Pharmacotherapy of obesity: an update on the available medications and drugs under investigation

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Summary

Obesity is an epidemic and a public health threat. Medical weight management remains one of the options for the treatment of excess weight and recent advances have revolutionized how we treat, and more importantly how we will be treating obesity in the near future. Metreleptin and Setmelanotide are currently indicated for rare obesity syndromes, and 5 other medications (orlistat, phentermine/topiramate, naltrexone/bupropion, liraglutide, semaglutide) are approved for non-syndromic obesity. Tirzepatide is about to be approved, and other drugs, with exciting novel mechanisms of action primarily based on incretins, are currently being investigated in different phases of clinical trials. The majority of these compounds act centrally, to reduce appetite and increase satiety, and secondarily, in the gastrointestinal tract to slow gastric emptying. All anti-obesity medications improve weight and metabolic parameters, with variable potency and effects depending on the specific drug. The currently available data do not support a reduction in hard cardiovascular outcomes, but it is almost certain that such data are forthcoming in the very near future. The choice of the anti-obesity medication needs to take into consideration the patient's clinical and biochemical profile, co-morbidities, and drug contra-indications, as well as expected degree of weight loss and improvements in cardio-renal and metabolic risk. It also remains to be seen whether precision medicine may offer personalized solutions to individuals with obesity, and whether it may represent the future of medical weight management along with the development of novel, very potent, anti-obesity medications currently in the pipeline.

Introduction

Obesity is a major public health threat, and obesity rates have been alarmingly increasing in the last few decades.[1] The highest prevalence is reported in the Pacific Islands states, where obesity affects more than 50% of the population.[2] In United States, individuals with obesity constitute almost one third of adults, with a prevalence ranging between 23% and 38% across various states.[2] The worldwide situation has worsened recently following the COVID-19 pandemic.[3,4]

Obesity is associated with an increased risk for various metabolic, cardiovascular, skeletal co-morbidities, and cancer,[5] in addition to a significant impact on psychosocial health.[6] Furthermore, obesity is linked to increased mortality.[7] The latest analysis of the Global Burden of Disease (GBD) study in 2017 showed that a body mass index (BMI) ≥ 25 kg/m^2 was associated with 2.4 and 2.3 million deaths in women and men, respectively.[7]

Monogenic obesity syndromes are rare and constitute <5% of all obesity cases.[8] Most commonly, obesity is multifactorial, with several factors contributing to the excess weight, including dietary pattern, physical activity, sleep patterns, medications, in addition to genetic, epigenetic, and environmental determinants.[9] Therefore, the treatment of obesity is very challenging, and *one size does not fit all.*

Obesity treatment guidelines agree that the appropriate approach for weight management should be multidisciplinary, including lifestyle modifications, behavioral therapy, pharmacotherapy and/or bariatric surgery.[10,11] Anti-obesity medications (AOM) are indicated in individuals with a BMI ≥ 30 kg/m^2 or if ≥ 27 kg/m^2 in the presence of one or more co-morbidities (Appendix B). However, the history of AOM was marked by the failure of several ones after their widespread use in the market, secondary to serious adverse effects, namely cardio-vascular events, suicidality, risk for abuse and dependence[12] and recently cancer.[13] Therefore, the Food Drug Administration (FDA) and European Medicines Agency (EMA) revised their regulatory approval criteria of AOM, highlighting in

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Review

Research in context

Evidence before this study
This manuscript represents an update of a previous comprehensive review on the pharmacotherapy of obesity (Pilitsi et al., 2019). We searched Medline and Embase to identify relevant systematic reviews on the topic in the last 5 years (period 2018–2022). We identified 15 articles that systematically reviewed the literature on medical weight management (Appendix A). They all searched one or more databases, and described the evidence on weight parameters. In addition to weight and body mass index, only 4 articles included data on metabolic and cardiovascular parameters and adverse events. None of the identified reviews presented an algorithm for drug therapy consideration based on the available safety and efficacy data. None of them included an overview of the medications in the horizon.

Added value of this study
This manuscript represents an overview on the currently available and FDA-approved anti-obesity medications (AOM) and those under development. For the FDA-approved AOM, we review the evidence on weight and cardio-metabolic parameters while trying to identify, when applicable, whether the beneficial impact on each parameter is a direct effect of the medication per se, or secondary to total body weight loss. In addition, we summarize the available evidence on AOM in individuals with mental illness. We also shed light on tirzepatide which is currently under a fast track review by the FDA, and promises to be the most effective anti-obesity medications to be approved in 2023. We suggest a treatment algorithm taking into consideration patient's profile and medications efficacy and safety data.

Implications of all the available evidence
This review sheds light on the scarcity of the currently available data describing the long-term effects of anti-obesity medications, and in particular, the lack of evidence for an impact on all-cause and cardio-vascular mortality risk, which is urgently needed. Large long-term trials are required to demonstrate the benefit of obesity pharmacotherapy on clinically relevant hard outcomes. We also provide a glimpse on drugs in the pipeline, which promise to revolutionize the way we will be treating obesity in the near future.

particular the importance of cardiovascular and central nervous system safety.[14,15] Importantly, this is also what most insurance companies would need to see to get AOM approved. The last decade observed the approval of 2 drugs for syndromic obesity, one of them indicated to treat the complications of leptin deficiency in patients with generalized lipodystrophy, and 6 drugs for the long term management of non-syndromic obesity.[10,16–18] One of them, Lorcaserin, was withdrawn in 2021, secondary to a signal for an increased risk of cancer, although it was not clarified whether the association was causal or due to early detection of cancer cases due to weight loss. Thus, this signal might have been related to the excess weight and/or increased screening for cancer in this population.[19,20]

The aim of this manuscript is to review the pharmacologic management of obesity in adults, suggest an algorithm for the treatment approach of excess weight, and describe potential drugs that are currently under investigation.

Methods

For FDA approved AOM, we conducted a systematic search on Medline and Embase to identify relevant trials (period 2017–2022) and systematic reviews/meta-analyses (SR/MAs) (period 2012–2022) on specific outcomes/parameters, to update a previous review on the topic.[21] We used Medical Subject Heading (MeSH) terms and keywords related to obesity or fat, adipose tissue, body composition and those related to FDA approved AOM (naltrexone/bupropion, liraglutide, orlistat, phentermine/topiramate (combination), semaglutide) (Appendix C). Three reviewers (M.G., R.H., R.T.) screened the title and abstract and full texts articles. We included randomized controlled trials (RCTs) and SR/MAs on adults (18 years and older), with obesity (BMI ≥ 30 kg/m^2), treated with an FDA-approved AOM, and reporting on one of the following: weight, glycemic parameters, blood pressure, fatty liver, sleep apnea, cardiovascular outcomes and mental illnesses. Three reviewers (M.G., R.H., R.T.) performed data abstraction in duplicate and independently, on population baseline characteristics, intervention dose and frequency, and outcome of interest.

For weight loss medications under development, we searched the clinicaltrials.gov (search update June 4, 2022), using the condition "obesity", and we included ongoing (active or recruiting) phase 1, 2 or 3 trials on adults and older adults. We also manually screened the citations of previous reviews on the topic.

In the narrative and tables, we report mean and standard deviation (SD) of continuous parameters. When SD was not reported, we derived it from the standard errors or the 95% confidence interval, if available, or stated not available if SD derivation was not possible.

Role of the funding source
There was no funding source for this study.

Results
The search strategy yielded 519 records, after removing duplicates. After title and abstract screening, we included 201 papers for full text screening. We included

in our manuscript 46 original RCTs (including landmark phase 3 trials and other trials in individuals with obesity (with or without comorbidities), assessing various cardio-metabolic parameters) and 8 SR/MAs on FDA-approved AOM.

FDA approved medications for monogenic syndromes of obesity

Setmelanotide

Setmelanotide, is a melanocortin-4 (MC4) receptor agonist that was FDA approved in 2020 as a subcutaneous injectable formulation for chronic weight management in patients 6 years and older with obesity resulting from proopiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1) or leptin receptor (LEPR) deficiency, confirmed by genetic testing.[18] These conditions are associated with insufficient activation of the MC4 receptor resulting in hyperphagia and severe childhood-onset obesity. Setmelanotide re-establishes the activity of the MC4 receptor pathway, thus reducing hunger and promoting body weight loss, by lowering caloric intake, and increasing energy expenditure in animal models.[18,22,23]

In a multicentre single arm trial, 11 patients with obesity secondary to LEPR deficiency (mean age 23.7 (8.4) years and a mean baseline BMI of 48.2 (10.4) kg/m^2), treated with Setmelanotide, showed a significant decrease in hunger score by 43.7% (p < 0.0001) and bodyweight by 12.5% (p < 0.0001), at one year compared to baseline.[24] In addition, 45% of patients achieved ≥10% total body weight loss at one year.[24] Similarly, 10 patients with obesity secondary to POMC deficiency (mean age of 18.4 (6.2) years and a mean BMI of 40.4 (9) kg/m^2), treated with Setmelanotide, showed a significant decrease in hunger score by 27.1% (p 0.0005) and bodyweight of 25.6% (p < 0.0001) at one year compared to baseline; 80% of those patients achieved ≥10% total body weight loss.[24] The most common adverse events observed with Setmelanotide were injection site reactions (100% of patients with POMC or LEPR deficiency) and hyperpigmentation disorders (100% in POMC deficiency and 45% in LEPR deficiency).[24] A total body weight loss of 7.6% was observed with Setmelanotide in another 1-year trial in patients with Bardet-Biedl or Alstrom Syndrome (p 0.0005).[25]

Metreleptin

Leptin is an adipokine that was investigated not only for its metabolic effect, but also for potential immune, neuroendocrine and neurocognitive functions.[26–31] Metreleptin is a leptin analog that was FDA approved in 2014 as a replacement therapy for leptin deficiency in patients with congenital or acquired lipodystrophy and associated co-morbidities.[17] It is administered as a subcutaneous injection once daily, with a dose depending on the patient weight (starting at 0.06 mg/kg/day with a maximum of 0.13 mg/kg/day for patients with baseline weight ≤40 kg, and 2.5 mg (for males) or 5 mg (for females) once daily with a maximum of 10 mg/day for patients with baseline weight >40 kg).[17] In a prospective non-randomized crossover study of 17 patients (mean age of 29 (16) years, a mean weight of 70.1 (17.3) kg), with generalized or partial lipodystrophy and low leptin levels, Metreleptin resulted in a significant improvement in metabolic parameters at 6 months compared to baseline: a decrease in total cholesterol by 73 mg/dL (p 0.04), a decrease in triglycerides by 240 mg/dL (p 0.02), a decrease in fasting glucose by 26 mg/dL (p 0.01), a decrease in urinary glucose excretion of 5 g/24 h (p 0.007) and an increase of 3.3 mg/kgFFM/min in insulin sensitivity (p 0.004). Metreleptin also resulted in a significant decrease in 24-h energy expenditure, by 5.0% (121 (152) kcal/day; p 0.006) and 7.9% (190 (272) kcal/day; p 0.04) at 2 weeks and 6 months, respectively, compared to baseline.[32] It also resulted in a reduction in lean body mass of 2 (10) kg (p 0.005) at 6 months compared to baseline.[32] In a post-hoc analysis combining data from 4 studies, it appeared that individuals with very low leptin levels at baseline could possibly respond to Metreleptin with a reduction of their body weight. However, these findings are limited by the small number of participants in the specific sub-group of interest, and therefore, the statistical significance and the clinical importance of this report need to be confirmed and further elucidated.[33] The development of antibodies against Metreleptin was reported, although the consequences are not well understood due to the small number or reports.[34]

FDA approved medications for non-syndromic obesity

Mechanism of action

The currently approved AOM target peripheral and central pathways to decrease energy intake by reducing appetite and increasing satiety[35–43] (Fig. 1; Table 1).

Orlistat has mainly a peripheral effect; it inhibits gastric and pancreatic lipases, thus decreasing dietary fat absorption.[44] Phentermine is a sympathomimetic that is less potent than other amphetamine on dopamine release, and therefore, is associated with a lower risk of substance abuse.[45,46] It stimulates serotonin release, but only at very high doses.[45,47] Animal data showed increased energy expenditure with phentermine,[48] although inconsistently,[49] and this has never been confirmed in humans. As a standalone therapy, it is only approved for short term treatment (<12 weeks).[10,12,50–52] Phentermine combined with topiramate is approved for long term treatment of obesity. Topiramate is a gamma-aminobutyric acid agonist, glutamate antagonist and carbonic anhydrase inhibitor that has been shown to suppress appetite, through mechanisms that are still unclear.[39] Animal studies have shown increased energy expenditure[53] and improved insulin sensitivity,[54] but this has not been yet confirmed in humans.[55] Naltrexone (opioid receptor
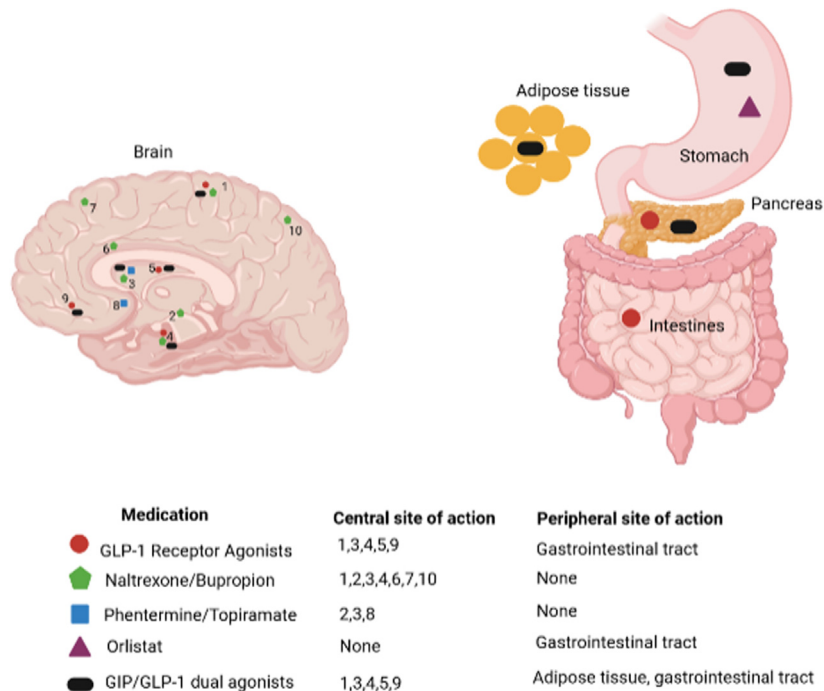
Fig. 1: Site of action of FDA approved anti-obesity medications. (1): parietal cortex, (2) hippocampus, (3) hypothalamus, (4) insula, (5) putamen, (6) dorsal anterior cingulate, (7) superior frontal cortex, (8) nucleus accumbens, (9) orbitofrontal cortex, (10) superior parietal cortex. For GLP-1 receptor agonists and naltrexone/bupropion, the central sites of action are derived from animal studies and brain functional MRI studies in humans; For phentermine/topiramate, the central sites of action are derived from animal studies. Animal studies showed that GLP-1 agonists act on the hypothalamus and the nucleus of the solitary tract.[35] GLP-1 agonists act also on the parietal cortex, insula, putamen, and orbitofrontal cortex in response of food images, as demonstrated in functional MRI studies.[37,38] Naltrexone/bupropion acts on the hypothalamus, superior parietal cortex, posterior insula, dorsal anterior cingulate, hippocampus. There are inconsistent data on its role in the superior frontal cortex, the amygdala and nucleus accumbens.[36,41–43] Phentermine acts on the hypothalamus. Topiramate acts on the hypothalamus and the hippocampus, as shown in animal models[39] and the nucleus accumbens, in a proof-of-concept study for the treatment of alcohol dependence, not for weight management.[40] GLP-1, glucagon-like peptide-1; HCl, hydrochloric acid. This figure was created using BioRender (https://biorender.com/).

