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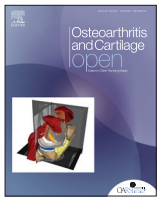

Obesity medications: A narrative review of current and emerging agents

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ABSTRACT

The aim of this narrative review is to synthesize the available data describing the efficacy and safety of medications approved for obesity management and to provide an overview of upcoming agents in development.

A literature search of PubMed, Medline, and Embase databases identified relevant articles describing medications approved in the U.S., Australia, U.K., and/or Europe. Papers were selected based on relevance and originality, with phase 3 clinical trials and meta-analyses preferentially included.

Six medications are widely approved for long-term weight management in conjunction with lifestyle interventions in people with body mass index (BMI) $\geq$30 kg/m^2 or BMI $\geq$27 kg/m^2 and at least one medical condition related to excess weight. Compared with lifestyle interventions alone, all medications approved for obesity management are more effective for long-term weight loss and improvements in cardiometabolic risk factors. Older obesity medications are associated with mean weight losses in the range of 5–10%. The new generation of agents, including the injectable incretin analogues semaglutide and tirzepatide are associated with sustained mean weight reductions of 15–20%, along with substantial benefits on a range of health outcomes. Several novel agents are under development, with multi-hormone receptor agonists and oral formulations likely to become available in the coming years.

As effective treatment options expand, cost and availability will need to be addressed to enable equitable access to treatment. Other important challenges for clinical practice and research include the need for long-term strategies to prevent and manage weight regain and loss of lean muscle and bone mineral density.

1. Introduction

Obesity is an increasing global health concern. Its worldwide prevalence continues to rise, estimated by the World Health Organization to have almost tripled since 1975 to affect more than 650 million adults in 2016 [1,2]. The adverse health and functional impacts of obesity itself, and the chronic diseases associated with it, including osteoarthritis (OA), cardiovascular disease (CVD), type 2 diabetes (T2D) and metabolic dysfunction-associated steatotic liver disease (MASLD), amongst many others, contribute significantly to health burden across the world [2–4]. At both an individual and a population level, the impact of obesity on quality of life, morbidity, and mortality is substantial, demanding greater priority be placed on its management [3,5,6].

Many obesity-related health conditions can be improved with weight reduction. Weight loss of 5% is associated with reductions in blood pressure, triglycerides, blood glucose, and hepatic steatosis, restoration of ovulatory cycles in women with polycystic ovarian syndrome, and prevention of T2D [7–10]. Greater weight loss has progressive benefits. Weight loss of >10% is associated with reductions in adipose tissue and systemic inflammation, steatohepatitis activity, obstructive sleep apnoea, health-related quality of life and cardiovascular events [7,11–14]. In people with knee OA, weight loss of >10% reduces mechanical stress, associated articular degeneration [15] and knee pain, and results in improvements in walking distance and speed [16,17]. Obesity has therefore been identified as a major modifiable risk factor for the severity and progression of OA, with current international guidelines for the management of osteoarthritis recommending weight loss as a component of its comprehensive management [15,18].

Improving nutritional quality and increasing physical activity are strong foundations for health improvement and, along with reducing energy intake, support obesity management. However, lifestyle changes alone rarely lead to sustained weight loss [19,20]. Weight loss is

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counteracted by numerous long-lasting physiological changes [21], rendering maintenance of lifestyle changes very challenging for most people, particularly in an 'obesogenic' environment.

Currently, pharmacotherapy is recommended in clinical guidelines for obesity management if treatment goals are not (or unlikely to be) achieved or maintained with lifestyle interventions alone [22–24]. As the options for obesity pharmacotherapy are advancing rapidly, the aim of this review is to synthesize the clinical data for current medications and provide an overview of agents in development for the treatment of obesity.

2. Methods

We searched PubMed, Medline, and Embase databases for articles published in English before 1 August 2023 using the names of medications approved in the U.S., Australia, Europe, or U.K. for the treatment of obesity. Medications in development were identified using generic medication search terms, including 'obesity', 'overweight', 'weight loss', 'weight management', 'pharmacotherapy', and 'medication'. We considered human studies based on relevance and originality and screened the reference lists of relevant articles for additional studies. Clinical guidelines, phase 3 clinical trials and systematic reviews with meta-analyses were preferentially included. Other relevant articles known to the authors published after the search date were also included. We excluded studies conducted entirely in paediatric cohorts, of medications withdrawn from the market, and pre-clinical studies.

3. Pharmacological therapies

In general, medications for obesity management have regulatory approval as an adjunct to lifestyle interventions for adults with body mass index (BMI) $\geq$30 kg/m^2, or BMI $\geq$27 kg/m^2 with at least one weight-associated medical condition. Exceptions to this indication are mentioned in the text where relevant. An overview of medications currently approved for chronic weight management is presented in Table 1, and proportions of clinical trial participants achieving weight change categories is depicted in Fig. 1.

3.1. Glucagon-like peptide 1 receptor agonists

Glucagon-like peptide 1 (GLP-1) is an incretin hormone released from enteroendocrine L cells in the distal small bowel and colon in response to nutrient intake. It is also synthesized by a population of neuronal cells in the brainstem [30]. Gut-derived GLP-1 has a circulating half-life of only 1–2 minutes as it is rapidly inactivated by the enzyme dipeptidylpeptidase-4 (DPP-4) and cleared via the kidneys. GLP-1 acts via the GLP-1 receptor, which is widely distributed including in the brain, pancreas, stomach, heart, kidney, and adipose tissue [30,31].

