain for Adults. *Med Sci Sports Exerc* 2009;41:459–71.
- 8 Ryan DH, Kahan S. Guideline Recommendations for Obesity Management. *Med Clin North Am* 2018;102:49–63.
- 9 Atallah R, Filion KB, Wakil SM, et al. Long-term effects of 4 popular diets on weight loss and cardiovascular risk factors: a systematic review of randomized controlled trials. *Circ Cardiovasc Qual Outcomes* 2014;7:815–27.
- 10 Mancini JG, Filion KB, Atallah R, et al. Systematic Review of the Mediterranean Diet for Long-Term Weight Loss. *Am J Med* 2016;129:407–15.
- 11 Foster-Schubert KE, Alfano CM, Duggan CR, et al. Effect of diet and exercise, alone or combined, on weight and body composition in overweight-to-obese postmenopausal women. *Obesity (Silver Spring)* 2012;20:1628–38.
- 12 Donnelly JE, Blair SN, Jakicic JM, et al. American College of Sports Medicine Position Stand. Appropriate physical activity intervention strategies for weight loss and prevention of weight regain for adults. *Med Sci Sports Exerc* 2009;41:459–71.
- 13 Church TS, Earnest CP, Skinner JS, et al. Effects of different doses of physical activity on cardiorespiratory fitness among sedentary, overweight or obese postmenopausal women with elevated blood pressure: a randomized controlled trial. *JAMA* 2007;297:2081–91.
- 14 Müller TD, Blüher M, Tschöp MH, et al. Anti-obesity drug discovery: advances and challenges. *Nat Rev Drug Discov* 2022;21:201–23.
- 15 Thorogood A, Mottillo S, Shimony A, et al. Isolated aerobic exercise and weight loss: a systematic review and meta-analysis of randomized controlled trials. *Am J Med* 2011;124:747–55.
- 16 Rueggsegger GN, Booth FW. Health Benefits of Exercise. *Cold Spring Harb Perspect Med* 2018;8:a029694.
- 17 Booth HP, Prevost TA, Wright AJ, et al. Effectiveness of behavioural weight loss interventions delivered in a primary care setting: a systematic review and meta-analysis. *Fam Pract* 2014;31:643–53.
- 18 Framson C, Kristal AR, Schenk JM, et al. Development and validation of the mindful eating questionnaire. *J Am Diet Assoc* 2009;109:1439–44.
- 19 Alberts HJEM, Thewissen R, Raes L. Dealing with problematic eating behaviour. The effects of a mindfulness-based intervention on eating behaviour, food cravings, dichotomous thinking and body image concern. *Appetite* 2012;58:847–51.
- 20 O'Reilly GA, Cook L, Spruijt-Metz D, et al. Mindfulness-based interventions for obesity-related eating behaviours: a literature review. *Obes Rev* 2014;15:453–61.
- 21 Goodwin CL, Forman EM, Herbert JD, et al. A pilot study examining the initial effectiveness of A brief acceptance-based behavior therapy for modifying diet and physical activity among cardiac patients. *Behav Modif* 2012;36:199–217.
- 22 Forman EM, Butryn ML, Juarascio AS, et al. The mind your health project: a randomized controlled trial of an innovative behavioral treatment for obesity. *Obesity (Silver Spring)* 2013;21:1119–26.
- 23 Timmerman GM, Brown A. The effect of a mindful restaurant eating intervention on weight management in women. *J Nutr Educ Behav* 2012;44:22–8.
- 24 Oliveira JPT, do Carmo SG, Aragão B de A, et al. Meditation practices and their relationship with eating behavior, weight changes, and mental health in adults from different regions of Brazil: A cross-sectional study. *Nutrition* 2023;109:111972.
- 25 Wharton S, Lau DCW, Vallis M, et al. Obesity in adults: a clinical practice guideline. *CMAJ* 2020;192:E875–91.
- 26 National Institute of Diabetes and Digestive and Kidney Diseases. "Diethylpropion," in *LiverTox: Clinical and Research Information on Drug-Induced Liver Injury*. Bethesda (MD), 2012.
- 27 Arias HR, Santamaria A, Ali SF. Pharmacological and neurotoxicological actions mediated by bupropion and diethylpropion. *Int Rev Neurobiol* 2009;88:223–55.
- 28 Farah D, Fonseca MCM. Short-term Evidence in Adults of Anorexic Drugs Acting in the Central Nervous System: A Meta-Analysis. *Clin Ther* 2019;41:1798–815.