antagonist that inhibits the POMC pathway inhibitor) and Bupropion (antidepressant, norepinephrine and dopamine reuptake inhibitor that directly stimulate POMC cells) work synergistically to increase POMC peptide production, and therefore decrease food intake.[36,56] In addition, the combination Naltrexone/Bupropion (NB) acts on the reward pathways, as demonstrated in functional magnetic resonance imaging (fMRI) studies.[36] NB increased activity in various cortical areas in response to food cues,[41–43] implying increased self-control and awareness of internal signals of fullness. Finally, glucagon like peptide receptor (GLP1-R) agonists, Liraglutide and Semaglutide, act centrally by decreasing appetite, and peripherally, on the pancreas by increasing insulin secretion and on the gastro-intestinal tract leading to decreased intestinal motility and delayed gastric emptying.[57]

Effect on weight
Orlistat (Xenical, Alli). The XENical in the Prevention of Diabetes in Obese Subjects (XENDOS) study enrolled men and women with obesity and without type 2 diabetes who were either assigned to take Orlistat 120 mg ter in die (TID) or placebo TID for a 4-year period.[58] All patients were prescribed a reduced calorie diet (–800 calories/day) with 30% from fat and not more than 300 mg cholesterol per day. They were also advised to walk 1 km per day. The range of mean age of all participants was 43.0–43.7 years, and 55% were women.[58] The baseline mean BMI was 37 kg/m^2.[58] At 1-year, mean total body weight loss was 10.6 kg in the intervention group (n = 1487) and 6.2 kg for the placebo group (n = 1295), SD not available (Fig. 2). At 4 years, mean total body weight loss, compared to baseline was 5.8 kg for the intervention group (n = 851) and 3.0 kg for the placebo group (n = 567) (SD not available) (Fig. 2). The compliance with the drug administration from the first dose until treatment dissolution was 93% for both orlistat patients and placebo patients,[58] and the overall dropout rate was 8%.[21,58] The XENDOS trial did not include patients with DM. However, several trials investigated the efficacy of orlistat, alone or in

Drug (trade name)	Approval FDA/EMA (year)	Mechanism of action	Adverse events[a]	Contraindications[b]
Orlistat (Xenical, Alli)	FDA 1999 EMA 1998	Gastric and pancreatic lipase inhibitor	Oily rectal leakage, abdominal distress, abdominal pain, flatulence with discharge, fecal urgency, steatorrhea, fecal incontinence, increased defecation	Patients with chronic malabsorption syndrome or cholestasis, pregnancy
Phentermine/ Topiramate (Qsymia)	FDA 2012	NE agonist/GABA agonist, glutamate antagonist	Elevation in heart rate, mood and sleep disorders, cognitive impairment, metabolic acidosis, paresthesia, dry mouth	Glaucoma, hyperthyroidism, during or within 14 days following the administration of monoamine oxidase inhibitors, hypersensitivity to sympathomimetic amines, pregnancy
Naltrexone/ Bupropion (Contrave/ Mysimba)	FDA 2014 EMA 2015	Opioid receptor antagonist/DA and NE reuptake inhibitor	Nausea, constipation, headache, vomiting, dizziness, insomnia, dry mouth, diarrhea, sleep disorder	Chronic opioid use, acute opioid withdrawal, uncontrolled hypertension, seizure disorder, bulimia or anorexia nervosa, abrupt discontinuation of alcohol, benzodiazepines, barbiturates, and antiseizure drugs; concomitant use of MAOIs, patient receiving linezolid or IV methylene blue, pregnancy
Liraglutide (Saxenda)	FDA 2014 EMA 2015	GLP-1 analogue	Increased heart rate, hypoglycemia, constipation, diarrhea, nausea, vomiting, headache	Personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2, pregnancy
Semaglutide (Wegovy)	FDA 2021 EMA 2021	GLP-1 analogue	Nausea, vomiting, diarrhea, abdominal pain, constipation, headache	Personal or family history of medullary thyroid carcinoma or in patients with multiple endocrine neoplasia syndrome type 2, pregnancy
Setmelanotide (Imcivree)	FDA 2020 EMA 2021	MC4R agonist	Injection site reactions, hyperpigmentation, nausea, headache, diarrhea, vomiting, abdominal pain	None
Tirzepatide[c]	Under consideration by FDA	GIP/GLP-1 dual agonist	Nausea, diarrhea, decreased appetite, vomiting, constipation, dyspepsia, and abdominal pain	Personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2, known serious hypersensitivity to tirzepatide or any of the excipients

Abbreviations: DA, dopamine; EMA, European Medicines Agency; FDA, Food and Drug Administration; GABA, gamma-aminobutyric acid; GI, gastrointestinal; GIP, gastric inhibitory polypeptide; GLP-1, glucagon-like peptide 1; IV, intravenous; MAOIs, monoamine oxidase inhibitors; MC4R: melanocortin-4 receptor; NE, norepinephrine. [a]Adverse events presented here are those that are present in more than 10% of the population, based on the FDA approval leaflet. [b]Contraindications are based on the FDA approval leaflet. [c]Under expedited consideration for FDA approval.

Table 1: Anti-obesity medications: approval, mechanism of action, adverse events, and contraindications.
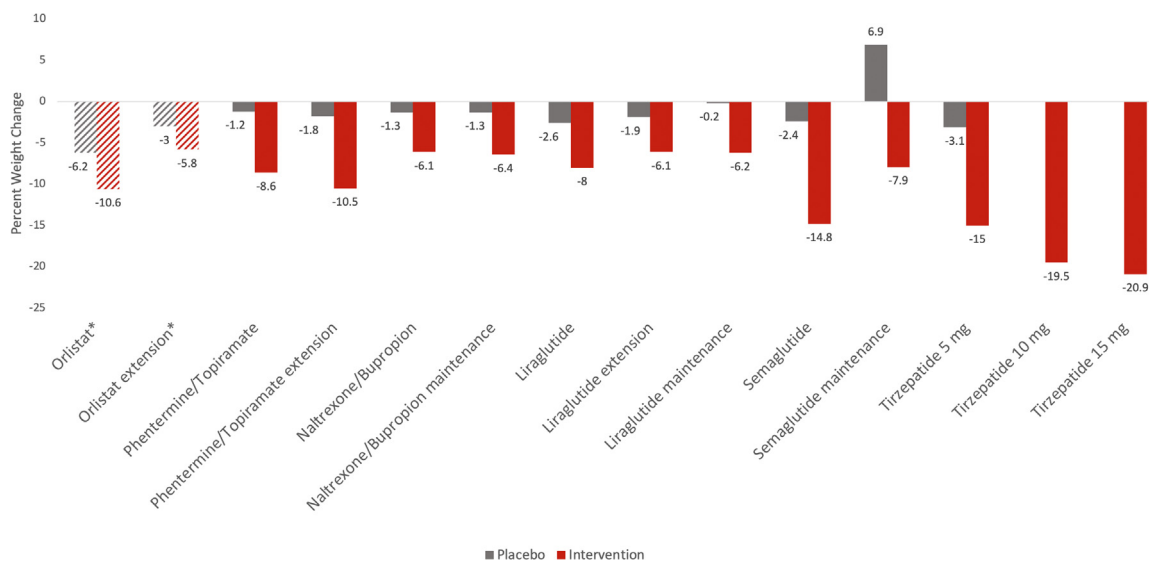

Fig. 2: Mean percent (%) weight change reported in the main phase 3 and extension trials of the FDA approved anti-obesity medications. Orlistat: XENDOS trial (years 1 and 4). Phentermine/topiramate: CONQUER and SEQUEL trials. Naltrexone/bupropion: COR-I and COR-II trials. Liraglutide: SCALE Obesity, SCALE Obesity and Prediabetes Extension, and SCALE maintenance trials. Semaglutide: STEP 1 and STEP 4 trial. All trials are listed in order as seen in the figure from left to right. The grey color represents placebo arms; the red color represents intervention arms. [a]The mean weight change in the orlistat group is in kg not in percent (stripped bar charts). [b]Under expedited consideration for FDA approval.

combination with Metformin or insulin treatment, in patients with overweight or obesity and DM with suboptimal control. In these studies, participants taking orlistat achieved a significantly greater percent in total body weight loss (range of mean percent weight loss 3.9–6.2), when compared to patients on placebo (mean percent weight loss 1.3–4.3).[59–62] The adverse events observed in more than 10% of the population in the main orlistat trials include gastrointestinal (GI) symptoms such as rectal leakage, abdominal pain, abdominal stress, flatulence with discharge, fecal urgency, steatorrhea, fecal incontinence, and increased defecation (Table 1).[63]

Phentermine/Topiramate (Qsymia). Three phase 3 RCTs assessed the efficacy of phentermine/topiramate on total body weight loss: EQUIP, CONQUER and SEQUEL.[64–66] In the EQUIP trial, patients with obesity (BMI $\geq$ 35 kg/m^2) were randomly assigned to receive phentermine/topiramate 3.75 mg/23 mg or 15 mg/92 mg or placebo, in addition to a reduced calorie diet for 56 weeks. The mean age of participants was 42.7 years, and 83% were women.[64] The mean baseline BMI was 42 kg/m^2.[64] The percent weight reductions were −5.1 (8.6) % for the low dose group (n = 234), −10.9 (8.5) % for the high dose group (n = 498), and −1.5 (8.5) % for the placebo group (n = 498). In CONQUER, men and women with overweight/obesity were randomly assigned to receive phentermine/topiramate 7.5 mg/46 mg or 15 mg/92 mg or placebo, for 56 weeks. All patients received standardized counseling for diet and lifestyle modification. The mean age of participants was 51.1 years, and 70% were women.[65] The range of mean baseline BMI was 36.2–36.7 kg/m^2.[65] Weight reductions of 6.6 (9.2) % was achieved for the low dose group (n = 498), 8.6 (10.4) % for the high dose group (n = 995), and 1.2 (8.8) % for the placebo group (n = 994) (Fig. 2).[65] The SEQUEL trial was a 52-week extension of CONQUER trial. Compared to baseline, the weight reduction was 9.3% in the low dose (n = 153), 10.5% in the high dose (n = 295) and 1.8% with the placebo (n = 227), SD not available (Fig. 2). A sub-group analysis according to diabetes mellitus (DM) status showed a higher weight loss in the intervention arms, compared to placebo arms, with a trend for a higher efficacy in patients without DM, compared to those with DM.[65] Furthermore, a trial on 130 patients with obesity and DM from the OB-202/DM-230 study, assessed weight change at 56 weeks when comparing phentermine/topiramate to placebo, and showed a significant decrease in mean percent body weight of 9.6% vs. 2.6% (p < 0.0001, SD not available), and a drop in HbA1c of 1.6% vs. 1.2% (p < 0.05, SD not available), respectively.[67] The dropout rate ranged between 31 and 47% in the EQUIP and CONQUEUR trials and was of 5–10% among those who remained in the extension trial. The adverse events observed in more than 10% of

the population in the main phentermine/topiramate trials include increased heart rate; central nervous system symptoms such as mood and sleep disorders, cognitive impairment, paresthesia, headaches, and dizziness; GI symptoms such as constipation, dysgeusia, and dry mouth; infections and infestations such as upper respiratory tract infections, nasopharyngitis, and sinusitis; metabolism and nutrition disorders such as metabolic acidosis (Table 1).[64–66,68]

A SR/MA of 6 RCTs on phentermine/topiramate compared to placebo showed a weighted mean difference in total body weight loss of 7.7 (6.6, 8.8) kg, favoring the intervention at 56–108 weeks, with a response that is dose dependent.[69]

Naltrexone/bupropion (Contrave/Mysimba). The Contrave Obesity Trials (COR) program included three main RCTs investigating the effect of NB on total body weight loss in patients with obesity.[70–72] These RCTs administered a combined oral sustained-release formulation of naltrexone and bupropion (NB32) (8 mg naltrexone/90 mg bupropion in each tablet, two tablets taken twice a day) or matching placebo twice daily, in addition to lifestyle modification, over a period of 56 weeks.[70–72] The COR-I trials, included a third arm with a lower total dose of 16 mg/day naltrexone with 360 mg/day bupropion (NB16) (4 mg naltrexone/90 mg bupropion in each tablet, two tablets taken twice a day).[70] The COR-II trial had the co-primary efficacy outcomes at 28 weeks, and re-randomized participants achieving <5% total body weight loss to NB32 or placebo.[71] The study population consisted of men and women with overweight/obesity and controlled co-morbidities, namely hypertension and/or dyslipidemia.[70–72] Across arms, the range of mean age of participants was 43.7–45.9 years, and the range of percentage of women was 84.6–91.6%.[70–72] The range of mean baseline BMI was 36.1–37.0 kg/m^2.[70–72] In the COR-I trial, the percent total body weight loss was 5 (6.5) %, 6.1 (6.5) %, and 1.3 (6.8) % in the NB16 (n = 578), NB32 (n = 583), placebo (n = 581) arms, respectively (Fig. 2). Total body weight loss was significantly different between the 2 NB doses in an exploratory analysis of the primary analysis.[70] The COR-II trial showed a weight reduction of 6.4 (8.6) % in the intervention group NB32 (n = 1001), compared to 1.2 (6.41) % (n = 495) in the placebo group (Fig. 2).[71] The COR-Behavioral Modification (COR-BMOD) trial included an intensive behavioral therapy co-intervention in both arms and showed a weight reduction of 9.3 (9.7) % in the NB group (n = 591) compared to 5.1 (8.5) % in the placebo group (n = 202).[72] In patients with DM, with a baseline characteristics profile similar to other COR trials (with the exception of the presence of DM), at 56 weeks, NB (32/360 mg) compared to placebo, resulted in a significant total body weight loss (percent total body weight loss 5 (4.9)% in NB, 1.8 (5)% in placebo,

p < 0.001).[73] The dropout rate in the COR program RCTs ranged between 11% and 27% for the intervention group and was around 11% for the placebo group.[70–72] The adverse events observed in more than 10% of the population in the main trials for approval of this drug include GI symptoms such as nausea, dry mouth, constipation, diarrhea, and vomiting; symptoms of the nervous system such as headaches and dizziness; or psychiatric disorders such as insomnia, and sleep disorders (Table 1).[74]

