New pharmacological approaches for obesity management

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Abstract

Obesity, which results from an imbalance between calorie intake and expenditure, now affects over 500 million individuals worldwide. Lifestyle and behavioural interventions aimed at reducing calorie intake and/or increasing energy expenditure have limited long-term effectiveness due to complex and persistent hormonal, metabolic and neurochemical adaptations that defend against weight loss and promote weight regain. Surgical treatments for obesity, although highly effective, are unavailable or unsuitable for many individuals with excess adiposity. Accordingly, few effective treatment options are available to most obese individuals. In the past, the use of antiobesity drugs, seemingly the logical choice to fill this therapeutic gap, has been limited because of a lack of efficacy, poor long-term adherence rates and serious adverse effects, such as valvulopathy. Recently, the FDA has approved two new medications: lorcaserin and phentermine–topiramate controlled release, and is currently reviewing the resubmission of naltrexone sustained release–bupropion sustained release. This Review presents the available data on the efficacy and safety of these three medications, and discusses future perspectives and challenges related to pharmacological weight management.

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Competing interests (print version)

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R. S. Padwal declares that he has acted as a consultant for VIVUS Pharmaceutical. A. M. Sharma declares that he has acted as a consultant for Arena Pharmaceutical, Orexigen Therapeutics and VIVUS Pharmaceutical in relation to their antiobesity drug programs. C. F. Rueda-Clausen declares no competing interests.

Key points

- Lifestyle interventions for obesity rarely result in sustained weight loss and are generally characterized by high rates of recidivism or weight regain
- The primary aim of pharmacological treatments for obesity is to suppress the biological drivers of weight gain and dampen the biological counter-response to weight loss

- Emerging medications show promise for obtaining clinically relevant weight loss as well as improvements in comorbidities
- Further studies are needed to assess the long-term benefits and cost-effectiveness of these new agents

Introduction

Obesity, which currently affects over 500 million people worldwide,[1] is a complex multifactorial disorder characterized by the accumulation of excess body fat. Once established, obesity often develops into a chronic, progressive, debilitating and treatment-refractory condition that adversely affects physical function, mental health and quality of life.[2] Obesity also has important economic effects for the individuals affected, their employers, and health-care systems.[3]

Although the primary driver of weight gain is an imbalance between calorie intake and expenditure, lifestyle and behavioural interventions aimed at correcting this imbalance have limited long-term effectiveness.[4] Lifestyle interventions for obesity are generally characterized by high rates of recidivism or weight regain, which are often interpreted as a lack of will power on the part of the patient. However, emerging evidence suggests that complex hormonal, metabolic and neurochemical changes are associated with weight gain, and result in powerful biological adaptations that both defend against subsequent weight loss and promote weight regain.[5] These counter-regulatory adaptations include persistent changes in neurohormonal activation of appetite[6] and marked reductions in resting and activity-related thermogenesis.[7, 8] Taken together, this orchestrated biological response to

weight loss explains why the vast majority of individuals who lose weight as a result of lifestyle interventions alone fail to keep the excess weight off.

The primary aim of pharmacological treatment for obesity is to suppress the biological drivers of weight gain and/or dampen the counter-regulatory response to weight loss, and thereby to enable patients to achieve and sustain clinically meaningful reductions in body weight. However, given the complexity and redundancy of the neurohormonal systems that control hunger, appetite, satiety and other aspects of energy intake and metabolism, successful pharmacological approaches to obesity have proven elusive. Despite considerable investments in pharmaceutical research, few effective obesity medications have been approved for marketing. In many cases, approved antiobesity drugs subsequently had to be withdrawn because of adverse risk profiles.[9]

In 2012, after a hiatus of nearly 13 years, the FDA approved two new antiobesity drugs, and is currently considering a third for approval. In this Review, we outline the pharmacology, efficacy and safety profile of these new agents, and discuss their use in the management of obesity.

Lorcaserin

Lorcaserin is a selective agonist of 5-hydroxytryptamine (serotonin) receptor 2C (5-HT2C, which is predominantly expressed in hypothalamic pro-opiomelanocortin (POMC)-producing neurons in the central nervous system.[10] Lorcaserin is rapidly absorbed, reaching its peak circulating concentration 2 h after ingestion, and freely enters the central nervous system.[11] Lorcaserin has a mean half-life of 10–11 h and is predominantly excreted in the urine.[11] By activating 5-HT2C receptors, lorcaserin stimulates the release of

melanotropin-α (also known as α-MSH), which decreases appetite through stimulation of melanocortin receptor 4 (MC4-R).[12] In mouse models of diabetes, lorcaserin not only decreases appetite but also seems to directly improve glucose tolerance and hepatic insulin sensitivity.[13]

Lorcaserin has low affinity for other serotonin receptor subtypes (such as 5-HT2B), targeting of which has previously been associated with the development of valvular heart disease in patients receiving older antiobesity drugs.[14] FDA approval of lorcaserin was based on the results of two phase II studies and three phase III randomized controlled trials (Table 1). The BLOOM (Behavioral Modification and Lorcaserin for Overweight and Obesity Management) study[15] included 3,182 participants without diabetes who had a BMI of 30–45 kg/m^2, or a BMI ≥27 kg/m^2 and a weight-related comorbidity (hypertension, cardiovascular disease, dyslipidaemia, impaired glucose metabolism, or sleep apnoea). Participants were randomly allocated to receive either lorcaserin 20 mg daily (*n* = 1,595) or placebo (*n* = 1,587) for 52 weeks. Study completion rates after 1 year were 55% for the lorcaserin group and 45% for the placebo group. A modified intention-to-treat (ITT) analysis excluded the 145 patients who did not take at least one dose of the assigned treatment, and missing data were managed by last observation carried forward (LOCF) imputation (Box). The lorcaserin-treated group experienced a statistically significant placebo-adjusted weight change of –3.6%. Almost twice as many participants in the lorcaserin group as in the placebo group lost ≥5% of their initial weight (47.5% versus 20.3%, respectively). Lorcaserin treatment was also associated with statistically significant improvements in levels of fasting serum glucose, total cholesterol, triglycerides and blood pressure (Table 1). A 1-year extension of the BLOOM study included all patients who had successfully

completed the first year (lorcaserin group *n* = 856, placebo group *n* = 697). The individuals initially assigned to the lorcaserin group underwent a second round of randomization (in a 2:1 ratio) to either continue taking lorcaserin 20mg daily (*n* = 573) or placebo (*n* = 283). Patients who were randomly reassigned to the placebo group regained more weight than those in the continued-lorcaserin group (final placebo–adjusted weight change of –0.9%, versus –3.2%) and were less likely to maintain the ≥5% weight loss benchmark (50.3% versus 67.9%), respectively. However, findings from the BLOOM extension phase are potentially confounded by selection bias, because the participants who completed the initial 1 year of lorcaserin therapy might have different characteristics from the overall population initially randomized.