Among its numerous actions, GLP-1 has effects on blood glucose, appetite, and cardiovascular physiology. In the pancreas and gastrointestinal tract, GLP-1 lowers blood glucose by enhancing glucose-dependent insulin secretion, reducing glucagon secretion and slowing gastric emptying. Centrally, GLP-1 acts in several brain regions involved in modulation of appetite and eating behaviours, including the hypothalamus, brainstem, and mesolimbic pathway, resulting in increased fullness, and reduced hunger and food reward, thereby reducing food intake and body weight [31].

In view of the effects of GLP-1 on blood glucose and body weight, pharmaceutical agents based on replicating GLP-1 activity (GLP-1 receptor agonists, GLP1RAs) with a longer half-life than native GLP-1 have been developed as therapies for T2D and obesity. Several GLP-1RAs are marketed for treatment of T2D (including exenatide, liraglutide, dulaglutide, lixisenatide, semaglutide) of which two (liraglutide and semaglutide) are registered also for obesity management.

3.1.1. Liraglutide

Liraglutide was the first GLP-1RA approved for use in obesity management. It has 97% homology to human GLP-1, with the addition of an albumin-binding 16 fatty acid side chain increasing its half-life to 13–15 hours [32], allowing once-daily dosing. For obesity management, the approved dose of liraglutide is 3.0 mg subcutaneously daily (compared with up to 1.8 mg daily for T2D). Its efficacy and safety for obesity management in people with and without T2D were evaluated in the SCALE clinical trial program. Like all clinical trials in obesity drug development programs to date, a structured, multicomponent lifestyle intervention was provided to all participants (i.e. in both drug and placebo arms).

In a 56-week randomised controlled trial (RCT) involving 3371 individuals with BMI $\geq$27 kg/m^2 and without diabetes [25], total weight loss with liraglutide 3.0 mg daily was 8.0% (8.4 kg) compared to 2.6% (2.8 kg) for placebo arm (difference 5.4%; 5.6 kg). A greater proportion of participants treated with liraglutide (vs placebo) achieved weight loss of at least 5% (63 vs 27%), 10% (33 vs 11%), and 15% (14 vs 4%) [25]. More recently, the efficacy and safety of liraglutide was demonstrated in adolescent populations, with the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) approving its use for obesity management in individuals aged 12–18 years, with BMI at or above the 95th percentile for their age and gender, and a weight over 60 kg.

3.1.2. Semaglutide

Semaglutide, a long-acting GLP-1 analog with the addition of a C18 fatty diacid resulting in an extended half-life of 165 hours, was approved for obesity management at a subcutaneous dose of 2.4 mg weekly. Semaglutide is also approved for T2D treatment at a dose of up to 1.0 mg weekly subcutaneously, and as an oral formulation at a dose of 7 and 14 mg daily.

The STEP phase 3 clinical trial program demonstrated semaglutide to be the first of a new generation of highly efficacious medications for obesity treatment. In a 68-week RCT involving 1961 individuals with BMI $\geq$27 kg/m^2, semaglutide 2.4 mg weekly resulted in a mean weight loss of 14.9% (15.3 kg) vs 2.4% (2.6 kg) in the placebo group (mean difference 12.4% (12.7 kg)) [26]. More individuals achieved weight reductions of at least 5% (86 vs 32%), 10% (69 vs 12%), 15% (51 vs 5%) and 20% (32 vs 2%) in semaglutide-treated vs placebo participants [26]. In a later randomised trial comparing once weekly semaglutide 2.4 mg and daily liraglutide 3.0 mg, greater proportions of semaglutide-treated participants achieved weight loss thresholds of 10% or more (71% vs 26%), 15% or more (56% vs 12%), and 20% or more (39% vs 6%) [33]. Similarly to liraglutide, semaglutide is approved by the FDA and EMA for management of obesity in adolescents aged 12–18 years.

Importantly, these studies demonstrated beneficial effects on glycaemic, cardiometabolic, and quality of life outcomes. Both semaglutide and liraglutide improved glycated haemoglobin A1c (HbA1c) and fasting glucose levels in clinical trials in people with and without T2D, and reduced the prevalence and development of prediabetes compared to placebo. Both agents reduced systolic and diastolic blood pressure, with improvements also noted in fasting lipid levels, markers of systemic inflammation including high sensitivity C-reactive protein, and physical function as measured by the SF-36 and Impact of Weight on Quality of Life (IWQOL)-Lite questionnaires.

Studies have identified the beneficial effects of GLP-1RAs on cardiovascular and renal outcomes when used at diabetes treatment doses in people with T2D [34], and on liver fat content in people with MASLD with and without T2D [35]. Additionally, the SELECT trial reported the cardiovascular benefit of semaglutide 2.4 mg weekly in people without diabetes. This trial is important in being the first RCT of an obesity treatment to show a reduction in major adverse cardiovascular events (MACE). In over 17,500 people with BMI $\geq$27 kg/m^2 and pre-existing cardiovascular disease, treatment with semaglutide led to a 20% reduction (hazard ratio, 0.80; 95% CI 0.72 to 0.90; $P < 0.001$) in a composite endpoint of death from cardiovascular causes, nonfatal myocardial infarction or nonfatal stroke over a mean of 40 months [36]. Whether these benefits are a class effect of GLP-1RAs, and to what extent they are independent of weight loss, remain to be established.