- 29 National Institute of Diabetes and Digestive and Kidney Diseases. *LiverTox: Clinical and Research Information on Drug-Induced Liver Injury*. Bethesda (MD), 2012.
- 30 Son JW, Kim S. Comprehensive Review of Current and Upcoming Anti-Obesity Drugs. *Diabetes Metab J* 2020;44:802–18.
- 31 Wang GJ, Volkow ND, Logan J, et al. Brain dopamine and obesity. *Lancet* 2001;357:354–7.
- 32 Caixàs A, Albert L, Capel I, et al. Naltrexone sustained-release/bupropion sustained-release for the management of obesity: review of the data to date. *Drug Des Devel Ther* 2014;8:1419–27.
- 33 Koch M, Varela L, Kim JG, et al. Hypothalamic POMC neurons promote cannabinoid-induced feeding. *Nature New Biol* 2015;519:45–50.
- 34 Dutia R, Meece K, Dighe S, et al. β -Endorphin antagonizes the effects of α -MSH on food intake and body weight. *Endocrinology* 2012;153:4246–55.
- 35 CONTRAVE (naltrexone HCL and bupropion HCL) [prescribing information]. Nalpropion Pharmaceuticals LLC; 2023. Available: <https://www.contravehcp.com/dosing/>
- 36 Greenway FL, Fujioka K, Plodkowski RA, et al. Effect of naltrexone plus bupropion on weight loss in overweight and obese adults (COR-1): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2010;376:595–605.
- 37 XENICAL [prescription label]. 2009. Available: https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020766s026lbl.pdf
- 38 Van Gaal LF, Broom JI, Enzi G, et al. Efficacy and tolerability of orlistat in the treatment of obesity: a 6-month dose-ranging study. Orlistat Dose-Ranging Study Group. *Eur J Clin Pharmacol* 1998;54:125–32.
- 39 O'Brien PE, Hindle A, Brennan L, et al. Long-Term Outcomes After Bariatric Surgery: a Systematic Review and Meta-analysis of Weight Loss at 10 or More Years for All Bariatric Procedures and a Single-Centre Review of 20-Year Outcomes After Adjustable Gastric Banding. *Obes Surg* 2019;29:3–14.
- 40 Nauck MA. The design of the liraglutide clinical trial programme. *Diabetes Obes Metab* 2012;14 Suppl 2:4–12.
- 41 Cohen JB, Gadde KM. Weight Loss Medications in the Treatment of Obesity and Hypertension. *Curr Hypertens Rep* 2019;21:16.
- 42 Antel J, Hebebrand J. Weight-reducing side effects of the antiepileptic agents topiramate and zonisamide. *Handb Exp Pharmacol* 2012;433–66.
- 43 QYSMIA [prescription label]. 2012. Available: https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022580s000lbl.pdf
- 44 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 (SEQUENCE): a randomized, placebo-controlled, phase 3 extension study. *Am J Clin Nutr* 2012;95:297–308.
- 45 Markham A. Setmelanotide: First Approval. *Drugs (Abingdon Engl)* 2021;81:397–403.
- 46 R Pharmaceuticals. Rhythm pharmaceuticals announces positive topline results from pivotal phase 3 clinical trial evaluating setmelanotide in bardet-biedl and alström syndromes [media release]. 2020.
- 47 Ryan DH. Next Generation Antiobesity Medications: Setmelanotide, Semaglutide, Tirzepatide and Bimagrimumab: What do They Mean for Clinical Practice? *J Obes Metab Syndr* 2021;30:196–208.
- 48 R Pharmaceuticals. IMCIVREE [prescription label]. 2020.
- 49 Clément K, van den Akker E, Argente J, et al. Efficacy and safety of setmelanotide, an MC4R agonist, in individuals with severe obesity due to LEPR or POMC deficiency: single-arm, open-label, multicentre, phase 3 trials. *Lancet Diabetes Endocrinol* 2020;8:960–70.
- 50 Hsia DS, Grove O, Cefalu WT. An update on sodium-glucose co-transporter-2 inhibitors for the treatment of diabetes mellitus. *Curr Opin Endocrinol Diabetes Obes* 2017;24:73–9.
- 51 Plodkowski RA, McGarvey ME, Hurlbal HM, et al. SGLT2 Inhibitors for Type 2 Diabetes Mellitus Treatment. *Fed Pract* 2015;32:8S–15S.
- 52 Halimi S, Vergès B. Adverse effects and safety of SGLT-2 inhibitors. *Diabetes Metab* 2014;40:S28–34.