The BLOSSOM (Behavioral Modification and Lorcaserin Second Study for Obesity Management)[16] trial included 4,008 participants (aged 18–65 years) with a BMI of either 30–45 kg/m^2 or 27.0–29.9 kg/m^2 plus an obesity-related comorbid condition (similar criteria to those used in BLOOM) who were randomly assigned to receive lorcaserin 10 mg (*n* = 801) or 20 mg (*n* = 1,602) daily, or placebo (*n* = 1,601), for 52 weeks. The modified ITT analyses excluded 131 patients who did not take at least one dose of the assigned agent and/or complete at least one follow-up visit. Missing data were handled using LOCF imputation. Similarly to the BLOOM trial, the proportions of patients who completed the study in BLOSSOM were 52.0% and 57.2% in the high-dose and low-dose lorcaserin groups, versus 59% in the placebo group, and the average placebo-adjusted weight change was –2.9% for patients receiving 20 mg lorcaserin daily and –1.8% for patients receiving 10 mg lorcaserin daily. The proportion of patients achieving ≥5% weight loss was significantly increased in the active-treatment groups (47% for 20 mg lorcaserin and 40% for 10 mg

lorcaserin, compared to 25% in the placebo group). Moreover, the patients receiving lorcaserin showed modest, but statistically significant, improvements in waist circumference, HDL cholesterol and triglyceride levels (Table 1) as well as quality of life compared to those in the placebo group (Impact of weight on quality of Life [IWQOL]-Lite score improvements of 12.2 and 12.6 with active treatment, versus 10.4 with placebo).

The BLOOM diabetes mellitus study (BLOOM-DM)[17] included overweight and obese patients with type 2 diabetes mellitus (T2DM) who were receiving metformin and/or a sulfonylurea. Patients were randomly assigned to one of three groups, stratified by T2DM treatment: lorcaserin 20 mg daily (*n* = 256) lorcaserin 10 mg daily (*n* = 95), or placebo (*n* = 253), for 52 weeks. The proportion of patients in each group who completed the study was higher than that reported in previous studies (66%, 79% and 62%, respectively) The modified ITT analysis excluded 11 patients who did not attend at least one follow-up visit and LOCF imputation was applied for missing data. Similarly to the results of BLOOM and BLOSSOM, the placebo-adjusted weight change achieved by the active-treatment groups was –3.1% in the 20 mg lorcaserin group and –3.4% in the 10 mg lorcaserin group. Moreover, significantly more patients in the active-treatment groups than in the placebo group achieved ≥5% weight loss (37.5% in the 20 mg lorcaserin group and 44.7% in the 10 mg lorcaserin group, versus 16.1% in the placebo group). In contrast to the BLOSSOM trial, however, no dose–response relationship was evident between the lorcaserin regimen and the extent of weight loss in the BLOOM-DM study. The specific reasons for this finding could not be explored during the study, but the researchers suggested that the higher age of the patients recruited in BLOOM-DM (mean age 52.7 years, versus 43.8 years in BLOSSOM) could be a contributory factor given that aging is associated with a physiological decrease in

baseline metabolic rate, physical activity and energy requirements.[18] The placebo-adjusted effects of lorcaserin 20 mg daily on fasting serum glucose levels (–0.86 mmol/l), fasting insulin levels (–9.72 pmol/l), Homeostasis Model Assessment (HOMA) index (–0.3 U) and the proportion of patients achieving target glycated haemoglobin (HbA_{1c}) levels of ≤7% (24%) and ≤6.5% (15%) were all statistically significant and clinically relevant. Similar results were obtained in the group receiving lorcaserin 10 mg daily, despite the lack of a clear dose–response effect. The effects of lorcaserin treatment on waist circumference, blood pressure and lipid profiles in patients with T2DM was modest, albeit comparable to those reported in BLOOM and BLOSSOM (Table 1).

Rates of serious and nonserious adverse events were slightly higher in the active-treatment groups in all three trials, although no single type of adverse event predominated. Pooled data from BLOOM and BLOSSOM[19] showed that the most common adverse events were headache (17% versus 10%), dizziness (9% versus 4%), nausea (8% versus 5%) and fatigue (7% versus 3%) for lorcaserin versus placebo, respectively. No differences were observed between the groups in the occurrence of depression, anxiety or other psychiatric adverse events. Among patients with diabetes, symptomatic hypoglycaemia was reported with greater frequency by those receiving lorcaserin (21–28%) than by those in the placebo group (12%).[19]

Given the association between valvular complications and treatment with previous serotonergic antiobesity medications (specifically fenfluramine and dexfenfluramine),[14] all these lorcaserin studies included echocardiographic assessments of the study participants. The incidence of new valvulopathies did not differ between the lorcaserin-treated and placebo-treated patients (pooled relative risk 1.16, 95% CI 0.81–1.67). However, given the

low incidence of valvulopathies in the placebo groups (~2%), these studies were statistically underpowered (β >0.4) to rule out a drug-related increase of 50% in the relative risk of valvulopathy.

Findings from the initial preclinical studies of lorcaserin suggest that at high doses this molecule might have potential oncogenic effects, particularly for mammary, thyroid and brain tumours.[19] Phase III studies did not detect increases in the incidence of any neoplasms; however, no formal cancer screening was conducted in any of these studies, and their periods of observation were too short to make any definitive conclusion in this regard.

Phentermine–topiramate CR

Phentermine

The amphetamine analogue phentermine is an effective, inexpensive and generally well-tolerated appetite suppressant[20] that has been widely used as an antiobesity drug for several decades.[21] Phentermine is rapidly absorbed after oral administration, undergoes minimal (5–10%) hepatic metabolism and is mainly excreted in urine (mean half-life 19–24 h).[22] The anorexic effect of phentermine is attributed to its sympathomimetic action, which is related to catecholamine release in the hypothalamus.[23] Combined with behavioural therapy, treatment with phentermine hydrochloride (15.0–37.5 mg daily) is associated with a weight loss of 4–6 kg in the first 12 weeks.[24] Some evidence suggests that prolonged treatment with phentermine results in slightly greater weight loss (8–10 kg after 6 months).[25] However, the tolerability and effectiveness of phentermine is limited by a number of factors. The sympathomimetic mode of action of phentermine, which can cause high blood pressure, tachycardia, restlessness and insomnia, also has a theoretical potential

to cause psychological dependence (in the USA, this agent is classified as a Schedule IV controlled substance under the Controlled Substances Act), and tolerance to the drug can develop with long-term use.[23] As a result of these concerns, phentermine monotherapy is currently only recommended for short-term use, normally up to 12 weeks.