The pooled effect of 4 NB RCTs in patients with obesity showed that the mean difference in total body weight loss in NB arms was 2.5 (1.9–3.2) kg, compared with placebo.[75]

Liraglutide (Saxenda). The Satiety and Clinical Adiposity Liraglutide Evidence (SCALE) program included four RCTs on liraglutide 3 mg once daily (QD), compared to placebo, each extending over 56 weeks,[76–78] except for the SCALE Obesity and Prediabetes Extension trials that spanned over 160 weeks.[79] The study population included patients with overweight/obesity, and the range of mean age of all participants was 45.0–49.0 years, and majority women (76–84% of participants).[76–79] The range of mean baseline BMI was 37.5–39.3 kg/m^2.[76–79] In the SCALE Obesity and Prediabetes trial, participants with overweight/obesity without type 2 diabetes (n = 3731) were randomized to liraglutide, 3.0 mg/d (n = 2487) or placebo (n = 1244), in addition to lifestyle modifications.[76] These lifestyle modifications included advising patients to increase their physical activity to at least 150 min per week and reduce their daily energy intake by 500 kcal below their individualized energy requirements.[76] At 56 weeks, the weight reduction was 8 (6.7) % in the Liraglutide arm and 2.6 (5.7) % in the placebo arm (Fig. 2).[76] At 160 weeks, weight reductions, compared to baseline, were 6.1 (7.3) % and 1.9 (6.3) % (Fig. 2) for patients on liraglutide 3 mg (n = 1472) and placebo (n = 738), respectively, implying a small weight regain after the first year of treatment. The SCALE maintenance trial included a run-in period aiming at achieving a least 5% total body weight loss, with a 500 kcal per day deficit diet, based on estimated 24-h energy expenditure. Participants were then randomized to liraglutide 3 mg (n = 207) or placebo (n = 206) and had thereafter additional percent weight reduction of 6.2 (7.3) % on and 0.2 (7.0) %, respectively.[77] The SCALE-Intensive Behavioral Therapy (SCALE-IBT) compared liraglutide 3 mg (n = 142) to placebo (n = 140), on top of a co-intervention in both arms, consisting of intensive behavioral therapy (IBT), an exercise plan, and a caloric prescription depending on the participant baseline weight.[78] Weight reduction was of 7.5% and 4.0% in liraglutide and placebo, respectively, at 56 weeks of treatment (SD not available). In patients with DM, with a baseline characteristics

profile similar to other SCALE trials (with the exception of the presence of DM), at 56 weeks, a significant total body weight loss was achieved (percent total body weight loss of 6% in liraglutide 3 mg, 4.7% in liraglutide 1.8 mg, 2.0% in the placebo, p < 0.001 between both arms and placebo, SD not available).[80] The dropout rate in the SCALE studies was 8–10% in the Liraglutide group and 11–20% in the placebo groups,[76,77] with an exceptionally high dropout rate of 65% in the extension study.[79] The adverse events observed in more than 10% of the population in the main trials for approval of this drug include a somewhat increased heart rate; GI symptoms such as constipation, diarrhea, nausea, dyspepsia, decreased appetite, and vomiting; infections such as nasopharyngitis and upper respiratory tract infection and influenza; hypoglycemia; symptoms of the nervous system such as dizziness and headaches (Table 1).[76,77,79,81]

Semaglutide (Wegovy). The Semaglutide Treatment Effect in People with Obesity (STEP) trials evaluated the efficacy and safety of Semaglutide 2.4 mg weekly compared to placebo, for a duration of 68 weeks each.[82–84] The study population included men and women with overweight/obesity with at least one treated or untreated weight-related comorbidity. The range of mean BMI was 37.8–38.4 kg/m^2.[82–84] For STEP 1 trial, the mean age of all participants was 46.0 years, and 74% were women.[82] The STEP 1 trial included individual counseling sessions every 4 weeks to help with the adherence to a reduced calorie diet of 500 kcal deficit and an increased physical activity prescription of 150 min per week. STEP 1 trial reported a weight reduction of 14.8% in the intervention group (n = 1306), compared to a reduction of 2.4% in the placebo group (n = 655); SD not available (Fig. 2).[82] Dropout rates was not reported. In STEP 4-Maintenance trial, mean age was 46.0 years, and 79% were women.[83] Participants were prescribed a reduced-calorie diet (500-kcal/d deficit relative to estimated energy expenditure) and increased physical activity (150 min/wk) in addition to Semaglutide 2.4 mg weekly for 20 weeks, after which mean body weight of participants dropped by 10.6%. Participants were then randomized to semaglutide 2.4 mg (n = 535) or placebo (n = 268). After randomization, Semaglutide group achieved a weight reduction of 7.9 (8.3) % while the placebo group had a weight gain of 6.9 (8.8) % (Fig. 2).[83] Dropout rate for both arms was very low of 0.8%.[83] STEP 3- IBT trial included 611 participants, mean age 46 years, and 81% were women.[84] All participants received a low-calorie diet prescription of 1000–1200 kcal followed by a hypocaloric diet of 1200–1800 kcal, in addition to a physical activity prescription. Participants also received individual IBT visits with a registered dietitian. In the intervention group (n = 407), weight reduction was 16.0%, while in the

placebo group (n = 204) weight reduction was 5.7%, SD not available.[84] Patients with DM in the STEP 2 trial had a baseline characteristics profile similar to other STEP trials in terms of mean age, range of percent females, mean body weight, mean BMI, mean blood pressure (systolic and diastolic), and coexisting conditions at the time of screening. At 68 weeks, the STEP 2 trial achieved a significant total body weight loss (percent total body weight loss 9.6 (8.0) % in semaglutide 2.4 mg; 7.0 (8.0) % in semaglutide 1.0 mg, 3.0 (8.0) % in placebo, p < 0.0001 between both arms and between semaglutide 1.0 mg and placebo).[85] Compliance data was not reported, and the dropout rate was remarkably low in the STEP studies, ranging from 0 to 6%.[82–84] The adverse events observed in more than 10% of the population in the main trials for approval of this drug include GI symptoms such as nausea, dyspepsia, vomiting, flatulence, diarrhea, abdominal pain, abdominal distention, or constipation; infections and infestations such as upper respiratory tract infections, urinary tract infection, and nasopharyngitis; musculoskeletal and connective tissue disorders such as back pain; and symptoms of the nervous system such as dizziness and headaches (Table 1).[16,82,84]

Pooled data from 3 RCTs on weekly semaglutide (2.4 mg) to placebo showed a mean difference in total body weight loss 12.6% (95% CI 10.3–14.8) at 68 weeks, favoring the intervention.[86]

Head to head comparison between FDA approved anti-obesity medications effect on weight. A network meta-analysis of RCTs on FDA approved AOM, until 2016, showed that compared to placebo, at 1 year, phentermine/topiramate was associated with the highest total body weight loss of 8.8 (7.4–10.2) kg, while liraglutide and NB had a similar total body weight loss, 5.3 (4.5–6.1) kg for liraglutide and 5.0 (4.0–5.9) kg for NB. The lowest total body weight loss was reported with orlistat of 2.6 (2.2–3.0) kg.[87] On the other hand, liraglutide and NB were associated with the highest risk of discontinuation secondary to adverse events.[87]

Two RCTs compared Liraglutide to Orlistat and Semaglutide, respectively.[88,89]

A 20-week RCT, followed by a 1-year extension, compared increasing doses of daily Liraglutide (1.2, 1.8, 2.4 or 3.0 mg) to placebo or open label Orlistat (120 mg TID).[89] After 1 year, all Liraglutide and placebo groups were switched to Liraglutide 2.4 or 3 mg.[89] At 1 year, total body weight loss was higher with liraglutide compared to placebo and Orlistat, with a difference in the achieved weight of 5.8 (3.7–8.0) kg and 3.8 (1.6–6.0) kg, respectively, favoring liraglutide; at 2 years, total body weight loss remained significantly higher in liraglutide groups (5.3 kg) compared to the orlistat group (2.3 kg) (p < 0.001).[89]

The STEP 8 trial compared semaglutide (2.4 mg weekly) to Liraglutide (3 mg daily) with matching daily and weekly placebo in patients with obesity, mean BMI 37.5 (6.8) kg/m^2.[88] Total body weight loss was higher in Semaglutide compared to Liraglutide, with a mean difference in total body weight loss of 9.4 (6.8–12.0) % at 68 weeks.[88] The adverse events were reported in more than 90% of participants of all groups, and they were mostly related to GI symptoms.[88] Treatment discontinuation secondary to adverse events was higher with Liraglutide (12.6%), compared to Semaglutide and placebo (3.5%).[88]

Combination of FDA approved anti-obesity medications and effect on weight. One 12-week trial compared the effect of phentermine (37.5 mg daily) and orlistat (120 mg TID) combined to Phentermine (37.5 mg daily) and placebo in 51 participants with overweight/obesity. The primary outcome was sterol metabolism, which was assessed by measuring the change in the serum levels of sterols from baseline to 12 weeks, and weight was one of the secondary outcomes.[90] At 12 weeks, the drop in weight was 8.6 (0.8) kg with phentermine and orlistat, compared to 6.9 (0.6) kg with phentermine and placebo (p 0.04). Adverse events were not reported.[90]

The benefit of adding phentermine to liraglutide was explored in a pilot study of 45 participants with obesity (mean BMI 34.3 (4.7) kg/m^2).[91] After achieving 12% total body weight loss with liraglutide (3 mg daily) and behavioral therapy over 1 year, participants were re-randomized to liraglutide (3 mg daily) and Phentermine (15 mg daily) or liraglutide (3 mg daily) and placebo.[91] There was a trend for a modest additional total body weight loss in the combination group compared to liraglutide and placebo group, but the difference did not reach statistical significance (difference 1.4 (–0.1 to 3.0) %, p 0.073).[91] Interestingly, hunger was significantly lower in the former compared to the latter group.[91] The most common adverse events were musculoskeletal and gastroesophageal reflux, without a significantly increased risk of hypertension or palpitations.[91]

A 26-week RCT compared phentermine, canagliflozin, as monotherapy or in combination to placebo in patients (n = 335) with obesity (mean BMI 37.3 (5.2) kg/m^2) with or without hypertension or dyslipidemia.[92] The combination canagliflozin and phentermine led to a significant reduction in weight compared to placebo with a difference in the percent total body weight loss of 6.9 (5.2–8.6) %; total body weight loss was also significantly higher in the combination arm compared to monotherapy.[92]

Effect on central obesity
Orlistat (Xenical, Alli). In XENDOS, at 1-year, and compared to baseline, the waist circumference (WC) decreased by 9.6 cm with orlistat and by 7.0 cm in the placebo group (p < 0.01). At 4 years, WC dropped by

6.4 cm and 4.4 cm, in the orlistat and placebo groups, compared to baseline (p < 0.01)[58] (Appendix D).

One trial evaluated the effect of orlistat on visceral adiposity.[93] Patients were randomized to receive orlistat 60 mg TID (n = 61) or placebo (n = 62), in addition to instructions on lifestyle modification and advice on distribution of fat intake and multivitamin intake for all participants for a total duration of 24 weeks. The investigators used computerized tomography (CT) scans to assess the visceral adipose tissue (VAT) mass in kilograms. Both interventions lead to a decrease in VAT mass, with a significantly higher drop in patients taking orlistat; mean drop of 0.6 (0.7) kg in orlistat arm, compared to a mean drop of 0.4 (0.6) kg in the placebo arm (p < 0.05).[93] Interestingly, in sub-group analysis according to total body weight loss, there was no difference between arms when total body weight loss was >5%, while the drop was larger with orlistat compared to placebo, in those who lost <5% of their weight.[93]

Phentermine/Topiramate (Qsymia). In EQUIP, at 56 weeks, mean WC reductions, were 5.6 (9.8) % for the low dose group, 10.9 (10.3) % for the high dose group, and 3.1 (10.3) % for the placebo group (p < 0.0001 between high dose group and placebo and between the two doses).[64] Similarly, at 56 weeks, CONQUER trial reported a similar pattern in the drop in WC[65] (Appendix D).

Naltrexone/Bupropion (Contrave/Mysimba). After 56 weeks, the COR-I trial a mean WC reduction of 5 (10.3) cm with NB16, 6.2 (10.4) cm with NB32, and 2.5 (10.4) cm in the placebo[70] (p < 0.0001 for both doses vs. placebo). The findings in the COR-II trial were of a similar magnitude compared to COR-I,[71] while the drop in WC was larger in the COR-BMOD trial; mean WC reduction of 10.0 (11.7) cm with NB16 compared to 6.8 (10.9) cm in the placebo arm[72] (Appendix D).

Liraglutide (Saxenda). In the SCALE Obesity and Prediabetes trial, at 56 weeks, the mean WC reduction was 8.2 (7.3) cm in the liraglutide arm and 3.9 (6.6) cm in the placebo arm (p < 0.001).[76] At 160 weeks, at the Extension trial, compared to baseline, mean WC reductions of 6.9 (8.3) cm and 3.4 (7.5) cm were achieved in liraglutide 3 mg and placebo groups (n = 738), respectively (p < 0.0001).[79] In the SCALE maintenance trial, the change in WC followed the same pattern but of a lower magnitude.[77] In the SCALE IBT, mean WC reductions of 9.4 cm and 6.7 cm in the liraglutide 3 mg and placebo groups, respectively (p 0.0063, SDs not available), reflecting a higher total body weight loss in both groups with behavioral therapy at 56 weeks of treatment[78] (Appendix D).

One trial assessed the percent change in VAT in patients taking liraglutide 3.0 mg (n = 73) compared to placebo (n = 55) for 40 weeks, where all participants received recommendations for diet and physical activity.[94] Participants underwent magnetic resonance imaging (MRI) scanning where retrieved images were analysed for several measures, including VAT. A significantly higher reduction in percent VAT was seen among patients on liraglutide with a mean drop of 12.5 (9.3) %, as compared to patients on placebo with a mean drop of 1.6 (12.3) % (p < 0.0001).[94]

Semaglutide (Wegovy). At 68 weeks, the STEP 1 trial reported a mean WC reduction of 13.5 (SD not available) cm in the intervention group and 4.1 (SD not available) cm in the placebo group (p < 0.001).[82] In STEP 4-Maintenance trial, and after the run-in period, a mean WC reduction of 6.4 (8.3) cm was achieved with semaglutide group and an increase of 3.3 (8.3) cm in the placebo after 68 weeks (p < 0.001).[83] STEP 3- IBT trial showed the same pattern of change in WC as reported in STEP 1[84] (Appendix D).

