New pharmacological approaches for obesity management

Christian F. Rueda-Clausen, Raj S. Padwal and Arya M. Sharma

Abstract | Obesity, which results from an imbalance between calorie intake and expenditure, now affects over 500 million people worldwide. Lifestyle and behavioral 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 the majority of individuals with excess adiposity. Accordingly, few effective treatment options are available to most individuals with obesity. 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. In 2012, the FDA 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.

Introduction

Obesity, which currently affects over 500 million people worldwide, 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. Obesity also has important economic effects for the individuals affected, their employers and health-care systems.

Although the primary driver of weight gain is an imbalance between calorie intake and expenditure, lifestyle and behavioral interventions aimed at correcting this imbalance have limited long-term effectiveness. 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. These counter-regulatory adaptations include persistent changes in neurohormonal activation of appetite and marked reductions in resting and activity-related thermogenesis. 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 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.

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 receptor 2C (5-HT2C), which is predominantly expressed in hypothalamic pro-opiomelanocortin (POMC)-producing neurons in the central nervous system and involved in the control of food intake and body weight. Lorcaserin decreases appetite and increases the feeling of fullness through stimulation of 5-HT2C receptors, resulting in a reduced caloric intake and increased energy expenditure. The pharmacological profile of lorcaserin is distinct from that of other antiobesity drugs, with a low risk of cardiovascular and central nervous system adverse effects.

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Further studies are needed to assess the long-term benefits and cost-effectiveness of these new agents.

Lorcaserin is rapidly absorbed, reaching its peak circulating concentration 2 h after ingestion, and freely enters the central nervous system. Lorcaserin has a mean half-life of 10–11 h and is predominantly excreted in the urine. By activating 5-HT2C receptors, lorcaserin stimulates the release of melanotropin-alpha (also known as α-MSH), which decreases appetite through stimulation of melanocortin receptor 4 (MC4-R). In mouse models of diabetes mellitus, lorcaserin not only decreases appetite but also seems to directly improve glucose tolerance and hepatic insulin sensitivity.

Lorcaserin has low affinity for other 5-hydroxytryptamine receptor subtypes, such as 5-HT2B, targeting of which has previously been associated with the development of valvular heart disease in patients receiving antiobesity drugs. 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 (Behavioural Modification and Lorcaserin for Overweight and Obesity Management) study included 3,182 participants without diabetes mellitus who had a BMI of 30–45 kg/m², or a BMI ≥ 27 kg/m² and a weight-related comorbid condition (hypertension, cardiovascular disease, dyslipidaemia, impaired glucose metabolism or sleep apnoea) (Table 1). 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 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 1). 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 2). A 1-year extension of the BLOOM study included all patients who had successfully completed the first year (lorcaserin group n = 886, placebo group n = 697). Individuals initially assigned to the lorcaserin group underwent a second round of randomization (in a 2:1 ratio) to either lorcaserin 20 mg 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 had a lower probability of maintaining 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 (Behavioural Modification and Lorcaserin Second Study for Obesity Management) trial included 4,008 participants (aged 18–65 years) with a BMI of 30–45 kg/m², or a BMI of 27.0–29.9 kg/m² 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 (Table 1). 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 with 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 2), as well as quality of life (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), compared with those in the placebo group.

The BLOOM diabetes mellitus study (BLOSSOM-DM) included overweight and obese patients with type 2 diabetes mellitus (T2DM) who were receiving metformin and/or a sulphonylurea. 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 (Table 1). 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, no dose–response...
Table 1  | Characteristics of phase III clinical trials of antidiobesity therapy

| Clinical trial design* (duration) | Inclusion criteria | Exclusion criteria | Participants