Topiramate

Topiramate is an anticonvulsant approved in the USA for the treatment of epilepsy since 1996, and (owing to its dilatory effect on the cerebral vasculature) for the prevention of migraine since 2004.[26] Like phentermine, this drug is rapidly absorbed after ingestion, excreted (mostly unchanged) in urine and has a mean half-life of 19–23 h. The precise mechanisms by which topiramate exerts its antiobesity effect are not completely understood, but its efficacy seems to be related to a number of pathways: reduction in compulsive or addictive food craving via antagonism of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors and kainate receptors; decreased lipogenesis and modification of food taste via inhibition of carbonic anhydrase isoenzymes; and increased energy expenditure via activation of γ-aminobutyric acid receptors.[26]

Topiramate monotherapy at doses of 100–400 mg daily for 24–54 weeks results in weight loss of 6–8 kg and improvements in metabolic profiles.[27] However, the use of topiramate monotherapy for weight management has been limited by several common dose-dependent adverse effects, including paresthesia, fatigue, dysgeusia, difficulty with concentration and mood changes.[28]

Fixed-dose combination therapy

Phentermine–topiramate controlled-release (CR) is a fixed-dose combination of fast-acting phentermine (recommended 7.5 and up to 15 mg/day) and CR topiramate (recommended 46 and up to 92 mg/day, which was approved by the FDA in 2012 for the treatment of obesity. Approval of phentermine–topiramate CR was based on data from four phase II studies that used commercially available tablets of phentermine and topiramate (separately ingested), and three phase III trials that used fixed-dose combinations of these two agents, administered as a single tablet (Table 2). EQUATE[29] was a small RCT that enrolled 756 patients with obesity(BMI 30–45 kg/m^2), but without T2DM. Participants were randomly assigned to one of seven treatment arms (placebo, phentermine 7.5 mg, phentermine 15 mg, topiramate 46 mg, topiramate 92 mg, or the combinations phentermine 7.5 mg–topiramate 46 mg, or phentermine 15 mg–topiramate 92 mg), in a factorial design, for 24 weeks. Completion rates were 63–69% and similar across all study arms. The intention-to-treat analyses showed that the groups receiving both phentermine and topiramate (both doses 7.5/46mg and 15/92mg) exhibited a significantly greater weight change from baseline (–8.2% and –9.0%) than either the group receiving placebo (–1.5%) or the groups receiving monotherapy with phentermine (–5.2% with 7.5 mg/day and –5.8% with 15 mg/day), or topiramate (–4.9% with 46 mg/day and –6.1% with 92 mg/day). Similarly, the proportion of patients who achieved ≥5% weight loss was significantly higher in the combination therapy groups (62% and 66%) than in the placebo group (15%) or the groups receiving the individual drugs (phentermine 43% and 46%; topiramate 39% and 49%, respectively).

The EQUIP trial[30] randomly assigned obese patients (BMI >35 kg/m^2) without T2DM to receive placebo (*n* = 514), low-dose phentermine–topiramate CR (3.75 mg–23 mg daily, *n* = 241) or high-dose phentermine–topiramate CR (15 mg–92 mg daily, *n* = 512) for 52 weeks. Completion rates ranged from 47% to 59% and were highest in the active-treatment groups. The intention-to-treat analyses demonstrated a statistically significant and dose-dependent superiority of phentermine–topiramate CR with regard to the amount of weight lost (10.9 kg with the high-dose combination, 5.1 kg with the low-dose combination versus 1.6 kg with placebo). These decreases in body weight were accompanied by improvements in waist circumference, triglyceride levels, and blood pressure (Table 2).

The CONQUER trial[31] included patients who were either overweight or obese (BMI 27–45 kg/m^2) and had two or more obesity-related comorbidities (hypertension, prediabetes, T2DM, dyslipidaemia or visceral adiposity). Participants were randomly assigned to receive placebo (*n* = 994) or one of two active treatments: phentermine 7.5 mg–topiramate CR 46 mg, (*n* = 498), or phentermine 15 mg–topiramate CR 92 mg, *n* = 995) for 56 weeks. Completion rates were 62–75% and highest in the active-treatment groups. Despite the increased heterogeneity of this study population (that resulted from including a wider range of BMI and including subject with and without diabetes), and the fact that the participants had more obesity-related comorbidities than the EQUIP cohort, results from the modified intention-to treat analyses were consistent with those from EQUIP. The CONQUER researchers reported a placebo-adjusted weight change of –8.6% in the high-dose combination therapy group, and the proportion of participants achieving ≥5% weight loss was 67% in the high-dose group versus 17% in the placebo group.

SEQUEL[32] was a double-blind 52-week extension of CONQUER, which included 676 of 866 (87%) eligible CONQUER participants. The modified intention-to-treat analyses of SEQUEL data demonstrate that the weight loss and favourable metabolic effects of phentermine–topiramate CR are largely maintained over 2 years (Table 2). Although blood pressure decreased to a numerically similar extent in all three treatment groups (3–5 mm Hg at 108 weeks), patients in the active-treatment groups experienced a net decrease in the number of antihypertensive medications used. Other cardiovascular risk factors, such as dyslipidaemia and high fasting serum glucose levels, improved to a greater extent with active treatment than with placebo, as reflected by significant reductions in the annualized incidence of T2DM (54% with phentermine 7.5 mg–topiramate CR 46 mg and 76% with phentermine 15 mg–topiramate CR 92 mg, both versus placebo).[33] However, data from the SEQUEL trial should be interpreted with caution, as the extension phase was prone to selection bias because it only included patients who completed the CONQUER trial.

The safety profile of phentermine–topiramate CR was largely consistent across all four studies. Patients on high-dose combination therapy were more likely than those on low-dose therapy to present with paresthesia (~20%), dry mouth (~20%), constipation (~15%) and other mild adverse events (Table 2). A slight, but statistically significant, increase in heart rate (1.7 bpm) was noted in the high-dose groups, and the proportion of participants who experienced a 10 bpm increase in basal heart rate was higher in the actively treated groups than in the placebo groups (23–26% versus 16%, respectively). Overall, the rate and type of serious adverse events did not differ between the placebo and active-treatment arms. The incidence of new cases of depression in the phase III trials was low, and comparable among experimental groups (3.4–5.0%); however, the reader should

note that patients receiving high-dose phentermine–topiramate CR were 4–7-fold more likely than those receiving placebo to discontinue treatment owing to a mental-health-related adverse event, such as anxiety, insomnia or depression. Cognitive disorders (confusion, disorientation and mental impairment) were also more frequent inpatients receiving active treatment than in those on placebo (7.6% versus 1.5%); these symptoms were commonly reported within the first month of treatment and seemed to be dose-related. Compared with earlier studies of phentermine monotherapy for weight management,[24] however, these trials of phentermine–topiramate combination therapy reported fewer adverse events and lower dropout rates. The use of low doses and controlled-release preparations might also have contributed to the reduction in adverse event rates observed in these combination-therapy trials.