Table 1
Available agents.

Medication	Phase 3 trial	Year	Weight loss (kg) - Intervention (total) - Placebo - Placebo-subtracted Weight loss (%) - Intervention (total) - Placebo - Placebo-subtracted	Glycaemic outcomes	Cardiometabolic outcomes	HR-QoL outcomes	Side effects and adverse effects	Approval status for paediatric and adolescent population
Liraglutide 3.0 mg	SCALE 56-week trial N = 3731, 2487 lira and 1244 placebo BMI >30 or >27 with comorbidities	2015	- Intervention (total): 8.4 kg - Placebo: 2.8 kg - Placebo-subtracted: 5.6 kg - Intervention (total): 8.0% - Placebo 2.6% - Placebo-subtracted 5.4%	Greater reduction in HbA1c, fasting glucose, and fasting insulin levels. Improved plasma glucose levels, higher insulin and C-peptide levels relative to placebo during OGTT. Prevalence of prediabetes was lower in lira group vs placebo after 56 weeks. T2D developed in more placebo patients than the liraglutide group	Systolic and diastolic blood pressure decreased more in the liraglutide group than in the placebo group by week 56 Improved fasting lipid levels, high sensitivity C-reactive protein, plasminogen activator inhibitor 1, and adiponectin	Greater improvements in liraglutide group for SF-36 and the IQWOL-Lite questionnaire.	GI most common – nausea, and vomiting	Approved by FDA and EMA for individuals aged 12–17 years, with BMI at or above the 95th percentile for age and sex, with a weight over 60 kg
Semaglutide 2.4 mg	STEP 1 68 week trial N = 1961, 1306 sema, 655 placebo BMI >30 or >27 with comorbidities	2021	- Intervention (total) 15.3 kg - Placebo 2.6 kg - Placebo-subtracted 12.7 kg (95% CI -13.7 to −11.7) - Intervention (total): 14.9% - Placebo 2.4% - Placebo-subtracted 12.4% (95% CI 13.4 to 11.5)	Greater improvements in semaglutide group for HbA1c, fasting plasma glucose. Greater percentage of patients in the semaglutide group with normoglycaemia at week 68–84.1% vs 47.8%	Greater improvements for systolic blood pressure, diastolic blood pressure, lipid levels, high sensitivity C-reactive protein	Significantly greater improvements in SF-36 physical functioning score and IWQOL-Lite-CT physical function score	GI most common – nausea, diarrhoea, vomiting, and constipation	Approved by FDA and EMA for individuals aged 12–17 years, with BMI at or above the 95th percentile for age and sex, with a weight over 60 kg
Tirzepatide	SURMOUNT 1 72 week trial N = 2539, 1:1:1:1 to varying doses tirzepatide and placebo - 5 mg n = 630 - 10 mg n = 636 - 15 mg n = 630 - Placebo n = 643 BMI >30 or >27 with comorbidities	2022	- Intervention (5 mg) NR - Intervention (10 mg) NR - Intervention (15 mg) NR - Placebo NR - Placebo-subtracted N/A - Intervention (5 mg) 15.0% - Intervention (10 mg) 19.5% - Intervention (15 mg) 20.9% - Placebo 3.1% - Placebo-subtracted 17.8% (15 mg)	Pooled data for tirzepatide doses. Improved return to normoglycaemia from prediabetes. Improved fasting insulin levels.	Improved systolic and diastolic blood pressure. Improved lipid profile	Improved SF-36 physical function scores.	GI most common – nausea, diarrhoea, vomiting, and constipation	No approval to date
Orlistat	No name for trial 52-week trial N = 688, 343 placebo +345 orlistat. 544	1998	- Intervention (total) 10.3 kg - Placebo 6.1 kg	Improvements in fasting blood glucose	Improvements in total cholesterol, LDL, blood pressure	Not assessed	Mainly GI Most common were fatty/oily stool, increased defecation, oily	Approved by FDA and EMA for individuals aged 12–17 years, with BMI at or

(*continued on next page*)

Table 1 (*continued*)