<table>
<thead>
<tr>
<th>Lorcaserin</th>
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<tbody>
<tr>
<td>BLOOM[^10] (original study 52 weeks; extension 52 weeks; total 104 weeks)</td>
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<tr>
<td>BLOSSOM[^16] (52 weeks)</td>
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<td>BLOOM-DM[^17] (52 weeks)</td>
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<tr>
<th>Phentermine–topiramate CR</th>
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<tr>
<td>EQUIP[^30] (52 weeks)</td>
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<tr>
<td>CONQUER[^11] (56 weeks)</td>
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<tr>
<td>SEQUEL[^32] (52-week extension of CONQUER; total 108 weeks)</td>
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<tr>
<th>Naltrexone SR–bupropion SR</th>
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<tbody>
<tr>
<td>OT-101</td>
</tr>
<tr>
<td>COR[^45] (56 weeks)</td>
</tr>
<tr>
<td>COR-BMOD[^46] (56 weeks)</td>
</tr>
<tr>
<td>COR[^45] (56 weeks)</td>
</tr>
<tr>
<td>COR-DIABETES[^56] (56 weeks)</td>
</tr>
</tbody>
</table>

*All trials were double-blind phase III RCTs unless otherwise stated. All values are mean ±1 SD. Abbreviations: BP, blood pressure; CR, controlled release; NR, not reported; RCT, randomized controlled trial; SR, sustained release; T2DM, type 2 diabetes mellitus.

The specific reasons for this finding could not be explored during the study. However, the researchers suggested that the higher age of the patients recruited in BLOOM-DM (mean age 52.7 years versus 43.8 years in the BLOSSOM trial) could be a contributory factor, given that ageing is associated with a physiological decrease in baseline metabolic rate, physical activity and energy requirements. 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 HbA1c 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 2).

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 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 mellitus, symptomatic hypoglycaemia was reported with greater frequency by those receiving lorcaserin (21–28%) than by those in the placebo group (12%).

Given the association between valvular complications and treatment with previous serotonergic antiobesity medications (specifically fenfluramine and dexfenfluramine), all 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 (\( \beta >0.4 \)) 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 has potential oncogenic effects, particularly for mammary, thyroid and brain tumours. Phase III studies did not detect increases in the incidence of any neoplasms; however, no formal cancer screening was conducted in these studies, and their periods of observation were too short to make any definitive conclusion in this regard.

**Phentermine–topiramate**

**Phentermine**

The amphetamine analogue phentermine is an effective, inexpensive and generally well-tolerated appetite suppressant that has been widely used as an antiobesity drug for several decades. 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). The anorexic effect of phentermine is attributed to its sympathomimetic action, which is related to catecholamine release in the hypothalamus. 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. Some evidence suggests that prolonged treatment with phentermine results in slightly greater weight loss (8–10 kg after 6 months). 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. 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. Similar to 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 incompletely understood, but its efficacy seems to be related to a number of pathways: reduction in compulsive or addictive food craving via antagonism of \( \alpha \)-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors and kainate receptors; decreased lipogenesis and modification of food taste via inhibition of carboxic anhydrase isoenzymes; and increased energy expenditure via activation of \( \gamma \)-aminobutyric acid receptors.

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. However, the use of topiramate monotherapy for weight management has been limited by several common dose-dependent adverse effects, including paraesthesia, fatigue, dizziness (distortion of taste), difficulty with concentration and mood changes.

**Fixed-dose combination therapy**

Phentermine–topiramate controlled-release (CR) is a fixed-dose combination of fast-acting phentermine (recommended dose 7.5–15 mg per day) and CR topiramate (recommended dose 46–92 mg per 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 3). EQUATE was a small randomized controlled trial that included 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 (Table 1). Completion rates were 63–69% and similar across all study arms. The ITT analyses showed that the groups receiving phentermine and topiramate (both combined doses) exhibited a significantly greater weight change from baseline (–8.2% and –9.0%) than either the group receiving placebo (–1.5%) or those 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 proportions 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).

Researchers of the EQUIP trial\(^\text{29}\) randomly assigned patients with obesity (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 (Table 1). Completion rates ranged from 47% to 59% and were highest in the active-treatment groups. The ITT 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 3).