A key limitation of the available evidence supporting the FDA approval of phentermine–topiramate CR is that most study participants were white American women, which limits the generalizability of the results to other ethnic groups. Results from the UK Epilepsy and Pregnancy Registry[34] suggest that exposure to topiramate during pregnancy increases the incidence of orofacial clefts (2.2% versus 0.2%) and hypospadias (5.1% versus 0.3%) compared to that in the general population. For female patients of reproductive age, a risk evaluation and mitigation strategy has been mandated by the FDA. This strategy includes education of patients and health-care providers, emphasizing the need for effective contraception, documentation of a negative pregnancy test before initiating topiramate treatment and monthly thereafter (while receiving this treatment, and special certification requirements for pharmacies that dispense the drug.

Naltrexone SR–bupropion SR

Bupropion is a norepinephrine and dopamine reuptake inhibitor that has been used in the treatment of depression for more than three decades[35] and, more recently, for smoking cessation.[36] Orally administered bupropion is rapidly absorbed and reaches peak plasma concentrations in 2 h. This agent is metabolized by the liver to multiple (less active) metabolites, and is eliminated primarily by urinary excretion.[37] The modest weight loss seen in patients receiving bupropion therapy has been attributed to its stimulatory effect on POMC-producing neurons in the arcuate nucleus of the hypothalamus.[36] Specifically, decreased energy intake and increased locomotor activity and thermogenesis[38] result from secretion of αMSH and subsequent activation of MC4-R. However, increased synaptic concentration of POMC increases the production of β-endorphin, an endogenous opioid, which inhibits POMC via a negative-feedback loop that reduces the secretion of αMSH.[39] This autoregulatory mechanism is believed to limit the antiobesity effect of bupropion monotherapy.[40]

Naltrexone is an opioid receptor antagonist that has been used since 1963 to treat opiate addiction and, more recently (2006), for alcohol addiction.[41] Naltrexone is almost fully absorbed but undergoes extensive first-pass hepatic metabolism that reduces its bioavailability to 5–40%. This agent reaches peak plasma concentrations after 1 h, has a half-life of 4 h, and is mainly excreted by the kidney.[41] Administration of naltrexone alone has no effect on body weight.[42] However, when co-administered with bupropion, naltrexone is postulated to reduce β-endorphin levels, thereby suppressing the negative-feedback regulation resulting from increased POMC levels and increasing and sustaining bupropion's effect on energy intake and expenditure.[43] Moreover, some evidence suggests that the antiopioid effect of naltrexone could reduce the β-endorphin–induced pleasurable

sensations associated with the ingestion of palatable food, which could have additional benefits in weight management.[44]

A total of 15 phase I and four phase II studies have investigated combinations of naltrexone and bupropion, which have been extensively reviewed elsewhere.[42] The finding that naltrexone 32 mg–bupropion 360 mg daily treatment was associated with smaller decreases in both systolic (–0.5 mmHg versus –1.6 mmHg) and diastolic (–0.7 mmHg versus –1.3 mmHg) blood pressure versus placebo led to the denial of FDA approval in early 2011 and initiation of the Cardiovascular Outcomes Study of Naltrexone SR–Bupropion SR in Overweight and Obese Subjects With Cardiovascular Risk Factors (The Light Study), which is expected to be completed by mid-2017. In the meantime, although not yet approved by the FDA, this novel fixed combination of sustained-release (SR) naltrexone and SR bupropion is currently undergoing review as a fast-track resubmission. In this Review, for consistency with the discussions of other antiobesity therapies, we limit our discussion to the results of the four large phase III randomized controlled trials (Table 3).

The Contrave Obesity Research Study (COR-I)[45] randomly assigned patients with uncomplicated obesity to placebo (*n* = 581), naltrexone 16 mg–bupropion 360 mg daily (n=578), or naltrexone 32 mg–bupropion 360 mg daily (*n* = 583) groups. Although neither of the active treatments reached the treatment efficacy benchmark proposed by the FDA—that is, ≥35% of participants in the active-treatment groups achieving ≥5% weight loss, and approximately double the proportion in the placebo-treated group—both combination therapies resulted in statistically significant placebo-adjusted weight changes (–3.7% in the low-dose group and–4.8% in the high-dose group). Furthermore, the proportion of patients reaching the ≥5% weight-loss target was significantly increased in the active-treatment

groups (39% in the low-dose group and 48% in the high-dose group, versus 16% in the placebo group). Patients in the active-treatment groups also had statistically significant (but rather modest) improvements in dyslipidaemia and hyperglycaemia (Table 3). Despite their increased weight reductions, patients receiving active treatment did not have a significant decrease in blood pressure from baseline, resulting in a slight, but statistically significant, placebo-adjusted increase of ~2 mmHg in blood pressure by the end of the study.

The Naltrexone/Bupropion Combination Therapy as an Adjunct to Behavior Modification (COR-BMOD) trial[46] participants were similar to those included in the COR-I study. Patients were randomly assigned to receive placebo (n = 202) or naltrexone 32 mg–bupropion 360 mg (n = 591) daily for 56 weeks, in conjunction with an intensive behaviour-modification program. Completion rates were close to 60% in both groups, although the modified intention-to-treat analyses (which included only participants with ≥1 post-baseline weight measurement while taking the study drug) excluded a higher proportion of patients taking the active treatment (18%) rather than the placebo (4.5%). Although the addition of behaviour modification increased the absolute weight loss in both groups (compared with the results from COR-I), the placebo-adjusted weight change in the active group (–4.2%) was similar to that observed in the COR-I study (–4.8%). The proportion of patients who attained ≥5% weight loss was also higher in the active-treatment group than in the placebo group (66% versus 42%), but this difference was less pronounced than in COR-I. Placebo-adjusted changes in metabolic parameters and blood pressure were also similar to those in COR-I. Patients in the active-treatment arm showed a less-pronounced drop in blood pressure compared to those in the placebo group (–1.3 ± 0.5 mmHg versus –

3.9 ± 0.7 mmHg), which resulted in an absolute placebo-adjusted increase in blood pressure of ~2.6 mmHg in the active-treatment group at the end of the study.