- 53 Brown E, Heerspink HJL, Cuthbertson DJ, et al. SGLT2 inhibitors and GLP-1 receptor agonists: established and emerging indications. *Lancet* 2021;398:262–76.
- 54 Lim GE, Huang GJ, Flora N, et al. Insulin regulates glucagon-like peptide-1 secretion from the enteroendocrine L cell. *Endocrinology* 2009;150:580–91.

- 55 Shetty R, Basheer FT, Poojari PG, *et al.* Adverse drug reactions of GLP-1 agonists: A systematic review of case reports. *Diabetes Metab Syndr* 2022;16:102427.
- 56 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. *JAMA* 2021;325:1414.
- 57 U. S. F. a. D. Administration. FDA approves novel, dual-targeted treatment for type 2 diabetes. n.d. Available: <https://www.fda.gov/news-events/press-announcements/fda-approves-novel-dual-targeted-treatment-type-2-diabetes>
- 58 Jastreboff AM, Aronne LJ, Ahmad NN, *et al.* Tirzepatide Once Weekly for the Treatment of Obesity. *N Engl J Med* 2022;387:205–16.
- 59 Yazawa R, Ishida M, Balavarca Y, *et al.* A randomized Phase I study of the safety, tolerability, pharmacokinetics and pharmacodynamics of BI 456906, A dual glucagon receptor/glucagon-like peptide-1 receptor agonist, in healthy Japanese men with overweight/obesity. *Diabetes Obes Metab* 2023;25:1973–84.
- 60 Wharton S, Blevins T, Connery L, *et al.* Daily Oral GLP-1 Receptor Agonist Orforglipron for Adults with Obesity. *N Engl J Med* 2023;389:877–88.
- 61 Jastreboff AM, Kaplan LM, Frías JP, *et al.* Triple–Hormone–Receptor Agonist Retatrutide for Obesity — A Phase 2 Trial. *N Engl J Med* 2023;389:514–26.
- 62 Swinburn B, Sacks G, Ravussin E. Increased food energy supply is more than sufficient to explain the US epidemic of obesity. *Am J Clin Nutr* 2009;90:1453–6.
- 63 Durrer Schutz D, Busetto L, Dicker D, *et al.* European Practical and Patient-Centred Guidelines for Adult Obesity Management in Primary Care. *Obes Facts* 2019;12:40–66.
- 64 Bays HE, Weinstein R, Law G, *et al.* Canagliflozin: effects in overweight and obese subjects without diabetes mellitus. *Obesity (Silver Spring)* 2014;22:1042–9.
- 65 Huh Y, Kim YS. Predictors for successful weight reduction during treatment with Dapagliflozin among patients with type 2 diabetes mellitus in primary care. *BMC Prim Care* 2022;23:134.
- 66 Häring H-U, Merker L, Seewaldt-Becker E, *et al.* Empagliflozin as add-on to metformin in patients with type 2 diabetes: a 24-week, randomized, double-blind, placebo-controlled trial. *Diabetes Care* 2014;37:1650–9.
- 67 Heymsfield SB, Raji A, Gallo S, *et al.* Efficacy and Safety of Ertugliflozin in Patients with Overweight and Obesity with Type 2 Diabetes Mellitus. *Obesity (Silver Spring)* 2020;28:724–32.
- 68 Frias JP, Bonora E, Nevarez Ruiz L, *et al.* Efficacy and Safety of Dulaglutide 3.0 mg and 4.5 mg Versus Dulaglutide 1.5 mg in Metformin-Treated Patients With Type 2 Diabetes in a Randomized Controlled Trial (AWARD-11). *Diabetes Care* 2021;44:765–73.
- 69 Pi-Sunyer X, Astrup A, Fujiooka K, *et al.* A Randomized, Controlled Trial of 3.0 mg of Liraglutide in Weight Management. *N Engl J Med* 2015;373:11–22.
- 70 Rosenstock J, Guerci B, Hanefeld M, *et al.* Prandial Options to Advance Basal Insulin Glargine Therapy: Testing Lixisenatide Plus Basal Insulin Versus Insulin Glulisine Either as Basal-Plus or Basal-Bolus in Type 2 Diabetes: The GetGoal Duo-2 Trial. *Diabetes Care* 2016;39:1318–28.
- 71 Ghosn W, De la Rosa A, Sacoto D, *et al.* Weight Loss Outcomes Associated With Semaglutide Treatment for Patients With Overweight or Obesity. *JAMA Netw Open* 2022;5:e2231982.