Effect on glycemic parameters
Orlistat (Xenical, Alli). At 1 and 4 years of treatment, the XENDOS trial did not report on any glycemic parameter (Table 2).[58] The trials that investigated the efficacy of orlistat in patients with overweight/obesity and DM (baseline HbA1c 8–9%) showed a significant decrease in glycemic parameters in participants taking orlistat compared to patients on placebo.[59–62]

Phentermine/Topiramate (Qsymia). Both CONQUER and SEQUEL trials reported small changes in mean HbA1c levels; although they differed significantly between arms, favoring the intervention groups, the clinical implication of such findings is questionable (Table 2). In the CONQUER trial, there was an improvement in insulin resistance with a mean drop in homeostatic model assessment of insulin resistance (HOMA-IR) of 0.9 (8.5) and 1.1 (8.8) in low and high dose phentermine/topiramate groups, and a gain of 0.5 (7.6) in the placebo group (p 0.0007 for low dose vs. placebo and p < 0.0001 for high dose vs. placebo, p comparing high to low dose not reported).[65]

Naltrexone/Bupropion (Contrave/Mysimba). In patients without DM, the COR-I trial reported a mean HOMA-IR reduction of 14.3 (73.6) % in the NB16 group, 20.2 (64.7) % in the NB32 group, compared to a 5.9 (78.8) % in the placebo group (p 0.044 for NB16 vs. placebo and p 0.0003 for NB32 vs. placebo).[70] The COR-II trial showed a change in mean HOMA-IR of a similar magnitude.[71] The COR-BMOD trial reported larger drop in HOMA-IR of 29.9 (60.1) % in the NB32 group compared to 16.6 (65.0) % in patients on placebo (p 0.003), probably reflecting the larger weight loss in this trial.[72]

Drug (trade name)[a]	Main phase 3 trial (duration)	Arms (N) Co-intervention Drop-out rate (%)	Age Mean (SD) Gender Women (%)	Proportion (%) of participants losing ≥5% or ≥10% of baseline weight	HbA1c % change from baseline Mean (SD)	Lipid % change from baseline Mean (SD)	SBP/DBP Change from baseline (mmHg)
Orlistat (Xenical, Alli)	XENDOS (1 y)[b 58]	I: 120 mg TID (1487) C: placebo TID (1295) + reduced calorie diet and physical activity (1 km walk per day) Drop-out: NA	I: 43.0 (8.0) C: 43.7 (8.0) I: 55.2 C: 55.3	≥5% loss I: 73 C: 45 ≥10% loss I: 41 C: 21	NA	HDL-C/LDL-C I: +3.4 (NA)/−11.4 (NA) C: +8.5 (NA)/−1.6 (NA) TC/TG I: −8.8 (NA)/−6.2 (NA) C: −1.3 (NA)/−6.3 (NA)	I: −7.3/−3.6 C: −5.2/−2.6
	XENDOS (4 y)[b 58]	I: 120 mg TID (851) C: placebo TID (567) + reduced calorie diet and physical activity (1 km walk per day) Drop-out: I: 48% C: 66%	I: 43.0 (8.0) C: 43.7 (8.0) I: 55.2 C: 55.3	≥5% loss I: 53 C: 37 ≥10% loss I: 26 C: 16	NA	HDL-C/LDL-C I: +6.5 (NA)/−12.8 (NA) C: +9.1 (NA)/−5.1 (NA) TC/TG I: −7.9 (NA)/+2.4 (NA) C: −2.3 (NA)/+2.9 (NA)	I: −4.9/−2.6 C: −3.4/−1.9
Phentermine/ Topiramate (Qsymia)	CONQUER (56 weeks)[c 65]	I1: 7.5 mg/46 mg (498) I2: 15 mg/92 mg (995) C: placebo (994) + standard LSM Drop-out: 31%	I1: 51.1 (10.4) I2: 51.0 (10.7) C: 51.2 (10.3) I1: 70 I2: 70 C: 70	≥5% loss I1: 62 I2: 70 C: 21 ≥10% loss I1: 37 I2: 48 C: 7	I1: 0.0 (0.7) I2: −0.1 (0.9) C: +0.1 (0.9)	HDL-C/LDL-C I1: +5.2 (19.4)/−3.7 (25.6) I2: +6.8 (20.8)/−6.9 (27.4) C: +1.2 (20.8)/−4.1 (27.4) TC/TG I1: −4.9 (15.4)/−8.6 (49.5) I2: −6.3 (17.0)/−10.6 (52.9) C: −3.3 (17.0)/+4.7 (52.9)	I1: −4.7/−3.4 I2: −5.6/−3.8 C: −2.4/−2.7
	SEQUEL (56-week extension of CONQUER)[c 66]	I1: 7.5 mg/46 mg (153) I2: 15 mg/92 mg (295) C: placebo (227) + standard LSM Drop-out: I1: 8.4% I2: 10.5% C: 4.9%	I1: 52.2 (10.6) I2: 51.2 (10.4) C: 52.7 (9.8) I1: 69.3 I2: 66.1 C: 64.8	≥5% loss I1: 75 I2: 79 C: 30 ≥10% loss I1: 50 I2: 54 C: 12	I1: +0.01 (0.6) I2: 0.0 (0.6) C: +0.2 (0.4)	HDL-C/LDL-C I1: +7.3 (NA)/−4.6 (NA) I2: +11.9 (NA)/−5.6 (NA) C: +4.7 (NA)/−10.7 (NA) TC/TG I1: NA/−12.5 (NA) I2: NA/−13.7 (NA) C: NA/+0.4 (NA)	I1: −4.7/−3.7 I2: −4.3/−3.5 C: −3.2/−3.9
	EQUIP (56 weeks)[c 64]	I1: 3.75 mg/23 mg (234) I2: 15 mg/92 mg (498) C: placebo (498) + standard LSM Drop-out: I1: 39.0% I2: 33.6% C: 47.1%	I1: 43.0 (11.0) I2: 41.9 (12.2) C: 43.0 (11.8) I1: 83.4 I2: 82.8 C: 82.7	≥5% loss I1: 45 I2: 67 C: 17 ≥10% loss I1: 19 I2: 47 C: 7	NA	HDL-C/LDL-C I1: +0.5 (17.1)/−7.7 (19.8) I2: +3.5 (18.3)/−8.4 (20.9) C: 0.0 (18.3)/−5.5 (20.9) TC/TG I1: −5.4 (13.3)/+5.2 (46.8) I2: −6.0 (14.3)/−5.2 (49.9) C: −3.5 (14.3)/+9.1 (49.9)	I1: −1.8/−0.1 I2: −2.9/−1.5 C: +0.9/+0.4
Naltrexone/ Bupropion (Contrave)	COR-I (56 weeks)[c 70]	I1: 4 mg/90 mg, 2 tablets BID (578) I2: 8 mg/90 mg, 2 tablets BID (583) C: placebo BID (581) + standard LSM Drop-out: I1: 24% I2: 21% C: 27%	I1: 44.4 (11.3) I2: 44.4 (11.1) C: 43.7 (11.1) I1: 85 I2: 85 C: 85	≥5% loss I1: 39 I2: 48 C: 16 ≥10% loss I1: 20 I2: 25 C: 7	NA	HDL-C/LDL-C I1: +7.6 (21.6)/−1.5 (25.7) I2: +8.0 (21.0)/−2.0 (21.3) C: +0.8 (21.7)/−0.5 (25.8) TC/TG I1: NA/−8.0 (43.0) I2: NA/−12.7 (155.7) C: NA/−3.1 (44.3)	% change I1: +0.3/+0.1 I2: −0.1/0.0 C: −1.9/−0.9
	COR-II (56 weeks)[c 71]	I: 8 mg/90 mg, 2 tablets BID (1001) C: placebo BID (495) + standard LSM Drop-out: I: 15% C: 21%	I: 44.3 (11.2) C: 44.4 (11.4) I: 84.6 C: 84.8	≥5% loss I: 50 C: 17 ≥10% loss I: 28 C: 6	NA	Mean change (mg/dl) HDL-C/LDL-C I: +3.6 (10.6)/−6.2 (23.8) C: −0.9 (10.7)/−2.1 (27.7) % change TC/TG I: NA/−9.8 (4.97) C: NA/−0.5 (2.09)	I: +0.6/+0.4 C: −0.5/+0.3
	COR-BMOD (56 weeks)[c 72]	I: 8 mg/90 mg, 2 tablets BID (591) C: placebo BID (202) + intensive group behavior modification Drop-out: I: 11% C: 20%	I: 45.9 (10.4) C: 45.6 (11.4) I: 89.3 C: 91.6	≥5% loss I: 66 C: 42 ≥10% loss I: 42 C: 20	NA	HDL-C/LDL-C I: +9.4 (24.7)/+7.1 (34.0) C: +2.8 (22.8)/+10.0 (31.2) TC/TG I: NA/−16.6 (38.4) C: NA/−8.5 (38.8)	NA

(Table 2 continues on next page)

Drug (trade name)[a]	Main phase 3 trial (duration)	Arms (N) Co-intervention Drop-out rate (%)	Age Mean (SD) Gender Women (%)	Proportion (%) of participants losing ≥5% or ≥10% of baseline weight	HbA1c % change from baseline Mean (SD)	Lipid % change from baseline Mean (SD)	SBP/DBP Change from baseline (mmHg)
(Continued from previous page)							
Liraglutide (Saxenda)	SCALE Obesity and Prediabetes (56 weeks)[c 76]	I: 3.0 mg QD (2487) C: placebo (1244) + standard LSM Drop-out: I: 12% C: 21%	I: 45.2 (12.1) C: 45.0 (12.0) I: 78.7 C: 78.1	≥5% loss I: 63 C: 27 ≥10% loss I: 33 C: 11	I: −0.3 (0.3) C: −0.1 (0.3)	Mean change (mg/dl) HDL-C/LDL-C I: +2.3 (NA)/−3.0 (NA) C: +0.7 (NA)/−1.0 (NA) TC/TG I: −3.1 (NA)/−13.3 (NA) C: −1.0 (NA)/−5.5 (NA)	I: −4.2/−2.6 C: −1.5/−1.9
	SCALE Obesity and Prediabetes Extension (160 weeks)[c 79]	I: 3.0 mg QD (1505) C: placebo (749) + standard LSM Drop-out: 65%	I: 47.5 (11.7) C: 47.3 (11.8) I: 76 C: 77	≥5% loss I: 50 C: 24 ≥10% loss I: 23 C: 10	I: −0.3 (0.3) C: +0.1 (0.3)	NA	I: −3.2/−2.3 C: −0.5/−1.9
	SCALE Maintenance (56 weeks)[c 77]	I: 3.0 mg QD (207) C: placebo (206) All participants had weight loss of ≥5% from a low-calorie diet before randomization Drop-out: I: 8% C: 11%	I: 45.9 (11.9) C: 46.5 (11.0) I: 84 C: 79	≥5% loss I: 51 C: 22 ≥10% loss I: 26 C: 6	I: −0.1 (0.3) C: 0.1 (0.3)	HDL-C/LDL-C I: +7.7 (7.7)/+7.7 (23.2) C: +3.9 (7.7)/+11.6 (23.2) TC/TG I: +7.7 (27.1)/0.0 (44.3) C: +11.6 (27.1)/+0.1 (44.3)	I: +0.2/+1.4 C: +2.8/+1.2
	SCALE IBT (56 weeks)[78]	I: 3.0 mg QD (142) C: placebo (140) + intensive behavioral therapy[d] Drop-out: I: 0.7% C: 7.1%	I: 45.4 (11.6) C: 49.0 (11.2) I: 83.8 C: 82.9	≥5% loss I: 62 C: 39 ≥10% loss I: 31 C: 20	I: −0.2 (NA) C: −0.1 (NA)	Mean change (mg/dl) HDL-C/LDL-C I: +1.9 (NA)/−1.5 (NA) C: +1.2 (NA)/+1.5 (NA) TC/TG I: −1.5 (MA)/−15.0 (NA) C: +2.3 (NA)/−4.4 (NA)	I: −2.8/−10 C: −0.6/−0.8
Semaglutide (Wegovy)	STEP 1 (68 weeks)[82]	I: 2.4 mg weekly (1306) C: placebo (655) + standard LSM Drop-out: NA	I: 46 (13.0) C: 47 (12.0) I: 73.1 C: 76	≥5% loss I: 86 C: 32 ≥10% loss I: 69 C: 12	I: −0.4 (NA) C: −0.1 (NA)	HDL-C/LDL-C[e] I: 1.0 (NA)/0.9 (NA) C: 1.0 (NA)/1.0 (NA) TC/TG[e] I: 0.9 (NA)/0.7 (NA) C: 1.0 (NA)/0.9 (NA)	I: −6.2/−1.1 C: −0.4/−0.4
	STEP 4 – maintenance (68 weeks)[83]	I: 2.4 mg weekly (535) C: placebo (268) All participants received Semaglutide 2.4 mg weekly for 20 weeks and were randomized to continued drug or placebo afterwards Drop-out: I: 1% C: 1%	I: 47 (12.0) C: 46 (12.0) I: 80.2 C: 76.5	≥5% loss I: 89 C: 48 ≥10% loss I: 79 C: 20	I: −0.1 (0.7) C: +0.1 (0.0)	HDL-C/LDL-C I: +18 (17.8)/+1 (23.6) C: +18 (25.0)/+8 (20.9) TC/TG I: +5 (11.7)/−6 (41.4) C: +11 (12.6)/+15 (66.8)	I: +0.5/+0.3 C: +4.4/+0.9
	STEP 3 - IBT (68 weeks)[84]	I: 2.4 mg weekly (407) C: placebo (204) + lifestyle intervention[f] Drop-out: I: 6% C: 5%	I: 46 (13.0) C: 46 (13.0) I: 77.4 C: 88.2	≥5% loss I: 87 C: 48 ≥10% loss I: 75 C: 27	I: −0.5 (NA) C: −0.3 (NA)	HDL-C/LDL-C I: +6.5 (NA)/−4.7 (NA) C: +5.0 (NA)/+2.6 (NA) TC/TG I: −3.8 (NA)/−22.5 (NA) C: +2.1 (NA)/−6.5 (NA)	I: −5.6/−3.0 C: −1.6/−0.8
Setmelanotide (Imcivree)	Placebo for a short period, then all took treatments (52 weeks)[g 24]	2 single-arm trials: Trial 1: patients with POMC deficiency receiving Setmelanotide Trial 2: patients with LEPR deficiency receiving Setmelanotide	Trial 1:18 (6.2) Trial 2: 23.7 (8.4) Trial 1: 50% Trial 2: 73%	≥5% loss Trial 1: 90 Trial 2: 64 ≥10% loss Trial 1: 80 Trial 2: 45	Trial 1: −0.3 (NA) Trial 2: −0.2 (NA)	HDL-C/LDL-C Trial 1: 45.0 (43.8)/−7.6 (23.1) Trial 2: 19.6 (24.0)/−10.0 (12.1) TC/TG Trial 1: NA (NA)/−36.6 (30.4) Trial 2: NA (NA)/−7.0 (26.6)	Trial 1: −1.8/−1.6 Trial 2: −6.6/−1.2