Medication	Phase 3 trial	Year	Weight loss (kg) - Intervention (total) - Placebo - Placebo-subtracted Weight loss (%) - Intervention (total) - Placebo - Placebo-subtracted	Glycaemic outcomes	Cardiometabolic outcomes	HR-QoL outcomes	Side effects and adverse effects	Approval status for paediatric and adolescent population
	completed treatment. BMI 28-47 All completed 4-week lead in period on a slightly hypocaloric diet		- Placebo-subtracted 4.2 kg - Intervention (total) 10.2% - Placebo 6.1% - Placebo-subtracted 4.1%				spotting, soft stool, liquid stool	above the 95th percentile for age and sex, with a weight over 60 kg
Phentermine-topiramate	CONQUER 56-week trial Low dose (LD) = PHEN 7.5/TOP 46 High dose (HD) = PHEN 15/TOP 92 N = 2487, n = 994 placebo, 1493 to PHEN-TOP (498 to lower dose, 995 to higher dose)	2011	- Intervention (LD) 8.1 kg - Intervention (HD) 10.2 kg - Placebo 1.4 kg - Placebo-subtracted 8.8 kg (HD) - Intervention (LD) 7.8% - Intervention (HD) 9.8% - Placebo 1.2% - Placebo-subtracted 8.6% (HD)	Improvements in fasting glucose, HbA1c, fasting insulin, HOMA-IR	Improvements in blood pressure, lipid profile, hsCRP, adiponectin	Reported improvements in IWQOL-Lite questionnaire and SF-36 scale but not shown in paper.	Dry mouth, parasthesia, constipation, insomnia, dizziness, dysgeusia. Depression and anxiety-related adverse events also reported.	Approved by FDA for individuals aged 12–17 years, with BMI at or above the 95th percentile for age and sex, with a weight over 60 kg
Naltrexone-bupropion	COR-II (CONTRAVE Obesity Research-II) 56-week trial N = 1496, 456 placebo (267 completed treatment) + 825 intervention (538 completed treatment) BMI 30–45 or 27–45 with comorbidity	2013	- Intervention (total) 6.2 kg - Placebo 1.3 kg - Placebo-subtracted 4.9 kg - Intervention (total) 6.4% - Placebo 1.2% - Placebo-subtracted 5.2%	Improvements in fasting insulin, HOMA-IR	Improvements in TG level, HDL, LDL, hsCRP, systolic blood pressure	Improvements in IWQOL-Lite questionnaire and control of eating questionnaire	Nausea, headache, constipation	No approval to date
Setmelanotide	LEPR and POMC trials 52-week trial 6 years and older Confirmed POMC, PCSK1, and LEPR deficiency N = 11 in POMC with 10 completing study N = 10 in LEPR	2020	POMC - Intervention (total) 25.6% LEPR - Intervention (total) 12.5%	Improvements in fasting glucose and triglycerides in the POMC deficiency cohort.	Improvements in HDL	Not assessed	Injection site reaction, nausea, vomiting	Approved by FDA for children aged 6 years or older with the relevant deficiency. Approved by EMA for children 12 years or older with the relevant deficiency.

Abbreviations: HR-QoL, health related quality of life; BMI, body mass index; HbA1c, glycated haemoglobin; OGTT, oral glucose tolerance test; T2D, type 2 diabetes; GI, gastrointestinal; IWQOL, impact of weight on quality of life; NR, not recorded; N/A, not applicable; TG, triglyceride; LDL, low density lipoprotein; HDL, high density lipoprotein; hsCRP, high sensitivity C-reactive protein; POMC, proopiomelanocortin; LEPR, leptin receptor; PCSK1, proprotein convertase subtilisin and kexin type 1; FDA, Food and Drug Administration; EMA, European Medicines Agency.

The adverse effects of GLP-1RA therapy noted in clinical trials are mainly gastrointestinal. Nausea is the most common (42%, vs 16% in placebo groups) [25,26], with a tendency to peak during dose escalation and improve with continuing exposure. Diarrhoea (26%), vomiting (21%), constipation (22%), abdominal pain (8%), and dyspepsia (10%) are also frequently reported, with gradual dose up-titration recommended to minimise incidence of such effects. Earlier concerns raised in epidemiological studies regarding acute pancreatitis and pancreatic cancer have not been supported by meta-analyses of clinical trials over 175,000 patients-years of observation [37].

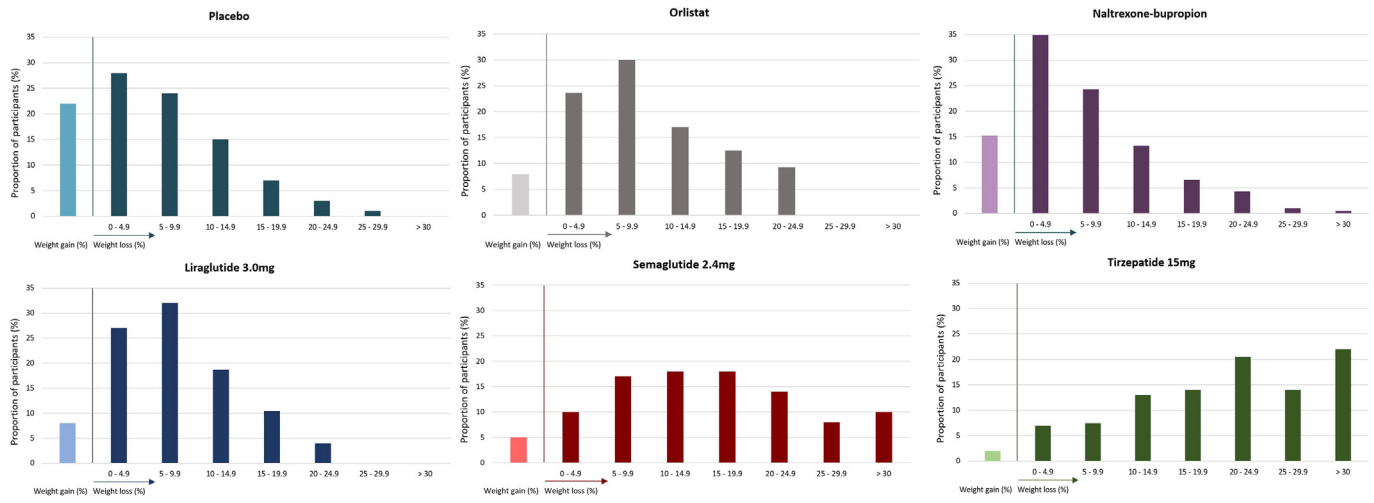

Fig. 1. Heterogeneity in weight loss response after approximately 12 months with currently available agents. Data presented are extracted from the respective phase 3 randomised clinical trials [25–29]. All trials included lifestyle intervention in both drug and placebo arms. Data for naltrexone-bupropion: COR data ad hoc analysis (NB-301). Data on file. iNova Pharmaceuticals (Australia) Pty Limited. Data for phentermine-topiramate are not presented due to the lack of available published data.