The results from COR-II and COR-DIABETES have yet to be fully published. The data presented in the FDA application are based on the results from 2,313 patient-years of therapy in the active-treatment group and 1,092 patient-years on placebo (pooled from patients with and without diabetes in all phase II and III studies).[47] This evidence suggests that administration of naltrexone 32 mg–bupropion 360 mg daily, in conjunction with behaviour modification (diet and exercise), led to statistically significant weight losses of 7.0% from baseline after 1 year of treatment (compared with losses of 2.3% when taking placebo). The proportion of patients achieving ≥5% weight loss in these studies was also significantly higher in the active-treatment groups than in the placebo groups (50% versus 17% for COR-II, and 45% versus 19% for COR-DIABETES, respectively). The decreases in body weight observed in the naltrexone 32 mg–bupropion 360 mg groups were also associated with statistically significant improvements in other metabolic parameters (waist circumference –7.1 cm versus –3.4 cm, HDL cholesterol levels 0.10 mmol/l versus 0 mmol/l, and triglyceride levels –0.13 mmol/l versus –0.03 mmol/l; all comparisons versus placebo). Across all phase III studies in individuals without T2DM, naltrexone 32 mg–bupropion 360 mg daily led to a significant increase in the proportion of patients achieving a clinically meaningful improvement in quality of life (defined as 7.7 points on the IWQOL-Lite scale)[48]—49–56% for naltrexone 32 mg–bupropion 360 mg daily versus 30–38% for placebo.[47] Interestingly, despite significant improvements in diabetes control compared to placebo (fasting serum glucose –0.66 mmol/l versus –0.22 mol/l, HbA_{1c} –0.6% versus –

0.1%, HOMA insulin resistance –20.6% versus –14.7%), no beneficial effect on quality-of-life was observed in patients with diabetes.

When compared with placebo, overall rates of adverse events (86% versus 75%) and rates of serious adverse events (2.3% versus 1.7%), as well as the proportion of patients who discontinued treatment owing to adverse events (24% versus 12%), were consistently higher in the active-treatment groups across all studies (Table 3). Adverse events related to active treatment tended to occur within the first four weeks of treatment the most frequent adverse events were (absolute values) nausea (32%), constipation (18%), headache (17%), vomiting (10%), dizziness (10%), insomnia (9%) and dry mouth (8%). Pooling the results from the abovementioned studies, no effect on the incidence of depression or mood changes was associated with bupropion–naltrexone treatment compared to placebo (2.8% versus 3.5%).

Conclusions

The FDA approval of lorcaserin, and phentermine–topiramate CR, and the pending FDA decision on naltrexone SR–buproprion SR, are developments that address important therapeutic gaps in the management of obesity. Given both the poor long-term outcome of lifestyle interventions and the risks and limited availability of bariatric surgery, use of antiobesity medications in conjunction with lifestyle modification can lead to clinically meaningful weight loss in the 5–10% range. As illustrated in Figure 1, an initial comparison of the results obtained with all three medications suggests that phentermine–topiramate CR might offer the greatest benefit (almost as twice as much as lorcaserin or naltrexone SR–bupropion SR). However, such indirect comparisons should be considered only as

hypothesis-generating, given that other factors—interindividual variation in patients' responses to these treatments, concurrent interventions and follow-up intensity—could account for these between-trial differences in the weight loss achieved.

Both lorcaserin and phentermine–topiramate CR have been approved in the USA as adjunct therapies for weight management in patients with a BMI >30 kg/m^2, or a BMI of 27–30 kg/m^2 and one or more weight-related comorbidity. FDA recommendations also indicate that management with either of these agents should be started at low doses and titrated upwards over 3–4 weeks, and that treatment should be discontinued in patients who do not reach a ≥5% weight loss after 12 weeks of therapy. The latter recommendation reflects the belief that the risk of taking these medications is greater than the benefits obtained when only a modest amount of weight loss occurs.

Although the approval of these two agents addresses an important therapeutic need in obesity management, the long-term effectiveness of such treatments outside the clinical trial setting remains to be demonstrated. 1-year attrition rates reported across the studies discussed in this Review ranged from 25% to 60%, and this factor needs to be considered when interpreting and extrapolating from the results. Moreover, the long-term adherence rates reported for previously approved antiobesity therapies are also very low (just 2% after 2 years), and whether newer agents have improved long term adherence remains to be seen.[49]

Potential pharmacological interactions with existing therapies and adverse effects associated with obesity-related comorbidities need to be considered before starting any pharmacological approach to weight management, especially in populations at increased risk of these adverse effects (Table 4). Given past experience with antiobesity

medications,[50] collection of postmarketing surveillance data to verify the safety of these treatments is paramount. The individual components of phentermine–topiramate CR and naltrexone SR–buproprion SR combinations have been available for decades and, therefore, unanticipated adverse effects are unlikely to emerge. However, lorcaserin, as a novel entity, might well deserve particular postmarketing scrutiny. Another factor that is also important to note is that although access to these agents might remain limited to the select group of patients who can afford or have insurance coverage for these medications (the estimated annual cost of which ranges from US$1,500 to $2,000), their use for the treatment of obesity could still expose a substantial population to drugs for which we do not yet have ample experience derived from widespread use.

In addition, the current indications for treatment with these antiobesity drugs are based solely on BMI criteria, which might poorly reflect these patients' actual health status or risk. Alternative systems for the assessment of obesity risk have been proposed that take into account the medical, mental and functional status of patients with excess weight.[51] We suspect that obesity treatments might prove to be cost-effective only in individuals who have an underlying comorbidity such as diabetes mellitus, sleep apnea or osteoarthritis, irrespective of their actual body weight. In contrast, use of antiobesity medications in obese individuals without accompanying comorbidity may prove to be less cost effective

Despite clinically significant improvements in metabolic and cardiovascular risk profiles seen with these agents, benefits have yet to be demonstrated in terms of improvements in 'hard' cardiovascular outcomes, for example, myocardial infarction, stroke and death. Results from large outcome trials investigating these new medications are likely to be completed in the coming 3-5 years.

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Author contributions

C. F. Rueda-Clausen researched the data for the article. C. F. Rueda-Clausen, R. S. Padwal and A. M. Sharma contributed substantially to discussions of content, writing, review and/or editing the manuscript before submission.

Figure 1. Absolute and placebo-adjusted weight loss after 1 year of treatment with lorcaserin, naltrexone SR–bupropion SR or phentermine–topiramate CR in phase III clinical trials. The length of the bars represents the relative weight loss observed in the active-treatment groups after 1 year (derived from the intention-to-treat analysis, in which missing data were imputed from the last observation carried forward). Coloured segments represent the placebo-adjusted weight loss achieved in each study. Black segments represent the proportion of the weight loss that is independent of the pharmacological intervention and does not represent the placebo-subtracted weight reduction.
Abbreviations: CR, controlled release; SR, sustained release.