(Table 2 continues on next page)

Drug (trade name)[a]	Main phase 3 trial (duration)	Arms (N) Co-intervention Drop-out rate (%)	Age Mean (SD) Gender Women (%)	Proportion (%) of participants losing ≥5% or ≥10% of baseline weight	HbA1c % change from baseline Mean (SD)	Lipid % change from baseline Mean (SD)	SBP/DBP Change from baseline (mmHg)
(Continued from previous page)							
Tirzepatide[h]	SURMOUNT-1 (72 weeks)[95]	I1: 5 mg weekly (630) I2: 10 mg weekly (636) I3: 15 mg weekly (630) C: placebo (643) All participants received tirzepatide or placebo, administered subcutaneously once weekly as an adjunct to lifestyle intervention. Drop-out: Total: 14% I: 10%	I1: 45.6 (12.7) I2: 44.7 (12.4) I3: 44.9 (12.3) C: 44.4 (12.5) I1: 67.6 I2: 67.1 I3: 67.5 C: 67.8	≥5% loss I1: 85 I2: 89 I3: 91 C: 35 ≥10% loss I1: 69 I2: 78 I3: 84 C: 19	NA	Pooled Tirzepatide Groups HDL-C/LDL-C I: 8.0/−5.8 C: −0.7/−1.7 TC/TG I: −4.8/−24.8 C: −1.8/−5.6	Pooled Tirzepatide Groups I: −7.2/−4.8 C: −1.0/−0.8

Abbreviations: BID, twice daily; DBP; Diastolic Blood Pressure; HbA1c, glycosylated hemoglobin; HDL-C: high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LEPR, Leptin receptor; LSM, lifestyle modification; NA, not available; POMC, Pro-opiomelanocortin; QD, once per day; RD, registered dietitian; SBP, systolic blood pressure; TC, total cholesterol; TGs, triglycerides; TID, three times daily; y, year. [a]Participants weighing less than 91 kg at randomization were prescribed 1200 kcal per day, while a caloric prescription was calculated for participants weighing between 91 and 136 kg by body weight in pounds multiplied by 6. Participants weighing more than 136 kg, they were prescribed an 1800 kcal diet per day. All were prescribed 100 min of physical activity per week, and it was increased by 25 min every four weeks, with an ultimate goal of 250 min per week. [b]Participants who dropped out were excluded from the primary analysis. [c]Non-compliant participants were excluded from the analysis. [d]Adapted from the Diabetes Prevention Program and delivered by registered dieticians. The program included recommendations for diet, physical activity, and behavior change. [e]Ratio of measurement at 68 weeks over baseline. [f]All participants received a diet prescription and physical activity prescription. Participants had 30 individual intensive behavioral therapy visits with a registered dietician. [g]Trial consisted of a dose titration phase, then an 8-week placebo-controlled withdrawal phase, then a 32 additional weeks of open-label treatment. [h]Under expedited consideration for FDA approval.

Table 2: Summary of landmark randomized controlled trials of the FDA approved anti-obesity medications (excluding trials in diabetes mellitus).

In patient with obesity and DM (baseline mean HbA1c of 8.0%), there was a significant decrease in HbA1c by 0.6 (1.3) in NB32 group compared to 0.1 (1.6) in the placebo group, p < 0.001, reflecting the weight loss changes in the corresponding arms.[73]

Liraglutide (Saxenda). In the SCALE Obesity and Pre-diabetes trial, at 56 weeks, the mean drop in HbA1c was 0.3 (0.3) % in the liraglutide arm and 0.1 (0.3) % in the placebo arm (p < 0.001).[76] At 160 weeks from baseline in the Extension trial, the mean drop in HbA1c was 0.4 (0.3) % in liraglutide group, while there was an increase of 0.1 (0.3) % in the placebo group, p < 0.0001.[79] The SCALE maintenance and the SCALE-IBT trials reported small changes in HbA1c that differed significantly between arms, favoring the intervention (Table 2).[78]

In patients with obesity and DM (mean baseline HbA1c 8%), there was a significant drop in HbA1c of 1.1–1.3% in liraglutide arms, compared to 0.3% in the placebo arm (p < 0.001).[80]

Semaglutide (Wegovy). At 68 weeks, the STEP 1 trial reported a mean HbA1c reduction of 0.5% in the intervention group, compared to 0.2% in the placebo group (SDs not available; p-value not reported).[82] A similar change was reported in the STEP 3-IBT trial.[84] In STEP 4-Maintenance trial, from randomization after the run-in period at week 20 to week 68, there was a drop in HbA1c by 0.1 (0.7) % with semaglutide 2.4 mg while

there was an increase of 0.1 (0) % with the placebo group (p < 0.001) (Table 2).[83]

In patients with obesity and DM (mean baseline HbA1c 8.1%), there was a drop in HbA1c by 1.5–1.6% in semaglutide arms, and by 0.4% in the placebo arms.[85] There was no significant difference between semaglutide doses.[85]

Effect on lipid profile

Orlistat (Xenical, Alli). After 1 year of treatment, patients taking Orlistat showed an increase in High-density lipoprotein cholesterol (HDL-C) and a decrease in Low-density lipoprotein cholesterol (LDL-C); changes of a small magnitude but significantly different than placebo (p < 0.01 for both HDL-C and LDL-C). Triglycerides level decreased in both arms (Table 2).[58] A similar pattern was seen at the 4-year mark in both HDL and LDL, while there was no difference in triglycerides level between arms (Table 2).[58]

Phentermine/Topiramate (Qsymia). In the EQUIP trial, at 56 weeks, the increase in HDL-C was dose dependent (p 0.0005 between high dose group and placebo and 0.0158 between the two doses). LDL decreased in all arms, with a significant difference between the high dose phentermine/topiramate and placebo (p 0.015), and no difference between doses (p 0.6). Finally, triglycerides dropped only in the high dose arm, while it increased in the low dose and placebo arms (p < 0.0001

between high dose group and placebo and 0.0027 between the two doses) (Table 2).[64]

The CONQUER trial showed similar, though larger, effects on lipid parameters after 56 weeks of treatment, possibly due to the addition of lifestyle modifications to all participants. The changes in the intervention arms were significantly different than the placebo arm for HDL-C, LDL-C and triglycerides levels (Table 2).[65] The changes in lipid level reported in the SEQUEL trial were very close to those in the CONQUER trial, and there was a trend for a dose dependent increase in HDL and decrease in TG (Table 2).[66]

Naltrexone/Bupropion (Contrave/Mysimba). The COR-I, COR-II, and COR-BMOD trials report data on HDL-C, LDL-C, and triglycerides after 56 weeks of treatment. In the COR-I trial, HDL-C increased significantly in intervention arms compared to placebo (p < 0.0001 for comparison of both doses with placebo). LDL-C did not differ significantly between arms, while the drop in triglycerides was higher in the intervention arms compared to placebo (p 0.0461 and <0.0001for NB16 and NB32 with placebo, respectively) (Table 2).[70] The changes in the COR-II trial followed the same pattern (Table 2).[71]

The COR-BMOD trial showed an increase in HDL-C and triglycerides for both arms, since all participants were receiving intensive behavioral therapy, but the change was significantly higher in the NB arm (p < 0.001 for HDL-C and p 0.004 for triglycerides). There was no difference in LDL-C between arms (Table 2).[72]

Liraglutide (Saxenda). The SCALE Obesity and Prediabetes reported mean change in lipid parameters at 56 weeks of treatment. Although the changes in HDL-C, LDL-C, and triglycerides were significantly different in liraglutide arm compared to placebo (p 0.001, p 0.002, p < 0.001, respectively) the magnitude of these changes was small.[76] The 160-week SCALE extension trial did not report on lipid parameters (Table 2).[79]

After 56 weeks of treatment, the SCALE maintenance trial showed no significant difference in lipid parameters between treatment arms, except for triglycerides level that did not change in the intervention arm, but increased by 8.86 (44.29) mg/dL in the placebo group (p 0.03) (Table 2).[77] Similarly, there was no significant difference in lipid parameters between arms in the SCALE-IBT trial (Table 2).[78]

Semaglutide (Wegovy). Across all STEP trials, there was no significant difference in the HDL level between arms after the intervention.[82–84] The STEP 1 trial reported the ratio of measurement at 68 weeks over baseline for all lipid parameters. LDL-C level was similar between both arms, with ratios of 0.97 and 1.01 for the intervention

compared to control, respectively. The change in triglycerides differed between arms, with a ratio of change over baseline of 0.78 for patients taking semaglutide compared to a ratio of 0.93 in patients on placebo (Table 2).[82] The STEP 4 maintenance trial reported mean percent changes in lipid parameters at 68 weeks of treatment. LDL-C increased in both arms, but to a lower extent in semaglutide compared to placebo (p < 0.001). Triglycerides decreased in patients on semaglutide, while they increased in patients on placebo (p < 0.001) (Table 2).[83]

In the STEP 3 trial LDL-C level dropped with semaglutide by 4.7%, while it increased by 2.6% with placebo (p < 0.001). Triglyceride levels decreased in both arms but favored semaglutide (p < 0.001) (Table 2).[84]

Effect on blood pressure
Orlistat (Xenical, Alli). At 1-year, systolic (SBP) and diastolic blood pressure (DBP) dropped by 7.3 mmHg and 3.6 mmHg respectively, for the intervention group, and 5.2 mmHg and 2.6 mmHg, respectively for the placebo group (p < 0.01 for comparison for both SBP and DBP; SD not available). At 4 years, the drop was at a lower extent but differences between arms remained significant (Table 2).[58]

Phentermine/Topiramate (Qsymia). In EQUIP, the reported reductions in SBP and DBP, at 56 weeks, were of a small magnitude, for both low dose and high dose groups. Conversely, there was a trend for an increase in SBP and DBP, in the placebo groups (p < 0.01 for high dose compared to placebo and for comparing doses for DBP only).[64] At 56 weeks, CONQUER trial reported mean SBP and DBP reductions of 4.7 (13.6) mmHg and 3.4 (9.2) mmHg respectively for the low dose phentermine/topiramate, 5.6 (15.1) mmHg and 3.8 (9.8) mmHg respectively for the high dose phentermine/topiramate, and 2.4 (14.5) mmHg and 2.7 (9.8) mmHg for the placebo group (p < 0.01 for any dose compared to placebo for SBP and only for high dose compared to placebo for DBP).[65] The decrease in BP seen in the EQUIP trial was relatively small compared to the changes reported in the CONQUER trial. In fact, the EQUIP trial enrolled normotensive participants while the CONQUER trial recruited a population with hypertension and other cardio-metabolic disorders. At 52 weeks, SEQUEL, the extension of CONQUER trial reported similar changes in SBP and DBP (Table 2).[66]

Naltrexone/Bupropion (Contrave/Mysimba). After 56 weeks, the COR-I trial reported minimal reductions in SBP and DBP in the NB and placebo groups (p < 0.01 for comparisons between any dose and placebo).[70] The reported changes in the COR-II trial were similar in magnitude.[71] The COR-BMOD trial didn't assess for changes in SBPs or DBPs (Table 2).[72]

Liraglutide (Saxenda). In the SCALE Obesity and Pre-diabetes trial, at 56 weeks, the reductions in SBP and DPB were 4.2 (2.2) mmHg and 2.6 (8.7) mmHg respectively in the liraglutide arm, and 1.5 (12.4) mmHg and 1.9 (8.7) mmHg respectively in the placebo arm (p < 0.001 for both SBP and DBP).[76] At 160 weeks, at the Extension trial, the drop in SBP and DBP was similar to the original trial.[79] The SCALE maintenance and SCALE IBT trials reported smaller changes in blood pressure parameters, that were not significant (Table 2).[77,78]

Semaglutide (Wegovy). At 68 weeks, the STEP 1 trial reported mean SBP and DBP reductions of 6.2 mmHg and 2.8 mmHg respectively in the intervention group, compared to 1.1 mmHg and 0.4 mmHg respectively in the placebo group (p < 0.001 for SBP; p not available for DBP; SDs not available).[82] In STEP 4-Maintenance trial reported mean SBP and DBP elevations of 0.5 (13.0) mmHg and 0.3 (8.8) mmHg respectively in the intervention group, compared to 4.4 (13.0) mmHg and 0.9 (10.5) mmHg, respectively, in the placebo group (p < 0.001 for SBP; p 0.46 for DBP), possibly explained by weight regain.[83] STEP 3-IBT trial resulted in reductions in SBP and DBP of 5.6 mmHg and 3.0 mmHg, respectively, for participants receiving semaglutide 2.4 mg, compared to 1.6 mmHg and 0.8 mmHg, respectively, for those receiving placebo at 68 weeks (p 0.001 for SBP; p 0.008 for DBP) (Table 2).[84]

Effect on fatty liver
Data on fatty liver are available for all AOM except phentermine/topiramate.

Orlistat (Xenical, Alli). In a 6-month trial in 170 Chinese patients (76% with nonalcoholic fatty liver disease (NAFLD)), orlistat (at a dose of 120 mg TID) compared to placebo showed no difference in liver enzymes levels, but a higher drop in liver fat, measured by MRI, in the orlistat arm, compared to placebo (mean difference in total fat of 4%, drop of 5.5% in orlistat and drop of 2.0% in the placebo, p < 0.001). Steatosis grade improved by four grades, two grades, and one grade in 1.5%, 11.8%, 44.1% of both study groups, respectively; a significant improvement in steatosis grades was seen when comparing arms (57.3% improvement in orlistat arm vs. 23.5% in placebo arm, p < 0.001).[96] The treatment effect remained significant even after adjusting for total body weight loss.[96] Conversely, in another RCT, the effect of orlistat on liver fibrosis parameters, assessed by the fibrosis-4 index and NAFLD fibrosis score, was studied.[97] The fibrosis-4 index did not show a significant decrease after 12 weeks of treatment with placebo (p 0.959) or orlistat (p 0.510). As for the NAFLD fibrosis score, a significant increase was seen in placebo treated group (p 0.025) compared to a non-significant decrease in orlistat treated group (p 0.715), suggesting a potential

protective effect with orlistat, yet not confirmed.[97] The main limitation of the study was the lack of liver biopsy data, considered the gold standard method to evaluate liver fibrosis.[97]

Naltrexone/Bupropion (Contrave/Mysimba). A post-hoc analysis of the COR trials showed a significant improvement in liver enzymes in the NB group compared to placebo; this effect was directly driven by total body weight loss. The only exception was the fibrosis-4 index, which incorporates data on age, platelet count and hepatic enzymes level, that was not only associated with total body weight loss but also with treatment arm.[98]

Liraglutide (Saxenda). Several small studies explored the impact of liraglutide on NAFLD.[99] Two small (n = 30) short term (16–26 weeks) studies in patients with obesity and NAFLD investigated the impact of liraglutide (3 mg daily), compared to placebo, on fatty liver, measured on MRI[100] or ultrasound.[101] The improvement in liver fat parameters was correlated with weight rather than treatment arms.[100,101] There was no improvement in liver fibrosis, possibly explained by the short intervention duration.[101] A 48-week small multicentre RCT on liraglutide (n = 26) compared to placebo (n = 26) in patients with non-alcoholic steatohepatitis, showed a significant improvement in liver histology.[102] Patients on liraglutide had a 4.3 higher chance of resolution of NAFLD on liver biopsy, compared to placebo (p 0.019).[102]

Semaglutide (Wegovy). In a 1-year phase 1 trial, patients with NAFLD disease (n = 67) were randomized to receive semaglutide (0.4 mg daily) or placebo,[103] and liver parameters were assessed using MRI. There was no difference in liver stiffness, the primary outcome, measured using magnetic resonance elastography.[103] Conversely, the proportion of participants who had at least 30% reduction in liver steatosis in the semaglutide group was almost 2-fold the proportion in the placebo group, 73% and 33%, respectively at 72 weeks (p 0.0006).[103] Total body weight loss was higher with semaglutide, with an estimated difference of –9.6% (p ≤ 0.0001), compared to placebo, and whether total body weight loss was the driver of the benefit on liver steatosis was not explored.