3.2. Tirzepatide

Tirzepatide is a single molecule agonist at receptors for both GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) [38,39]. GIP is released from K cells in the duodenum and jejunum. Like GLP-1, GIP is an incretin hormone, augmenting glucose-stimulated insulin secretion. GIP also acts via GIP receptors in adipose tissue to improve lipid homeostasis and insulin sensitivity [38,40]. The role of GIP in alteration of appetite and body weight is not fully understood.

Tirzepatide is approved in many parts of the world for the treatment of T2D at weekly subcutaneous doses of 5 mg, 10 mg, and 15 mg. It is also approved in the U.S. and U.K. at the same doses for obesity management, with regulatory approval for an obesity indication expected to follow in other regions.

Tirzepatide's efficacy for obesity treatment is being investigated in the SURMOUNT program of phase 3 RCTs, which showed mean weight reductions of greater than 20% with pharmacotherapy for the first time. In individuals with BMI $\geq$27 kg/m^2 without T2D, mean (95% confidence interval) percentage change in weight with tirzepatide 5, 10 and 15 mg over 72 weeks was −15.0% (−14.2 to −15.9), −19.5% (−20.4 to −18.5) and −20.9% (−19.9 to −21.8) compared to−3.1 (−4.3 to −1.9) with placebo [27]. The proportions of individuals who achieved 5% (85–91% vs 35%), 10% (69–84% vs 19%), 15% (48–71 vs 9%), 20% (30–57% vs 3%), and 25% (15–36% vs 2%) weight reduction were much greater in all tirzepatide treated groups compared with placebo [27].

Similarly to GLP1RAs, tirzepatide has also demonstrated improvements in glycaemic and cardiometabolic outcomes. In individuals with obesity and glucose intolerance, a greater proportion returned to normoglycaemia with tirzepatide treatment, with improved fasting insulin levels, systolic and diastolic blood pressure, fasting lipid profile and physical function [27].

In an RCT of tirzepatide for treatment of obesity in individuals with T2D, significant weight reduction was achieved with all investigated doses (10 mg and 15 mg) compared to placebo. As with all obesity medications, the magnitude of weight loss was lower than in people without T2D, however, this is the first medication for which a clinical trial has demonstrated mean weight loss of >10% in participants with T2D (12.8% for 10 mg and 14.7% for 15 mg at 72 weeks) [41]. Moreover, HbA1c reduced by 2.1% (95% CI 2.0 to 2.2) with both 10 mg and 15 mg tirzepatide, compared to reduction of 0.5% (95% CI 0.4 to 0.6) in the placebo group after 72 weeks of treatment [41], despite a lower requirement for additional glucose-lowering therapy.

When compared to semaglutide 1 mg, tirzepatide induced greater reductions in weight and HbA1c with treatment differences of 1.9 kg and 0.15%; 3.6 kg and 0.39%; and 5.5 kg and 0.45% (respectively) for 5 mg, 10, and 15 mg tirzepatide over a 40-week duration [42].

Adverse effects are similar to those observed with GLP-1RA therapy, with gastrointestinal effects including nausea (20–33%), diarrhoea (18–22%), and vomiting (8–13%) being the most common, and mostly mild to moderate in severity during dose escalation [27,41].

3.3. Orlistat

Orlistat (tetrahydrolipstatin) is a reversible inhibitor of gastric and pancreatic lipases. It reduces absorption of dietary fats, mainly triglycerides, by up to 30–35%, which are then excreted via the faeces [43–46]. It is orally administered at doses of 60–120 mg up to three times daily with meals. Its efficacy for obesity management was demonstrated in a phase 3 RCT involving 688 individuals with BMI 28–47 kg/m^2, which reported weight loss after 52 weeks of 10.2% (10.3 kg) with orlistat vs 6.1% (6.1 kg) in the placebo group (between-group difference of 4.1% (4.2 kg)). More individuals achieved weight reductions of at least 5% (69% vs 49%), 10% (39% vs 18%), and 20% (9% vs 2%) initial body weight in the orlistat group [28].

A meta-analysis of 12 studies indicated overall weight loss of approximately 4.3 kg at 12 months in combination with lifestyle intervention, compared to 2.3 kg with lifestyle intervention alone [44].

While there are no randomised trials examining cardiovascular outcomes with orlistat, a cohort study of 36,876 UK adults prescribed orlistat found a hazard ratio of 0.74 (95% CI 0.66–0.83) for major cardiovascular events, with lower rates of myocardial infarction, ischaemic stroke, and new-onset heart failure compared to a propensity-score matched cohort not treated with the drug [47] over a median 6 year follow up.