New Table X. Characteristics of phase III clinical trials of antiobesity therapy.			
Clinical trial Design (duration)	**Inclusion criteria**	**Exclusion criteria**	**Participants***
Lorcaserin			
BLOOM[15] Double-blind phase III, RCT (original study 52 weeks; extension 52 weeks; total 104 weeks)	Original study: BMI 30–45 kg/m^2 or 27–45 kg/m^2 and weight-related comorbidity Extension: patients who completed the original study	T2DM, uncontrolled hypertension, valvulopathy, mental illness	Original study: age 44 ± 11 years, 84% female, 67% white, initial weight 100 ± 15 kg, Initial BMI 36 ± 4 kg/m^2 Extension: Initial weight 100 ± 15 kg, initial BMI 36 ± 5 kg/m^2
BLOSSOM[16] Double-blind phase III RCT (52 weeks)	BMI 30–45 kg/m^2 or 27–30 kg/m^2 and metabolic syndrome	T2DM, uncontrolled hypertension or dyslipidaemia	Age 44 ± 12 years, 80% female, 67% white, initial weight 100 ± 16 kg, initial BMI 36 ± 4 kg/m^2
BLOOM-DM[17] Double-blind phase III RCT (52 weeks)	Patients with T2DM receiving metformin and/or a sulfonylurea	**Insulin therapy**	Age 53 ± 8 years, 54% female, 60% white, initial weight 104 ± 18 kg, initial BMI 36 ± 5 kg/m^2
Phentermine–topiramate CR			
EQUATE[29] Double-blind phase II/III RCT (24 weeks)	BMI 30–45 kg/m^2	T2DM	Age 45 ± 11 years, 82% female, 80% white, initial weight 101 ± 15 kg, initial BMI 36 ± 6 kg/m^2
EQUIP[30] Double-blind phase III RCT (52 weeks)	BMI >35 kg/m^2 (and controlled dyslipidaemia, in patients with hypertension)	Impaired fasting glycaemia or T2DM	Age 42 ± 10 years, 82% female, 79% white, initial weight 116 ± 21 kg, initial BMI 42 ± 6 kg/m^2
CONQUER[31] Double-blind phase III RCT (56 weeks)	BMI 27–45 kg/m^2 and metabolic syndrome or T2DM	**Insulin therapy**	Age 51 ± 10 years, 70% female, 86% white, initial weight 103 ± 18 kg, initial BMI 36 ± 5 kg/m^2
SEQUEL[32] 52-week extension of CONQUER (total 108 weeks)	Patients who completed CONQUER	NA	Age 52 ± 10 years, 68% female, initial weight 102 ± 19 kg, initial BMI 36 ± 4.5 kg/m^2
Naltrexone SR–bupropion SR			
OT-101 Phase II/III double-blind RCT (24 weeks)	BMI 30–40 kg/m^2 or BMI 27–45 kg/m^2 and controlled dyslipidaemia or hypertension	T2DM	Age 43 ± 10 years, 89% female, initial weight 101 ± 15 kg, initial BMI 36 ± 6 kg/m^2
COR-I[45] Double-blind phase III, RCT (56 weeks)	BMI 30–45 kg/m^2 or BMI 27–45 kg/m^2 and controlled dyslipidaemia or hypertension	T2DM	Age 44 ± 11 years, 85% female, initial weight 101 ± 15 kg, initial BMI 36 ± 6 kg/m^2
COR-BMOD[46] Double-blind phase III RCT (56 weeks)	BMI 30–45 kg/m^2 or BMI 27–45 kg/m^2 and controlled dyslipidaemia or hypertension	T2DM	Age 46 ± 10 years, 90% female, initial weight 101 ± 15 kg, initial BMI 36 ± 6 kg/m^2
COR-II Double-blind phase III RCT (56 weeks)	BMI 30–45 kg/m^2 or BMI 27–45 kg/m^2 and controlled dyslipidaemia or hypertension	T2DM	Age 44 ± 11 years, 85% female, initial weight 101 ± 15 kg, initial BMI 36 ± 6 kg/m^2
COR-DIABETES Double-blind phase III, RCT (56 weeks)	T2DM and BMI 27–45 kg/m^2 ± controlled dyslipidaemia or hypertension	**Insulin therapy**	Age 54 ± 11 years, 56% female, initial weight 101 ± 15 kg, initial BMI 36 ± 6 kg/m^2
*All values are mean ± 1SD . Abbreviations: BP, blood pressure; CR, controlled release; NA, not applicable; RCT, randomized controlled trial; SR, sustained release; T2DM, type 2 diabetes mellitus.			

Table 1. Efficacy and safety of lorcaserin therapy for weight management											
Parameter	**BLOOM-DM**[17]			**BLOSSOM**[16]			**BLOOM**[15]				
							Original study		**Extension**		
Treatment groups	Placebo	10 mg	20 mg	Placebo	10 mg	20 mg	Placebo	20 mg	Placebo (2 years)	20 mg then placebo (1 year each)	20 mg (2 years)
Enrolled (*n*)	252	95	256	1,601	801	1,602	1,499	1,538	697	283	573
Completed the study *n* (%)	157 (62)	75 (79)	169 (66)	834 (52)	473 (59)	917 (57)	716 (45)	883 (55)	550 (79)	195 (69)	383 (67)
Weight change											
%	–1.6	–5*	–4.7*	–2.9	–4.7*	–5.8*	–2.2	–5.8*	–2.4	–3.3	–5.6*
kg	–1.5	–5*	–4.5*	–2.8	–4.7*	–5.8*	–2.2	–5.8*	–2.4	–3.3	–5.6*
Placebo-corrected (%)	—	–3.4*	–3.1*	—	–1.8*	–2.9*	—	–3.6*	—	–0.9	–3.2*
≥5%	16	45*	38*	25	40*	47*	20	48*	—	na	na
≥10%	4	18*	16*	10	17*	23*	8	23*	—	na	na
Metabolic changes‡											
Waist circumference (cm)	—	–1.7*	–2.2*	—	–1.7*	–2.2*	—	–2.9*	—	–0.76	–2.43*
SBP (mmHg)	—	1.5	0.1	—	–0.1	–0.7	—	–0.6*	—	1.4	–1.0*
FSG (mmol/l)	—	–0.88*	–0.82*	—	na	na	—	–0.11*	—	–0.01	–0.09*
TC (%LS)	—	1.3	–0.6	—	–1.3*	–0.7	—	–1.47*	—	0.16	–1.17
HDL (%LS)	—	2.8*	3.6*	—	2.2*	2.4*	—	0.26	—	3.12	1.69
TG (%LS)	—	–0.7	–5.9	—	–4.6*	–3.4*	—	–6.0*	—	–1.44	9.12*
Common adverse events (%)											
SAE	6.7	8.4	6.3	2.2	3.4	3.1	2.5	2.7	3.6	2.8	3.0
New valvulopathy	2.9	2.5	0.5	2.0	1.4	2.0	2.3	2.7	2.7	na	2.6
Headache	7	17	15	9.2	16	16	11	18	4.3	6.4	7.2
Dizziness	6	12	7	3.9	6.2	8.7	3.8	8.2	2.4	2.8	1.7
Nausea	8	8	9	5.3	7.6	9.1	5.4	7.5	4.2	3.2	3.5
Fatigue	4	5	7	4.1	6.6	8.4	3.0	6.0	2.3	1.8	2.6
Dry mouth	na	na	na	2.3	3.4	5.4	2.3	5.2	0.3	1.1	0.2

Results quoted are from the modified intention-to-treat population; missing data were imputed from the last observation carried forward. All groups received standardized lifestyle counselling. **P* <0.05 versus placebo. ‡Placebo-corrected changes from baseline. Abbreviations: FSG, fasting serum glucose; LS, least-squares; na, not available; SAE, serious adverse events; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides.