In a phase 2 trial, 320 patients with biopsy proven non-alcoholic steatohepatitis (NASH), using the definition of the NASH Clinical Research Network, were randomized to receive semaglutide (0.1, 0.2 or 0.4 mg daily) or placebo.[104] Histologic findings at 72 weeks showed that the proportion of NASH resolution was higher in semaglutide groups, and the highest proportion 59% reported in the 0.4 mg semaglutide group and only 17% of the placebo group (p < 0.001).[104] However,

there was no difference in the fibrosis parameters between groups.[104] Whether total body weight loss, rather than the intervention per se, is responsible of the beneficial impact of NASH still needs further investigation.[104]

Effect on obstructive sleep apnea

We identified three studies evaluating the effect of FDA approved AOM on obstructive sleep apnea (OSA), one trial on each of phentermine/topiramate,[105] and liraglutide[106] and a pooled analysis of 5 trials on NB.[107]

Phentermine/Topiramate (Qsymia). In one trial, participants with obesity and moderate OSA were randomized to receive the combination treatment of phentermine/topiramate (15/92) (n = 22) or placebo (n = 23) with a standardized advice on lifestyle modification for a duration of 28 weeks.[105] The primary outcome was the apnea-hypopnea index (AHI) with a score of 5–14 events per hour considered mild, 15–29 moderate, and 30 or more considered severe. The reduction in apnea-hypopnea events was more favorable in patients taking phentermine/topiramate compared to placebo; a reduction of 31.5 (19.9) events per hour in the intervention and 16.6 (19.9) events per hour in the placebo (p 0.0084).[105]

Naltrexone/Bupropion (Contrave/Mysimba). A pooled analysis of 5 RCTs on NB32 (n = 2545) compared to placebo (n = 1515) assessed the prevalence of OSA at 24–56 weeks and showed no significant difference between groups.[107]

Liraglutide (Saxenda). The change in AHI was studied in one trial on patients with moderate to severe OSA (AHI of 15–29 or 30 or more events per hour) taking liraglutide 3.0 mg (n = 180) or placebo (n = 179).[106] After 32 weeks of treatment, there was a significant reduction in AHI in liraglutide group (drop of 12.2 (1.8) events per hour) compared to placebo (drop of AHI 6.1 (2.0) events per hour), p 0.015.[106]

Effect on cardiovascular outcomes

Naltrexone/Bupropion (Contrave/Mysimba). The LIGHT trial was a non-inferiority cardiovascular (CV) outcome trial aiming to investigate the safety of NB in patients with obesity and a high CV risk.[108] CV outcomes were defined as major adverse cardiovascular events (MACE), which includes cardiovascular death, nonfatal stroke, or nonfatal myocardial infarction. The interim analysis at 25% of the total sample size showed a risk reduction in CV risk, HR 0.6 (0.4–0.9).[108] However, the trial was stopped prematurely after the release of the interim analysis results to the public, threatening the scientific integrity of the trial.[108] The CV safety was recently evaluated in a network meta-analysis of phase 3 trials on NB, using each drug separately or in combination, for smoking cessation or for weight management, and showed no increased risk of major adverse cardiovascular events, defined as MACE.[109]

Liraglutide (Saxenda). A post-hoc analysis combined data from the phases 2 and 3 SCALE RCTs where liraglutide was compared to placebo, in various patient populations pooled together (n = 5980), including those with pre-diabetes, DM and OSA, and investigated the time to first occurrence of a composite CV outcome, defined as death, non-fatal myocardial infarct or non-fatal stroke. Although it did not reach statistical significance, there was a trend for a lower risk for CV outcomes (hazard ratio (HR) for composite outcome 0.4 (0.2–1.1).[110]

Semaglutide (Wegovy). The Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity – (SELECT) ongoing trial enrolls 17,500 participants and investigates the effect of Semaglutide compared to placebo on a composite CV outcome, defined as MACE, including CV death, non-fatal myocardial infarction, or non-fatal stroke, as a primary outcome; expected completion in October 2023.[111]

A recent SR/MA of RCTs (2010–2020) on AOM and mortality (all-cause and cardiovascular) and cardiovascular events (myocardial infarction, stroke, heart failure) identified 28 RCTs comparing one AOM (orlistat, NB, phentermine/topiramate, liraglutide and lorcaserin) to placebo.[112] Pooling all RCTs together showed no significant reduction in overall mortality, cardiovascular mortality nor cardiovascular outcomes, with the use of AOM compared to placebo.[112] Interestingly, the meta-regression showed that total body weight loss was inversely associated with mortality risk.[112]

Anti-obesity drugs in patients with mental illnesses

While the main trials of FDA approved AOM excluded participants with mental illness, the EQUIP, CONQUER and SEQUEL included 16–22% of participants with a history of depression or on anti-depressant medications, suggesting the potential safe use of phentermine/topiramate in this specific population.[64–66]

Four small pilot RCTs (N = 10–25) on patients with obesity and binge eating disorder, extending over 3–6 months showed that NB and phentermine/topiramate are safe, with a significant reduction in binge eating episodes and in weight, without an increase in adverse events, providing preliminary data for larger trials to confirm such findings.[113–116] A 3-month RCT administered NB or placebo to patients with schizophrenia for weight reduction or smoking cessation and did not show any difference in the measured parameters between the 2 treatment arms.[117]

A 16-week RCT from Denmark investigated the effect of liraglutide (1.8 mg daily; n = 52) compared to placebo (n = 51) in patients with obesity (mean BMI 33 kg/m^2) and schizophrenic disorders on clozapine or olanzapine.[118] There was a significant improvement in glycemic parameters (64% in the liraglutide and 16% in the placebo group had normal glucose tolerance, p < 0.001) and weight (mean difference in weight reduction 5.3 (3.7–7.0) kg, favoring liraglutide).[118] There was no significant difference in adverse events.[118] Another 6-month small RCT (N = 47) compared the safety and efficacy of liraglutide 3 mg daily to placebo in patients with obesity (range of mean BMI 37–41 kg/m^2) and schizophrenia or schizoaffective disorder.[119] The mean difference in the percent total body weight loss was 4.6 (0.7–8.4)% and there was no difference in the adverse event profile between the 2 arms.[119]

A post-hoc analysis of the LIGHT trial provided evidence regarding the efficacy and safety of the use of NB in patients with anti-depressants (N = 2277 on antidepressants; N = 6617 without antidepressants).[120] The effect of NB on weight reduction was the same regardless of the presence or absence of anti-depressant use.[120] In patients on anti-depressants, there was a significantly larger total body weight loss in the NB group compared to the placebo group at 56 weeks, while at 102 weeks there was a trend favoring the NB group that did not reach statistical significance (a drop of 6.3% vs. 4.3% in the NB and placebo, respectively).[120]

A pooled analysis of liraglutide phase 2 and 3 trials showed no difference in the incidence of depression and anxiety, but a potential increased risk of suicidality ideation.[121]

Medication under consideration for FDA-Approval
Tirzepatide
Tirzepatide is a gastric inhibitory polypeptide (GIP)/GLP-1 dual agonist, that works centrally, in the hypothalamus to decrease food intake and possibly increase energy expenditure by desensitizing the GIP receptor, through chronic GIP agonism, in preclinical models. However, animal and human data on the effect of GIP on energy expenditure has been controversial and it is expected that increased energy expenditure will not be seen in humans.[122–127] Tirzepatide also works peripherally by delaying gastric emptying.[128] It was approved in 2022 for the treatment of type 2 DM.[129] In a 40-week phase 3 trial-SURPASS -2-, patients with DM (n = 1879) were randomized to receive tirzepatide at doses 5, 10 and 15 mg or semaglutide 1 mg.[130] Tirzepatide, at any dose, was superior to semaglutide in reducing HbA1c.[130] The drop in weight was 6.7% for semaglutide, while it was 8.5, 11.0 and 13.0% in each of Tirzepatide doses (p < 0.01).[130] It should be noted however that the dose of semaglutide used in this study is not the approved anti-obesity dose 2.4 mg weekly. The SURMOUNT-1 trial compared different doses of Tirzepatide to placebo in patients with obesity but without DM.[95] Tirzepatide at weekly doses 5 mg, 10 mg and 15 mg, led to a mean total body weight loss of 15, 19 and 21%, respectively, compared to only 3% in the placebo arm, at 72 weeks (p < 0.001 for all comparisons with placebo) (Fig. 2).[95] In this trial, WC at 72 weeks, decreased by 14.0 cm with Tirzepatide 5 mg, 17.7 cm with the 10 mg dose, 18.5 cm with the 15 mg dose, and by 4.0 cm in the placebo group (p < 0.001)[95] (Appendix D). A recent trial sequential analysis exploring the optimal dose of tirzepatide in patients with DM, showed a dose dependent effect on glycemic control and weight reduction, without a significant increase in the rate of adverse events with higher doses.[131] Interestingly, pooled data from SURMOUNT-1 and SURPASS clinical trials programs showed a significant relative risk reduction in major adverse CV events and CV death, by 48 and 49% respectively, with Tirzepatide, compared to control.[132]

Tirzepatide is currently being investigated in several phase 3 trials (n = 210–900 participants) in patients with overweight/obesity.[133–138] It may be associated with less gastro-intestinal side effects compared to GLP-1 agonists. The FDA has recently granted tirzepatide a *Fast Track designation* to investigate its effect as a treatment for individuals with obesity or overweight with metabolic co-morbidities.[139]

Suggested algorithm
All obesity treatment guidelines recommend pharmacotherapy, in addition to lifestyle modification and behavioral therapy, when BMI is ≥30 kg/m^2, or ≥27 kg/m^2 in the presence of comorbidities related to excessive weight.[10,140–149] Lifestyle modifications are the first line treatment for all. Given that the short[150,151] and long[152] term efficacy of different diets are the same, the prescribed diet should be a one with a proved efficacy, taking into consideration safety data, patient preference and health status.[153] In addition, reviewing the patient's medications is crucial, to identify the ones that might be contributing to weight gain, and potentially withhold them, after communication with the primary physician.[10] In fact, data from the National Health and Nutrition Examination Survey (2017–2018) showed that 20% of US adults are on weight inducing medications.[154]

In older patients and those with co-morbidities and polypharmacy, the choice of AOM needs to account for the availability of safety and efficacy data in this specific population, and the potential interaction with other drugs (Fig. 3). For instance, in patients with tachycardia or hypertension, phentermine/topiramate and NB should not be considered. As per the FDA leaflets, uncontrolled hypertension is a contra-indication for the use of Phentermine and NB; arrhythmias are also a contra-indication for the use of phentermine and tachycardia is listed under adverse events for NB.[68,74] For liraglutide and semaglutide, increased heart rate
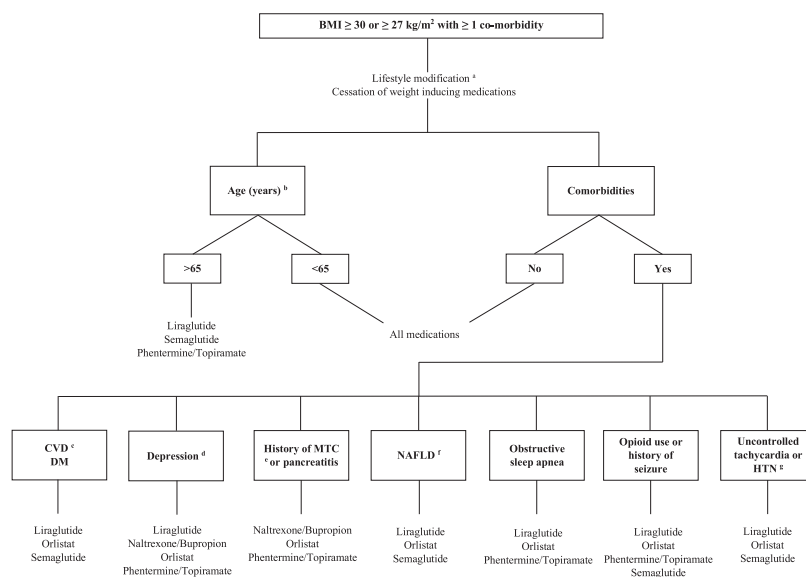
Fig. 3: Suggested algorithm for the selection of anti-obesity medications, taking into consideration the availability of drug safety, contra-indications, and preliminary efficacy data for a specific patient profile.[a] CVD, cardiovascular disease; DM, diabetes mellitus; HTN, hypertension; MTC, medullary thyroid cancer; NAFLD, non-alcoholic fatty liver disease. [a]With the exception of data in patients with NAFLD, Orlistat was not investigated in patients with CVD, mental diseases and sleep apnea. However, given its safety profile, Orlistat can be considered in these conditions. None of the drugs is approved for use during pregnancy. Additional contra-indications for specific medications are described in Table 1. [b]Age >65 years: Liraglutide and Phentermine/Topiramate trials included 7% of participants ≥65 years. For Semaglutide, SUSTAIN trials in patients with diabetes mellitus showed that efficacy is preserved regardless of age.[155] The COR program included only 2% of participants from the elderly population,[156] and the XENDOS included none. [c]CVD includes patient with previous history of CVD and those at high risk for CVD. The suggestion for the use of GLP-1 receptors agonist is based on the availability of indirect evidence on cardiovascular risk reduction in patients with diabetes mellitus, LEADER trial for liraglutide[157] and SUSTAIN trial for semaglutide.[158] There was no signal of increased CVD in patient with obesity on liraglutide. The suggestion for the use of Liraglutide and Semaglutide in patients with obesity and DM is based on the fact that GLP-1 receptor agonists are anti-diabetic medications. [d]Depression: For Phentermine/topiramate, NB and liraglutide, the FDA includes "Suicidal Behavior and Ideation" under "Warning and Precautions" and recommend to monitor patients for depression and suicidal thoughts, and to stop the drug in case of symptoms development.[68,74,81] [e]MTC: personal or family history of MTC, a contra-indication for Liraglutide and Semaglutide. [f]Small trials on Orlistat, Liraglutide and Semaglutide showed improvement in steatosis, but none of them showed improvement in liver fibrosis; only post-hoc data are available on NB. [g]The FDA leaflet of Phentermine states the following under contra-indications "History of cardiovascular disease (e.g., coronary artery disease, stroke, arrhythmias, congestive heart failure, uncontrolled hypertension).[159] The FDA leaflet of NB states that uncontrolled hypertension is a contra-indication.[74] For liraglutide and semaglutide, increased heart rate is considered under "Warning and Precautions" in the FDA leaflets, with a suggestion to monitor as the clinical implication of the increase in heart rate by few beats per minutes is not known.[16,81]