Orlistat is most commonly associated with gastrointestinal adverse effects related to increased fat excretion (steatorrhea, faecal urgency, oily leakage) [43,46]. Concern has been raised about fat-soluble vitamin absorption, with vitamin D deficiency noted in a small proportion of at-risk patients after commencing orlistat therapy [48]. Acute kidney injury has also rarely been reported, relating to hyperoxaluria and oxalate nephropathy [49].

3.4. Phentermine and phentermine-topiramate

Phentermine is one of the oldest obesity medications available, obtaining FDA approval in 1959 [50]. It is a sympathomimetic amine,

acting mainly on norepinephrine transporters to increase synaptic norepinephrine, and also exerting weak activity at dopamine and serotonin transporters [51]. As monotherapy for obesity management, phentermine is indicated for short-term use (generally interpreted as up to 12 weeks). A meta-analysis of RCTs of phentermine monotherapy found a placebo subtracted mean weight loss of 3.6 kg over a mean of 13 weeks [52]. Common adverse effects are insomnia, dry mouth and palpitations. Although weight loss usually leads to reduction in blood pressure, phentermine can cause blood pressure elevation, hence it is not recommended in people with a history of uncontrolled hypertension.

A combination of phentermine with extended release topiramate was approved by the FDA for chronic weight management in 2012. Topiramate has many actions including inhibition of carbonic anhydrase and glutamate activity, increasing GABA activity and blocking voltage dependent sodium channels, although the mechanism for its effect on reducing appetite and weight is not known [53,54].

A 56-week phase 3 RCT of phentermine-topiramate involving 2487 individuals with BMI $\geq$27 kg/m^2 found that both low-(phentermine 7.5/topiramate 46 mg) and high-dose (phentermine 15/topiramate 92 mg) combinations resulted in greater weight loss than placebo; 9.8% (10.2 kg) high dose, 7.8% (8.1 kg) low dose, 1.2% (1.4 kg) placebo. More participants achieved weight reductions of 5% (70% high dose, 62% low dose, 21% placebo) and 10% (48% high dose, 37% low dose, 7% placebo) initial body weight in the phentermine-topiramate groups [55]. Weight loss was sustained at 108 weeks, and improvements were seen in cardiometabolic parameters with reductions in systolic and diastolic BP, triglycerides and fasting glucose compared with placebo [56].

When compared to monotherapy of either drug alone, combination phentermine-topiramate was more effective, with mean percentage weight loss of 11.6%, 8.8% and 7.4% at 28 weeks for phentermine 15/topiramate 92 mg, topiramate 92 mg and phentermine 15 mg respectively [56,57].

The most common side effects of phentermine-topiramate include paraesthesia, constipation, and dry mouth, and an increase in heart rate has been reported (mean 1.7 bpm on phentermine/topiramate vs −0.1 bpm placebo) [55].

3.5. Naltrexone-bupropion

Bupropion, an antidepressant, increases the activity of anorexic proopiomelanocortin (POMC) neurons in the hypothalamus [58]. Naltrexone, an opioid antagonist, works to potentiate this activity by blocking endogenous opioid-mediated auto-inhibition of POMC neurons [58]. In combination, these two agents have effects on central pathways controlling both appetite and food reward to reduce food intake.

In a 56-week phase 3 RCT in which 1498 individuals with obesity were treated with either naltrexone-bupropion or placebo along with lifestyle intervention, the naltrexone-bupropion group had weight reduction of 6.4% (6.2 kg) compared to 1.2% (1.3 kg) in the placebo group, with a between-group difference of 5.2% (4.9 kg). More individuals treated with naltrexone-bupropion (vs placebo) achieved weight reductions of 5% (51 vs 17%), 10% (28 vs 6%), and 15% (14 vs 2%) [59].

Attrition in clinical trials of the naltrexone-bupropion combination has been high (40–50% at 1 year), with around one quarter of participants withdrawing due to adverse effects in medication groups (vs 12% in placebo arms) [60]. The most common side effects include nausea, abdominal pain, constipation, dry mouth and insomnia. Lowering of seizure threshold and increases in heart rate and blood pressure are also potential adverse effects. Importantly, naltrexone-bupropion has potential interactions with many medications due to cytochrome P450 interactions. Bupropion is metabolised by CYP2B6, therefore concomitant treatment with inhibitors (e.g clopidogrel) or inducers (e.g. antiretroviral and anticonvulsant medications) of this enzyme can affect bupropion exposure. Through its effect on CYP2D6, bupropion can also increase concentrations of antidepressants, antipsychotics, beta blockers and type 1C antiarrhythmics.

3.6. Setmelanotide

Monogenic obesity is rare, affecting around 5% of people with severe early-onset obesity. Loss-of-function mutations in the POMC, proprotein convertase subtilisin and kexin type 1 (PCSK1), and leptin receptor (LEPR) genes are all causes of monogenic obesity. Leptin is an adipocyte hormone that acts via LEPR in the hypothalamus to inhibit orexigenic Agouti-related protein (AgRP) and neuropeptide Y (NPY) neurons and stimulate anorexigenic cocaine- and amphetamine-regulated transcript (CART) and POMC neurons. POMC is cleaved by the enzyme PCSK1 to give rise to numerous peptides including α-melanocyte-stimulating hormone, which activates the melanocortin pathway via the melanocortin 4 receptor (MC4R). This pathway is critical in reducing food intake and increasing energy expenditure [61–63].