Table 2. Efficacy and safety of phentermine–topiramate CR therapy for weight management																
Parameter	**EQUATE[29]**							**EQUIP[30]**			**CONQUER[31]**			**SEQUEL[32]**		
Experimental groups	Placebo	P 7.5 mg	P 15 mg	T 46 mg	T 92 mg	P–T 7.5–46 mg	P–T 15–92 mg	Placebo	P–T 3.75–23 mg	P–T 15–92 mg	Placebo	P–T 7.5–46 mg	P–T 15–92 mg	Placebo	P–T 7.5–46 mg	P–T 15–92 mg
Enrolled *n*	103	104	106	102	105	103	103	514	241	512	994	498	995	227	153	295
Completed study *n*, (%)	69 (63)	74 (68)	72 (67)	72 (67)	67 (63)	73 (69)	68 (63)	241 (47)	138 (57)*	301 (59)*	616 (62)	374 (75)*	733 (74)*	165 (73)	99 (65)	195 (66)
Weight loss																
%	–1.5	–5.2*	–5.8*	–4.9	–6.1*	–8.2*	–9.0*	–1.6	–5.1*	–10.9*	–1.2	–7.8*	–9.8*	–1.8	–9.3*	–10.5*
kg	–1.5	–5.2*	–5.9*	–4.9	–6.4*	–8.4*	–8.9*	–1.8	–6*	–12.6*	–1.4	–8.1*	–10.2*	–2.1	–9.6*	–10.9*
Placebo-corrected (%)	—	–3.7*	–4.3*	–3.4	–4.6*	–6.8*	–7.5*	—	–3.5*	–9.3*	—	–6.6*	–8.6*	—	–7.5*	-8.7*
>5%	16	43*	46*	39	49*	62*	66*	17	45*	67*	21	62*	70*	30	75*	79*
>10%	7	13	21	19	24*	39*	41*	3	19*	47*	7	37*	48*	12	50*	54*
Metabolic changes‡																
Waist circumference (cm)	—	–3.1*	–3.3*	–2.1*	–2.9*	–5.5*	–5.4*	—	–2.5*	–7.8*	—	–5.2*	–6.8*	—	na	na
SBP (mmHg)	—	–1.5	–1.7	–5	–2.1	–5.2	–3.4	—	–2.7	–3.8*	—	–2.3*	–3.2*	—	–1.5	–1.1
FSG (mmol/l)	—	0.01	–0.04	0.05	0.01	0.01	–0.02	—	–0.06	–0.14*	—	–0.12*	–0.20*	—	–0.20	–0.27*
TC (%LS)	—	–1.8	0	–0.1	–1.8	–2.6	–1.4	—	–1.9	–2.5*	—	–1.6*	–3*	—	na	na
HDL (%LS)	—	5.8	5.9	0.1	–0.6	1.8	2.1	—	0.5	3.5*	—	4*	5.6*	—	2.6	7.2*
TG (%LS)	—	–16.2*	–12.7*	1.5	–8.3	–1.6	–12.6*	—	–3.9	–14.3*	—	–13.3*	–15.3*	—	–12.9*	–14.1*
Common adverse events (%)																
SAE	3.5	na	na	na	na	3	4	2.5	2.5	2.5	4	3	5	4	2.6	4.1
Dry mouth	na	na	na	na	na	16	19	4	7	17*	2	13*	21*	0.4	0.7	1.4*
Paresthesia	na	na	na	na	na	13	20	2	4	19*	3	14*	21*	0	1	3
Constipation	na	na	na	na	na	13	16	7	8	14	6	15*	15*	3	7	4
Dysgeusia	na	na	na	na	na	7	9	1	1	8*	1	7*	10*	0	1	1
Insomnia	7	7	11	6	7	14	16	5	5	8	5	6	10*	3	6	4
Dizziness	na	na	na	na	na	7	9	4	3	6	3	7*	10*	1	1	0.3
Nausea	na	na	na	na	na	4	7	5	6	7	4	4	7*	1	6	1
Lifestyle modification was advised for all individuals using the LEARN Program for Weight Management. Results quoted are from the modified																

intention-to-treat (CONQUER) or intention-to treat (EQUATE, EQUIP, SEQUEL) populations and missing data were imputed from the last observation carried forward. **P* <0.05 versus placebo. ‡Placebo-corrected changes from baseline. Abbreviations: FSG, fasting serum glucose;LS, least-squares; na, not available; P, phentermine; SAE, serious adverse events; SBP, systolic blood pressure; T, topiramate; TC, total cholesterol; TG, triglycerides.