is considered under "Warning and Precautions", with a suggestion to monitor as the clinical implication of the increase in heart rate by few beats per minutes is not known.[16,81] No adverse effects related to heart rate were reported with Orlistat.[63] For other cardio-metabolic co-morbidities, such as OSA, DM and CVD, the suggestion for AOM take into consideration the safety and/or direct or indirect evidence on efficacy with specific drugs. Phentermine/topiramate, NB and liraglutide were investigated in patients with depression. The data on the safety of phentermine/topiramate in participants with a history of depression or on anti-depressive medications was derived from the main trials that did not reveal any signal for increased risk of adverse events.[64–66] In a post-hoc analysis from the LIGHT trial, in the sub-group of participants who were on

anti-depressants, the adverse events related to mental illness/depression were similar in NB and placebo arms.[120] A pooled analysis of Liraglutide trials, on participants with psychiatric diseases (depression and others) showed a signal for increased suicidal ideation, but no increase in the incidence of mental diseases. For phentermine/topiramate, NB and liraglutide, the FDA includes "Suicidal Behavior and Ideation" under "Warning and Precautions" and recommends to monitor patients for depression and suicidal thoughts, and to stop the drug in case of symptoms development.[68,74,81] Data on orlistat and semaglutide in patients with mental diseases is still lacking. The safety and efficacy of AOM in patients with schizophrenia is scarce. Small trials on NB and Phentermine/Topiramate have shown some safety and efficacy on total

body weight loss. Lisdexamphetamine is FDA approved for moderate and severe binge eating disorder.[160] The AOM suggestions for patients with history of medullary thyroid cancer, pancreatitis, seizures and opioid users take into consideration AOM contra-indications, as described in Table 1.

After starting AOM, responders are those who lose at least 5% of their baseline weight after 3 months of therapy and should continue their treatment.[10] Conversely, those who don't achieve this target are considered as non-responders and should be switched to another drug.[10]

Medications in the horizon

Several drugs in pipeline are currently being investigated as potential AOM. Except for sodium glucose cotransporter-2 (SGLT2) inhibitors, vitamin E and gladribin analogues, these drugs act centrally to reduce appetite and increase satiety (Fig. 4, Table 3).

Medications in phase 3 trials

Methylphenidate. Methylphenidate is a stimulant approved for the treatment of attention deficit hyperactivity disorders (ADHD).[161] It is a dopamine reuptake inhibitor that is suggested to reduce energy intake.[162] A prospective study on 78 adults with ADHD and severe obesity (mean BMI 42 kg/m^2) who received psychostimulants, including amphetamine, methylphenidate or dextroamphetamine, showed a total body weight loss of 12% in treated participants over a mean time of 466 days of observation.[163] A cross-over placebo-controlled trial of 14 adults (mean BMI 25.0 (4.0) kg/m^2) with ADHD, compared methylphenidate to placebo, and showed a significant reduction in fat and energy intake 1 h after the ingestion of a buffet styled lunch.[164] In a small trial, 9 adult men with obesity and without ADHD, were randomized to receive placebo, moderate (0.5 mg/kg) or high (1 mg/kg) dose methylphenidate. There was a significant reduction in energy intake by 23% in the intervention arms, compared to placebo (p < 0.02) as measured by pizza consumption in an acute laboratory setting 1 h after ingestion of the medication.[162] The most common side effects associated with the use of methylphenidate are headache, insomnia, upper abdominal pain, tachycardia and anorexia.[161]

A currently ongoing 2-month phase 3 trial compares the effect of methylphenidate at a dose of 0.50 mg/kg BID (n = 20) to placebo (n = 20) in adolescents and adults
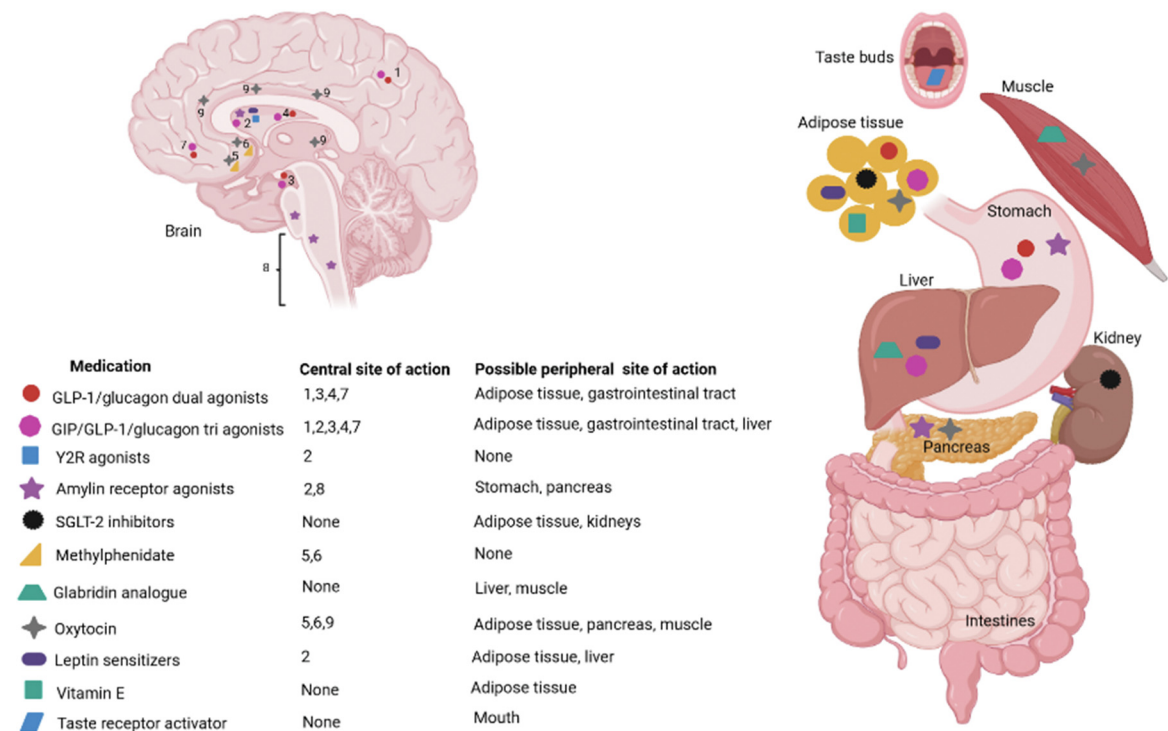

Medication	Central site of action	Possible peripheral site of action
GLP-1/glucagon dual agonists	1,3,4,7	Adipose tissue, gastrointestinal tract
GIP/GLP-1/glucagon tri agonists	1,2,3,4,7	Adipose tissue, gastrointestinal tract, liver
Y2R agonists	2	None
Amylin receptor agonists	2,8	Stomach, pancreas
SGLT-2 inhibitors	None	Adipose tissue, kidneys
Methylphenidate	5,6	None
Glabridin analogue	None	Liver, muscle
Oxytocin	5,6,9	Adipose tissue, pancreas, muscle
Leptin sensitizers	2	Adipose tissue, liver
Vitamin E	None	Adipose tissue
Taste receptor activator	None	Mouth

Fig. 4: **Site of action of drugs under development for treatment of obesity.** (1) parietal cortex, (2) hypothalamus, (3) insula, (4) putamen, (5) nucleus accumbens, (6) striatum, (7) orbitofrontal cortex, (8) hindbrain, (9) mesolimbic area. GLP-1/glucagon dual agonists, GIP/GLP-1 dual agonists, Y2R, amylin receptor agonists, methylphenidate, oxytocin, and leptin sensitizers act centrally to reduce food intake. Few drugs act solely peripherally: SGLT-2 inhibitors on the kidney; Gladribin on liver and muscle; Vitamin E on adipose tissue. GIP, Gastric inhibitory polypeptide; GLP-1, Glucagon receptor agonist; SGLT2, Sodium-glucose Cotransporter-2 (SGLT2) Inhibitors; Y2R, Y2-receptor. Tesofensine is not included in the figure as we did not identify any related ongoing study. This figure was created using BioRender (https://biorender.com/).

Drug	Site of action	Development stage	Dose	Indication	Sample size	Expected completion	Registration number
GLP1/glucagon dual agonists	Parietal cortex, insula, putamen, orbitofrontal cortex, gastrointestinal tract, adipose tissue, liver						
BI 456906		Phase II	Very low, low, medium and high SQ dose groups once weekly	Obesity	387	October-22	NCT04667377
IBI362		Phase II	Low, moderate, and high SQ dose groups once weekly	Obesity	320	September-23	NCT04904913
		Phase II	5 different SQ doses	Obesity	66	January-24	NCT04440345
GIP/GLP1 dual agonists	Arcuate nucleus and other hypothalamic regions, parietal cortex, insula, putamen, orbitofrontal cortex, adipose tissue, gastrointestinal tract						
Tirzepatide		Phase III	10 mg and 15 mg SQ once weekly	Obesity and DM	900	April-23	NCT04657003
		Phase III	Regimen A and B SQ once weekly	Obesity	261	June-23	NCT04844918
		Phase III	N/A	Obesity	750	May-23	NCT04660643
		Phase III	N/A	Obesity and weight maintenance after intensive lifestyle	800	May-23	NCT04657016
CT-868		Phase II	Low and maximally tolerated SQ daily doses	Obesity and DM	96	February-23	NCT05110846
GMA106		Phase I	Single SQ injection	Obesity	48	April-23	NCT05054530
CT-388		Phase I	SQ injection	Obesity and DM	96	October-23	NCT04838405
GIP/GLP1/glucagon tri-agonists	Parietal cortex, insula, putamen, orbitofrontal cortex, arcuate nucleus and other hypothalamic regions, gastrointestinal tract, adipose tissue, liver						
LY3437943		Phase II	4 different SQ doses	Obesity	388	November-22	NCT04881760
GLP1R agonists	Parietal cortex, insula, putamen, orbitofrontal cortex, gastrointestinal tract						
Liraglutide vs. Exenatide		Phase III	Liraglutide: 0.6 mg up to 1.8 mg SQ injection daily; Exenatide: 10 mcg daily for 4 weeks then twice a day for 8 weeks, and 2 mg SQ injection once weekly	Obesity	150	September-22	NCT03671733
XW003 Vs Liraglutide		Phase II	XW003: up-titrated to 1.2, 1.8, or 2.4 mg SQ once weekly starting with 0.2 mg; Liraglutide: uptitrated over 4 weeks to 3 mg SQ once daily	Obesity	200	October-22	NCT05111912
PF-06882961		Phase II	5 doses (40, 80, 120, 160 or 200 mg oral twice daily)	Obesity	497	October-23	NCT04707313
Oral LY3502970		Phase II	4 different oral doses	Overweight and obesity	272	November-22	NCT05051579
SHR20004 Noiiglutide		Phase II	Low, medium and high SQ doses	Obesity	254	May-22	NCT04799327
Y2R agonist	Hypothalamus						
NNC0165-1875 with semaglutide		Phase II	Semaglutide 2.4 mg SQ and NNC0165-1875 1 or 2 mg SQ	Obesity	119	December-22	NCT04969939
Amylin receptor agonist	Area postrema of the caudal hindbrain, hypothalamus, gastrointestinal tract, pancreas						
NNC0174-0833		Phase I	0.3 mg, 0.9 mg or 1.8 mg SQ	Obesity	24	September-22	NCT05254158
Cagrilintide with Semaglutide		Phase III	Cagrilintide: 2.4 mg SQ weekly Semaglutide: 2.4 mg SQ weekly	Obesity and DM	1200	January-25	NCT05394519

(Table 3 continues on next page)

Drug	Site of action	Development stage	Dose	Indication	Sample size	Expected completion	Registration number
(Continued from previous page)							
SGLT-2 inhibitors	Kidney, adipose tissue						
Dapagliflozin with metformin vs. metformin		Phase III	Dapagliflozin: 10 mg orally daily Metformin: 850 mg orally twice daily	Obesity and DM or prediabetes	90	July-21	NCT03968224
Dopamine reuptake inhibitor							
Methylphenidate	Nucleus accumbens, striatum	Phase III	One tablet twice daily	Obesity	40	December-18	NCT02754258
Acetylcholine blockers							
Botulinum toxin type A	gastrointestinal tract	Phase III	20 injections of 0.5 ml each	Obesity	18	July-22	NCT04274608
		Phase II	Injection in muscles of stomach wall	Morbid obesity	20	December-22	NCT02035397
Glabridin analogue	Muscles, liver						
HSG4112		Phase II	200, 400 and 600 mg orally daily	Obesity	81	December-22	NCT05197556
Oxcytocin	Muscles, liver, adipocytes, pancreas, paraventricular nucleus, nucleus accumbens, striatum, mesolimbic area						
		Phase II	24 IU nasal spray, 4 times per day	Obesity	61	July-22	NCT03043053
Vitamin E	Adipose tissue						
Tocotrienols		Phase II	One 430 mg tocotrienol softgel daily	Obesity in postmenopausal women	60	December-23	NCT03705845
Taste receptors activator	Taste buds						
ARD-101		Phase II	200 mg orally twice daily	Obesity	20	November-22	NCT05121441
Leptin sensitizers	Adipose tissue, liver, hypothalamus						
ERX1000		Phase I	4 mg orally	Obesity	48	June-23	NCT04890873
Others							
PPAR gamma modular: AMG 133		Phase I	N/A	Obesity	110	November-22	NCT04478708
MBL949		Phase II	5 different SQ doses	Obesity	127	June-23	NCT05199090
NO-13065		Phase I	N/A	Obesity	84	September-22	NCT04838639
NNC0247-0829		Phase I	Single or multiple SQ doses	Obesity	103	June-22	NCT04010786
LY3841136		Phase I	Single or multiple SQ ascending doses	Obesity	160	September-23	NCT05295940
BMS-986172		Phase I	Specified oral dose on specified days	Obesity	40	May-22	NCT04926051

Abbreviations: DM, diabetes mellitus; IU, international unit; SQ, subcutaneous. [a]Indication included obesity with or without DM.