Setmelanotide is an agonist of the MC4R, approved by the FDA and EMA for the management of obesity in people with POMC, PCSK1 or LEPR deficiency. Two small (n = 10–11) single-arm, open-label, multicentre, phase 3 clinical trials showed its efficacy for weight reduction and control of hyperphagia in individuals with monogenic obesity due to POMC, PCSK1, and LEPR deficiency. After a year of treatment, the primary outcome, weight reduction of 10% or more, occurred in 80% of participants with LEPR mutations, and 45% of those with POMC deficiency. Adverse effects are mainly related to injection site reactions, hyperpigmentation, and gastrointestinal symptoms such as nausea and vomiting [61].

4. Emerging agents in development

Many new agents are under development for the treatment of obesity (Table 2). Most of these are based on replicating (or inhibiting) the action of one or more gut-derived hormones, including GLP-1, GIP, amylin and glucagon. Early-phase clinical trials are reporting unprecedented weight loss and glycaemic improvements for several of these agents, approaching the results achievable with bariatric surgery, at least in the short-term.

5. Considerations for current and future management of obesity

No single agent is considered “first-line” among medications for obesity management. The new generation of medications, including semaglutide and tirzepatide, are more effective in terms of mean weight loss and reductions in cardiometabolic risk factors compared with older agents (although there are few head-to-head comparisons). However, efficacy is not the only consideration. Other factors that may influence the choice of medication include contraindications and adverse effect profiles, as well as expected benefits for each patient (e.g. GLP-1RAs are likely to be preferred in people at high risk of T2D), mode of delivery (injectable vs oral), and frequency of administration. In practice, out-of-pocket costs are often a major factor as there is limited insurance coverage or public funding for obesity medications in most parts of the world, leading to considerable inequities in access to treatment. Current supply issues are also limiting the choice of available medications in some regions of the world.

In keeping with the chronic nature of obesity, a long-term approach to treatment is necessary. Substantial weight regain has been observed in all clinical trials examining the effect of ceasing obesity medications, with a particularly steep trajectory seen in the first 3 months following cessation in some studies [64], and participants regaining on average half to two-thirds of lost weight in the year following treatment cessation [65–67]. A supervised exercise program may reduce the rate of weight regain [67] and long-term continuation of medication is likely to be required for many people. The sustained efficacy of semaglutide over 4 years was recently demonstrated in a trial of >17,000 participants [36] and further clinical data on longer-term efficacy, safety and cost-effectiveness are needed.

These issues are increasingly important with the emergence of new medications with potential not only to treat obesity more effectively, but also to influence a broad range of outcomes including cardiometabolic

Table 2
Agents under development for obesity management.

Medication	Mechanism of action	Phase 2/3 clinical trial	Weight loss results	
Orforglipron	Oral GLP1RA	GZGI clinical trials Phase 2 randomised, double-blind trial Orforglipron 12, 24, 36, 45 mg or placebo 36-week duration BMI >30 or BMI >27 with comorbidity N = 272 Primary outcome = change in body weight at week 26 Secondary outcome = change in body weight at week 36	Primary outcome (week 26) - 8.6% to −12.6% across doses - 2.0% in placebo Secondary outcome (week 36) - 9.4% to −14.7% across doses - 2.3% in placebo	Week 36 >5% weight reduction Orforglipron 72–92% Placebo 24% >10% weight reduction Orforgliptin: 46–75% Placebo 9% >15% weight reduction Orforglipron 22–48% Placebo 1%
Danuglipron	Oral GLP1RA	Phase 2a, double-blind, placebo-controlled trial involving individuals with T2D and obesity without T2D Individuals with obesity and not T2D n = 28 12-week duration	Weight reduction (obesity without T2D) -7.17 kg danuglipron -0.30 kg placebo	
Oral semaglutide	Oral GLP1RA	OASIS 1 clinical trial Phase 3 randomised, double-blind, placebo-controlled Oral semaglutide 50 mg or placebo 68-week duration BMI >30 or BMI >27 with comorbidity N = 667 Primary outcome = percentage change in body weight + 5% body weight reduction	Weight reduction at week 68 -15.1% semaglutide -2.4% placebo	>5% weight reduction Oral sema 85% Placebo 26% >10% weight reduction Oral sema 69% Placebo 12% >15% weight reduction Oral sema 54% Placebo 6% >20% weight reduction Oral sema 34% Placebo 3%
AMG133	GIP antagonist and GLP1RA	Phase 2 trial underway, no results yet		
Survodutide (BI 456906)	Dual glucagon receptor/GLP1R agonist	Phase 2 randomised, double-blind, placebo-controlled Subcut survodutide 0.6,2.4,3.6,4.8 mg vs placebo 46-week duration BMI >27 N = 387	Weight reduction at week 46 0.6 mg −6.2% 2.4 mg −12.5% 3.6 mg −13.2% 4.8 mg −14.9% Placebo −2.8%	>5% weight reduction 4.8 mg 82.8% Placebo 25.9% >10% weight reduction 4.8 mg 68.8% Placebo 11.1% >15% weight reduction 4.8 mg 54.7% Placebo 5.6%
Retatrutide	GLP1/GIP/Glucagon receptor triple agonist	Phase 2 double-blind, randomised, placebo-controlled trial Retatrutide subcut 1, 4, 8, 12 mg, or placebo 48 week duration BMI >30 or BMI >27 with comorbidity N = 338 Primary outcome = change in weight at week 24 Secondary outcome = change in weight at week 48	Weight reduction at week 24 1 mg −7.2% 4 mg −12.9% 8 mg −17.3% 12 mg −17.5% Placebo −1.6% Weight reduction at week 48 1 mg −8.7% 4 mg −17.1% 8 mg −22.8% 12 mg −24.2% Placebo −2.1%	>5% weight reduction 4 mg 92% 8 mg 100% 12 mg 100% Placebo 27% >10% weight reduction 4 mg 75% 8 mg 91% 12 mg 93% Placebo 9% >15% weight reduction 4 mg 60% 8 mg 75% 12 mg 83% Placebo 2%
Cagrilintide	Modified long-acting acetylated amylin analogue	Phase 2 multicenter, randomised, double-blind, placebo-controlled trial Weekly cagrilintide 0.3, 0.6, 1.2, 2.4, 4.5 mg vs liraglutide 3 mg vs placebo 26-week (6 week dose escalation period) BMI >30 or BMI >27 with comorbidity N = 706	Weight reduction at week 26 0.3 mg −6.0% 0.6 mg −6.8% 1.2 mg −9.1% 2.4 mg −9.7% 4.5 mg −10.8%	>5% weight reduction 0.3 mg 57.5% 0.6 mg 62.0% 1.2 mg 75.8% 2.4 mg 74.1% 4.5 mg 88.7%