Table 3. Efficacy and safety of naltrexone–bupropion CR therapy for weight management															
Parameter	**OT-101**						**COR-I** [45]			**COR-BMOD** [46]		**COR-II**		**COR-DIABETES**	
Treatment groups	Placebo	N 48 mg	B	NB16	NB32	NB48	Placebo	NB16	NB32	Placebo	NB32	Placebo	NB32	Placebo	NB32
Enrolled *n*	85	56	60	64	63	61	581	578	583	202	591	495	1,001	170	335
Completed study *n* (%) [Included in MITT]	60 (68)	33 (66)	44 (66)	37 (55)	45 (64)	25 (37)	290 (50) [511]	248 (49) [471]	296 (51) [471]	118 (59) [193]	342 (58) [482]	267 (54) [456]	538 (54) [825]	100 (59) [159]	175 (52) [265]
Weight loss															
%	–0.8	–1.2	–2.7	–5.4*	–5.4*	–4.3*	–1.3	–5*	–6.1*	–5.1	–9.3*	–1.2	–6.4*	–1.8	–5*
kg	–0.9	–1.1	–2.6	–5.1*	–5.1*	–4*	–1.4	–4.9*	–6.1*	–5.2	–9*	na	na	—	na
Placebo-corrected (%)	—	–0.4	–1.9	–4.6*	–4.6*	–3.5*	—	–3.7*	–4.8*	—	–4.2*	—	–4.6*	—	–3.2*
>5%	15*	10*	26*	52*	51*	39*	16	39*	48*	42	66*	17	50*	19	45*
>10%	2	2	7	17*	19*	15*	7	20*	25*	20	41*	6	28*	6	18*
Metabolic changes‡															
Waist circumference (cm)	—	–2.9	–2	–2.8	–3.7*	–3.8*	—	–2.5*	–3.7*	—	–3.2*	—	–4.6*	—	–2.1*
SBP (mmHg)	—	1.9	1.9	0.4	–3.3	2.7*	—	2.2*	1.8*	—	2.6*	—	na	—	na
FSG (mmol/l)	—	0.09	0.08	-0.04	–0.07	0.07	—	–0.06	–0.11*	—	–0.07	—	–0.08	—	–0.44
TC (%LS)	—	–6.9	–3.4	–1.2	–9.5*	–4.9	—	na	na	—	na	—	na	—	na
HDL (mmol/l)	—	0.01	0.05	0.07*	0.07*	0.06	—	0.09*	0.09*	—	0.08*	—	0.12*	—	0.09*
TG (%LS)	—	–5.8	–17.4	–11.9	–27.2*	–8.5	—	–4.9*	–9.6*	—	–8.1*	—	–9.3*	—	–10.4*
Common adverse events (%)															
SAE	na	na	na	na	na	na	1.4	1.6	1.6	1.3	2.3	0.2	0.4	4.7	3.9
Nausea	32	39	40	63	57	59	69	80*	83*	10	34*	na	na	na	na
Headache	7	9	5	6	14	12	9	16*	14*	18	24	na	na	na	na
Constipation	0	0	0	5	8	5	6	16*	16*	14	24*	na	na	na	na
Dizziness	0	7	8	13	10	12	3	8*	9*	5	15*	na	na	na	na
Insomnia	6	9	12	6	8	2	5	6	8	6	9	na	na	na	na
Dry mouth	1	0	5	8	5	5	2	7*	8*	3	8*	na	na	na	na

Results quoted are from the modified intention-to-treat (all COR studies) or intention-to treat (OT-101) populations and missing data were imputed from the last observation carried forward. All patients received intensive lifestyle modification counselling or customary diet and behavioural counselling. **P* <0.05 versus placebo. ‡Placebo-corrected changes from baseline. Abbreviations: B, 360 mg bupropion sustained release; FSG, fasting serum glucose; LS, least-squares; N, naltrexone sustained release; na, not available; NB16, N 16 mg–B; NB32, N 32 mg–B; NB48, N 48 mg–B; SAE, Serious adverse events; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides.

Table 4. Recommended considerations for special populations

Special population	Lorcaserin	Phentermine–topiramate CR	Naltrexone SR–bupropion SR
Women of reproductive age*	No teratogenesis reported in preclinical studies	Increased incidence of orofacial clefts and hypospadias Risk evaluation and mitigation strategy in place Negative pregnancy test required before initial treatment and monthly thereafter Effective contraception methods required	No teratogenesis reported with either individual agent
Renal failure	Urinary excretion Renal impairment: mild, no dose adjustment required; moderate, use with caution; severe, use not recommended	Urinary excretion Might increase creatinine levels Renal impairment: mild, no dose adjustment required; moderate/severe, do not exceed phentermine 7.5 mg–topiramate 46 mg daily	Urinary excretion Renal impairment: mild, no dose adjustment required; moderate/severe, use with caution
Hepatic failure	Use with caution if Child–Turcotte–Pugh score >9	If Child–Turcotte–Pugh score >7 do not exceed phentermine 7.5 mg–topiramate 46 mg daily	No hepatotoxicity reported with naltrexone at low doses Reduced clearance in patients with severe hepatic impairment Contraindicated in severe hepatic failure
Bradycardia or arrhythmia‡	Slight reduction in heart rate, use carefully in patients with bradycardia or greater than first-degree heart block	Might increase heart rate	Small (1–3 bpm) transient increase in heart rate No effect on incidence of arrhythmia reported
Hypertension	No specific haemodynamic effects reported	Might increase blood pressure Potential risk of hypotension in patients treated with antihypertensive medications	Transient (in first 8 weeks) increases in blood pressure (1 mmHg)
Type 2 diabetes mellitus	Potential improvement of hepatic glucose sensitivity Increased risk of hypoglycaemia No studies in patients taking insulin	Increased risk of hypoglycaemia No studies in patients taking insulin	No increased risk of hypoglycaemia reported No studies in patients taking insulin
Depression and/or at risk of suicide	Close monitoring of depression required	Co-administration with monoamine oxidase inhibitors contraindicated Close monitoring of depression required Avoid if history of suicidal attempts or active suicidal ideation	Risk of serotonin syndrome or reactions resembling neuroleptic malignant syndrome
Psychotic disorders	Might increase incidence of hallucination, euphoria or dissociative episodes	Phentermine has dose-related effects on psychosis, hallucination, euphoria or dissociative episodes	No increased risk of psychosis or psychotic episodes reported
Previous or current addiction	No dependency or risk of abuse reported	Potential for tolerance, dependency and abuse	No dependency or abuse potential reported
Cancer	Safety still to be determined in large studies	No increased cancer incidence has been reported with any component in this preparation	No increased cancer incidence has been reported with any component in this preparation
Age >65 years	Increase incidence of cognitive impairment No adequate safety or efficacy studies in this population	Can cause dose-related impairment of concentration, attention, memory and speech No adequate safety or efficacy studies in this population	Increased incidence of cognitive impairment No adequate safety or efficacy studies in this population
Other	None	Glaucoma, hyperthyroidism, kidney stones,	None

contraindications		oligohydrosis	
For all three agents, driving or operating machinery must be restricted during therapy initiation in patients who are drivers or machinery operators. *All three agents are excreted in breast milk. ‡No studies have been conducted in patients with heart failure.			

Box 1 Data analytical terms

Intention-to-treat analysis

In an intention-to-treat analysis, participants in each experimental group are included in the analyses if they undergo randomization regardless of whether they fully complete the protocol, receive the assigned treatment or are lost after the first study visit. The logic behind using this type of analysis is to compare the effects of different intervention in a real-life scenario (since patients who are not in clinical trials might discontinue management for a number of reasons), rather than just in patients who successfully complete the therapy as prescribed. Modified ITT refers to variations of this analyses technique in which subjects need to reach certain milestones in the protocol (such as complete one or more visits after randomization) before they can be include din the analyses.

Last observation carried forward

Missing data in longitudinal datasets is often imputed by carrying forward the last known observation for the patient. Although this method is well-recognized and commonly used in longitudinal data analysis, its use might underestimate the variability of the observations over time and, consequently, overestimate the significance of the differences observed among groups. Notably, the US National Academy of Sciences recommends the use of multiple imputation methods instead of simple imputation methods (such as carrying the last observation forward) as the primary approach to deal with missing data in clinical trials.[52]