Table 3: Anti-obesity medications[a] in the horizon identified from Clinicaltrials.gov.

aged 16–40 years with obesity, on energy intake as a primary outcome, energy expenditure and body weight as secondary outcomes.[165] The study completion date was December 2018, but no results are available online yet.[165]

Tesofensine. Tesofensine is a noradrenaline, serotonin and dopamine reuptake inhibitor that acts as an appetite suppressant and may increase dopaminergic activity in the forebrain.[166,167] A phase 2 RCT in 203 patients with obesity (BMI 30–40 kg/m^2) evaluated the effect of an increasing dose of Tesfensine 0.25 mg, 0.5 mg, and 1 mg to placebo, on top of caloric restriction.[168] At 24 weeks, there was a dose dependent drop in weight of 4.5%, 9.2% and 10.6% in Tesofensine arms, and only 2.0% in the placebo arm.[168] A longer term RCT including 2 phases, each extending over 24 weeks, investigated the effect of increasing doses of Tesofensine on appetite and showed a dose dependent response.[169] The main concern with Tesofensine was the risk of increased sympathetic activity with elevations in blood pressure and heart rate. The Viking Trial extended over 24 weeks and enrolled 372 participants, randomized to Tesofensine 0.25 mg or 0.5 mg or placebo.[170] There was on average 10% total body weight loss at 24 weeks in the intervention arm, and no significant adverse events.[170] However, the

peer-reviewed publication of the trial has not been available online yet.

Exenatide. Exenatide, a GLP1-RA, was explored in the treatment of patients with obesity, without DM. A 24-week RCT in patients with a range of mean baseline weight 107–109 kg, compared Exenatide (n = 73) with placebo (n = 79), on top of lifestyle modification as a co-intervention for both arms.[171] A significant difference in total body weight loss of 3.3 (0.5) % (p < 0.001), favoring Exenatide.[171] Conversely, a more recent study did not confirm the same findings.[172] One ongoing study with 3 arms explores the effects of exenatide 10 mcg twice daily, exenatide 2 mg once weekly and liraglutide 1.8 mg once daily, on weight change at 3 months, as a primary outcome.[173]

The combination of weekly exenatide (2 mg) with dapagliflozin 10 mg was explored in a small (n = 50) placebo-controlled trial of patients with obesity (mean BMI 35 kg/m^2), 73% of whom had prediabetes.[174] At 24 weeks, there was a difference in total body weight loss of 4 kg, favoring the combination arm.[174] A 16-week RCT is currently ongoing, investigating the effect of dapagliflozin and exenatide, administered as single agents or combined.[175] The primary outcome is food-related neural activity in the reward system using fMRI and weight is being assessed as a secondary outcome.[175]

Dapagliflozin + Metformin. One ongoing RCT compares dapagliflozin combined with metformin to metformin alone in patients with obesity (BMI > 40 kg/m^2) and newly diagnosed DM or prediabetes and controlled on Metformin. The primary outcome is weight change at 12 months.[176]

Cagrilintide. Cagrilintide is an amylin analogue that increases satiety signals centrally and decreases gastric emptying peripherally; it is currently being investigated for total body weight loss in a phase 3 trial in combination with semaglutide compared to placebo in patients with obesity and DM (n = 1200).[177]

Medications with completed phase 2 trials
Several potential drugs for total body weight loss have completed phase 2 trials but have not been yet investigated in phase 3 trials (Appendix E), and these include: GSK1521498,[178] LAPS-Exendin,[179] LIK 066,[180] MEDI0382,[181] nasal PYY3-36,[182] and RZL 012.[183]

Medications in phase 1 and 2 trials
Several drugs in the horizon, investigated in phase 1 or phase 2 trials, target different mechanisms.

New GLP1-RA reached phase 2 trials for patients with obesity: XW003,[184] in comparison to liraglutide; PF-06882961,[185] LY3502970,[186] and SHR20004 Noiiglutide,[187] in comparison to placebo.

In addition to GLP-1 RA and GIP agonists, a glucagon agonist is an attractive option for weight management as it stimulates thermogenesis by acting on adipose tissue, in addition to its lipolytic effects in the liver.[188] Several dual (GLP1/glucagon; GIP/GLP1) agonists BI 456906,[189] IBI362.[190,191] CT-868,[192] GMA106,[193] and CT-388,[194] and one tri-agonist (GIP/GLP1/glucagon LY3437943)[195] are being explored.

Y2R inhibits food intake by acting centrally on the hypothalamus,[196] and one Y2R agonist NNC0165-1875 is being explored for weight management in comparison to semaglutide.[197]

Amylin, co-secreted with insulin from pancreatic β cells in response to food intake, acts as a satiety signal on homeostatic and hedonic brain regions, slows gastric emptying, and suppresses post-prandial glucagon surge.[198] NNC0174-0833 is an amylin receptor agonist being studied in a phase 1 trial in patients with obesity.[199]

Glabridin analogue HSG4112 regulates metabolic gene expression by increasing energy expenditure in the liver and muscles[200] and is being studied in a phase 2 trial.[201]

Oxytocin has hypophagic effects, by acting centrally, and leads to a reduction in the intake of appetizing food.[202] It is being investigated for weight management in a phase 2 trial.[203]

Tocotrienols can increase adiponectin expression and reduce adipose tissue inflammation, allowing improvement in insulin resistance.[204] They are under investigation for postmenopausal women with obesity.[205] Taste buds' activators alter nutrient-sensing mechanisms and therefore activate anorexigenic pathways.[206] ARD-101, a taste activator receptor is being evaluated in an ongoing phase 2 trial for obesity.[207]

Additional molecules being tested for their potential use in medical weight management include: leptin sensitizer,[208,209] PPAR gamma modulator AMG,[210] MBL949,[211] NO-13065,[212] NNC0247-0829,[213] LY3841136[214] and BMS-986172.[215]

Medications for weight loss in specific conditions
Several ongoing trials investigate the role of FDA approved AOM in patients with obesity and specific conditions (Table 4). Phase 3 RCTs on Semaglutide, in its subcutaneous formulation, evaluate its effect on weight in patients with obesity and prediabetes (n = 201[216]), obesity and heart failure (phase 3, n = 516[217]), obesity and knee osteoarthritis (n = 375[218]), obesity and cardiovascular disease (n = 17,500[219]), obesity and albuminuria (n = 98[220]) obesity, diabetes and kidney transplant candidacy (n = 50[221]).

Semaglutide, in its oral formulation is being investigated in phase 3 trials for total body weight loss purposes in East Asian patients with obesity (n = 198[222]), and patients with obesity (n = 660[223]).

Drug	Development stage	Dose	Indication	Sample size	Expected completion	Registration number
Tirzepatide	Phase III	Doses 1 and 2 SQ once weekly	Obesity in Chinese	210	December-22	NCT05024032
	Phase III	N/A	Obesity and heart failure with preserved ejection fraction	700	July-24	NCT04847557
Semaglutide	Phase III	2.4 mg SQ once weekly	Obesity and prediabetes	201	July-23	NCT05040971
	Phase III	0.25 mg up to 2.4 mg SQ once weekly	Obesity and heart failure	516	April-23	NCT04788511
	Phase III	2.4 mg SQ once weekly	Obesity and knee osteoarthritis	407	September-23	NCT05064735
	Phase III	50 mg orally once daily	East Asian obese	198	August-23	NCT05132088
	Phase III	3 mg up to 50 mg orally once daily	Obesity (oral tablet)	660	May-23	NCT05035095
	Phase III	0.24 mg up to 2.4 mg SQ once weekly	Obesity and cardiovascular disease	17,500	September-23	NCT03574597
	Phase III	escalated up to 2.4 mg SQ once weekly	Obesity (±DM)	375	August-22	NCT04251156
	Phase III	0.24 mg up to 2.4 mg SQ once weekly	Obesity and reduction in microalbuminuria	98	May-23	NCT04889183
	Phase III	0.25 mg up to 1 mg SQ once weekly	Obesity, DM and kidney transplant candidacy	15	January-23	NCT04741074[a]
Liraglutide	Phase III	0.6 mg up to 3 mg SQ daily	Obesity and comorbidities	300	June-22	NCT04487743
	Phase III	0.6 mg up to 3 mg SQ daily	Obesity and comorbidities	414	December-22	NCT04605861
	Phase II	0.6 mg/day SQ on week 1 then 1.2 mg/day SQ on week 2 then to 1.8 mg/day SQ	Obesity and DM on hemodialysis	30	July-23	NCT04529278
Contrave	Phase III	Naltrexone sustained-release (32 mg/day) with bupropion SR (360 mg/day) orally daily	Obesity and binge eating	136	December-22	NCT03045341
Setmelanotide	Phase III	SQ injection once daily	Obesity associated with defects in leptin-melanocortin pathway	300	December-23	NCT03651765
	Phase III	0.5 mg up to 2 mg SQ daily	Bardet–Biedl Syndrome, POMC Deficiency, PCSK1 Deficiency, LEPR Deficiency	12	September-23	NCT04966741
	Phase III	2 mg, 3 mg, 20 mg and 30 mg SQ daily	Bardet–Biedl Syndrome, POMC Deficiency	30	August-23	NCT05194124
	Phase III	SQ injection once daily	Rare genetic disorders	213	March-22	NCT03013543
	Phase II	1, 2, 3 mg SQ daily for patients 6 to <16 years of age, and 2–3 mg SQ daily for patients ≥16 years of age	Hypothalamic Obesity	18	June-22	NCT04725240
Cannabidiol RAD011 (Oral Solution)	Phase III	Low, medium and high oral doses	Prader–Willi Syndrome	7	October-22	NCT05098509[a]
Somatropin	Phase III	0.245 or 0.084 mg/kg/week SQ	Prader–Willi Syndrome	32	May-24	NCT04697381
Oxytocin	Phase II	Intranasal 3 times per day, dosage based on weight: 16 IU–24 IU; dose escalation, if appropriate at 2 weeks	Hypothalamic Obesity	18	May-22	NCT02849743
	Phase II	Intranasal 16 IU daily	Prader Willi	50	August-23	NCT03197662
Taste receptors activator ARD-101	Phase II	200 mg orally twice daily	Prader Willi	12	May-23	NCT05153434

[a]Trial terminated by the sponsor for reasons other than safety.

Abbreviations: BID, twice daily; IU, International Unit; LEPR, Leptin receptor; PCSK, Proprotein convertase subtilisin/kexin type 9 serine protease; POMC, Proopiomelanocortin; SQ, subcutaneous.

Table 4: **Anti-obesity medications for special conditions identified from clinicaltrials.gov.**

Two phase 3 ongoing trials on liraglutide on patients with obesity and comorbidities (n = 300[224] and n = 414[225]) and one phase 2 trial in patients with obesity and type 2 diabetes on hemodialysis (n = 30[226]) investigate total body weight loss at week 26, as a primary outcome.

One phase 3 trial on NB on patients with obesity and binge eating (n = 136[227]), assesses binge eating frequency and BMI as co-primary outcomes.

Setmelanotide is being studied in ongoing phase 3 trials of patients with rare genetic disorders,[228–231] and an ongoing phase 2 trial in 15 patients with hypothalamic obesity.[232]

Discussion

While early total body weight loss of at least 5% labels patients as responders to AOM, a higher response should be targeted; 5–10% total body weight loss is associated with a reduction in the risk of various metabolic, skeletal, and anatomical complications of obesity,[11] and a total body weight loss >15% may be needed to result in improvement of CV outcomes, as observed in studies assessing effects of weight loss in response to lifestyle modifications.[233] The effectiveness of the currently available weight loss monotherapies is still modest, with the exception of GLP-1 RA, and in particular semaglutide, which in combination with behavioral modification therapy, may achieve more than 15% weight loss.[82] The combination of more than one molecule may be needed to achieve a larger total body weight loss; for instance, tirzepatide, a GIP/GLP-1 dual agonist, led to ~23% weight loss with the highest dose.[95] New drugs seem thus have a much higher potency and are expected to change

the medical weight management landscape in the not-so-distant future. Trials on AOM showed improvement in various metabolic parameters, some of which were of a small magnitude with a limited clinical implication. Furthermore, whether this effect has been driven solely by total body weight loss, rather than a direct effect of the drug per se, and whether it differs between metabolically healthy and metabolically unhealthy individuals with obesity, has been poorly investigated.[234] While some available data showed improvement in liver steatosis with GLP1-RA, there is no evidence of reduction in liver fibrosis with any AOM, a parameter that requires longer term studies to show benefit. To-date, data on the effect of AOM on CV outcomes are still lacking. However, indirect evidence from trials in patients with DM is promising. The LEADER trial compared liraglutide (1.8 mg/d) to placebo in patients with DM on a composite CV outcome (cardiovascular death, non-fatal myocardial infarct and non-fatal stroke).[157,235] After a median follow up of 3.8 years, there was a 13% relative risk reduction in the composite CV outcomes and 22% relative risk reduction in cardiovascular death, in liraglutide group, compared to placebo.[157,235] In a similar study design in patients with DM, semaglutide showed a 26% relative risk reduction the composite CV outcome, compared to placebo, while there was no difference in CV death.[158] Interestingly, new findings suggest a potential neuroprotective effect of GLP-1 agonist, with a reduction of the risk of dementia and age-related cognitive decline, associated with diabetes and obesity[236,237]; such a promising effect needs to be demonstrated in large prospective studies, extending over several years to decades.

The evidence to-date on the efficacy of AOM is derived from Western studies, conducted in middle-aged women. Data in older individuals and those from non-Western countries, in particular Middle Eastern and African populations, are still lacking. Furthermore, the long-term safety and efficacy of various AOM is scarce.[238]

One of the main challenges in weight management is the inability to predict patient's response to medications, with a wide variability in individuals weight change in response to a given medication.[239] With the exception of semaglutide trials where the majority of participants had a significant weight loss, in the AOM trials, 20–50% of participants lost <5% of their total weight loss, and the reasons for non-response has been poorly investigated. Precision medicine may be the future of weight management, implying a tailored approach depending on patient profile.[240,241] Such approach requires the availability of large cohorts to collect data on genetics, epigenetics, and genomics, and therefore derive a therapeutic algorithm.[241] The OBEsity Diverse Interventions Sharing (OBEDIS) – focusing on dietary and other interventions - aims at streamlining and harmonizing variables and endpoints of AOM clinical trials, to allow data pooling and derivation of prediction models.[242]

Conclusion

In summary, accumulating evidence indicates that the next few years will be a period during which novel pharmacotherapies for obesity will revolutionize the way we treat obesity, and through improvements in body weight, the way we treat cardio-renal and metabolic complications of obesity including, diabetes, cardiometabolic and liver comorbidities of obesity.

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