(*continued on next page*)

Table 2 (*continued*)

Medication	Mechanism of action	Phase 2/3 clinical trial	Weight loss results	
			Liraglutide 3 mg −9.0% Placebo −3.0%	Liraglutide 3 mg 76.2% Placebo 30.9% >10% weight reduction 0.3 mg 15.3% 0.6 mg 24.1% 1.2 mg 35.8% 2.4 mg 44.0% 4.5 mg 53.5% Liraglutide 3 mg 39.4% Placebo 10.4% >15% weight reduction 0.3 mg 3.1% 0.6 mg 5.4% 1.2 mg 14.5% 2.4 mg 21.7% 4.5 mg 18.7% Liraglutide 3 mg 14.0% Placebo 2.9%
Cagrilintide + Semaglutide	Modified long-acting acetylated amylin analogue + GLP1RA	Only has phase 2 trial data in individuals with T2D		
Bimagrumab	Activin type II receptor (ACTRII) A and B monoclonal antibody (inhibitor)	Phase 2 randomised double-masked, placebo-controlled study Bimagrumab (10 mg/kg up to 1200 mg) IV infusion vs placebo every 4 weeks 48-week duration T2D with BMI 28–40, HbA1c 6.5%–10% N = 75, 37 bimagrumab, 38 placebo Phase 2 looking at bimagrumab vs bimagrumab + semaglutide underway (BELIEVE trial) NCT05616013	Total body fat mass: -20.5% (−7.49 kg) in bimagrumab -0.5% (−0.18 kg) in placebo -Placebo-subtracted weight loss of 7.31 kg	>5% weight reduction 96% vs 21% >10% weight reduction 92% vs 10% >15% weight reduction 77% vs 10%

Abbreviations: GLP1RA, glucagon-like peptide 1 receptor agonist; BMI, body mass index; T2D, type 2 diabetes; GIP, glucose-dependent insulinotropic polypeptide.

health, psychological and physical function, quality of life and mortality. As well as their known side effect profiles, medications that more effectively reduce appetite have the potential to increase the risk of micronutrient deficiencies if patients are not made aware of the need to prioritise nutritional quality (or are unable to eat adequately). Weight loss is typically associated with loss not only of fat but also skeletal muscle (up to 25% [68]) and bone mineral density, although medications that increase muscle mass (such as bimagrumab) are currently under development [69]. Whether new incretin-based medications will lead to larger (than expected) muscle loss [26], and how they affect muscle quality and physical function remain to be determined. Lifestyle interventions will continue to have an important role in conjunction with new obesity medications, to support eating and physical activity patterns that minimise these risks and optimise overall health [70].

6. Conclusion

With the global incidence of obesity rapidly continuing to rise, its impact on individuals and health systems will continue to grow. Older obesity medications have been limited in efficacy, with mean weight losses of 4–8% above placebo. A new generation of agents based on incretin hormones has shifted the expectations of medical obesity management with mean weight losses in excess of 15%, and important benefits on cardiometabolic and quality of life outcomes. Whilst gastrointestinal side effects are common with use of these agents, they are usually transient and tolerable. Additionally, multiple novel agents are in development, with the likelihood of a greater arsenal of medications for obesity management in coming years. Importantly, in the era of more effective obesity treatment, associated risks of substantial weight loss, such as skeletal muscle and bone mineral density losses must be considered, with research required to elucidate long-term functional effects of such changes and to identify strategies to minimise or mitigate potential harms and optimise long-term health outcomes.

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Conflict of interest

PS reports co-authorship of manuscripts with medical writing assistance from Novo Nordisk and Eli Lilly. There are no other competing interests to declare.

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