The CONQUER trial\(^\text{31}\) 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 (Table 1). Completion rates were 62–75% and highest in the active-treatment groups. Despite the

\(\text{Table 2 | Efficacy and safety of lorcaserin therapy for weight management}\)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>BLOOM-DM(^\text{17})</th>
<th>BLOSSOM(^\text{16})</th>
<th>BLOOM(^\text{15}) (original study)</th>
<th>BLOOM(^\text{15}) (extension)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrolled (n)</td>
<td>Placebo 10 mg 20 mg</td>
<td>Placebo 10 mg 20 mg</td>
<td>Placebo 20 mg</td>
<td>Placebo (2 years) 20 mg then placebo (1 year each) 20 mg (2 years)</td>
</tr>
<tr>
<td>Completed the study n (%)</td>
<td>157 (62) 75 (79) 169 (66)</td>
<td>834 (52) 473 (59) 917 (57)</td>
<td>716 (45) 883 (55)</td>
<td>550 (79) 195 (69) 383 (67)</td>
</tr>
<tr>
<td>Weight change</td>
<td>%</td>
<td>–1.6 –5* –4.7*</td>
<td>–2.9 –4.7* –5.8*</td>
<td>–2.2 –5.8*</td>
</tr>
<tr>
<td>Kg</td>
<td>–1.5 –5* –4.5*</td>
<td>–2.8 –4.7* –5.8*</td>
<td>–2.2 –5.8*</td>
<td>–2.4 –3.3 –5.6*</td>
</tr>
<tr>
<td>Placebo-corrected (%)</td>
<td>–3.4* –3.1*</td>
<td>–1.8* –2.9*</td>
<td>–3.6*</td>
<td>–0.9 –3.2*</td>
</tr>
<tr>
<td>≥5%</td>
<td>16 45* 38*</td>
<td>25 40* 47*</td>
<td>20 48*</td>
<td>NR NR</td>
</tr>
<tr>
<td>≥10%</td>
<td>4 18* 16*</td>
<td>10 17* 23*</td>
<td>8 23*</td>
<td>NR NR</td>
</tr>
</tbody>
</table>

### Common adverse events (%)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>SAE</th>
<th>New valvulopathy</th>
<th>Headache</th>
<th>Dizziness</th>
<th>Nausea</th>
<th>Fatigue</th>
<th>Dry mouth</th>
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<tbody>
<tr>
<td>Placebo</td>
<td>6.7 8.4 6.3</td>
<td>2.9 2.5 0.5</td>
<td>2.9 17</td>
<td>15</td>
<td>9.2 16 16</td>
<td>11 18</td>
<td>4.3 6.4</td>
</tr>
<tr>
<td>BLOOM-DM 10 mg</td>
<td>2.2 3.4 3.1</td>
<td>2.5 2.7 3.6</td>
<td>2.8</td>
<td>3.0</td>
<td>2.9 1.4 2.0</td>
<td>2.3 2.7</td>
<td>2.7</td>
</tr>
<tr>
<td>BLOOM-DM 20 mg</td>
<td>2.0 1.4 2.0</td>
<td>2.3 2.7</td>
<td>2.7</td>
<td>5.3</td>
<td>6.9 5.4</td>
<td>5.4</td>
<td>7.5</td>
</tr>
</tbody>
</table>

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.

\(\text{*}P<0.05\) versus placebo. \#Placebo-corrected changes from baseline. Abbreviations: FSG, fasting serum glucose; LS, least-squares; NR, not reported; SAE, serious adverse events; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides.
increased heterogeneity of this study population, which included a wide BMI range and patients both with and without diabetes mellitus, and the fact that the participants had more obesity-related comorbidities than the EQUIP cohort, results from the modified ITT 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 was a double-blind 52-week extension of CONQUER, which included 676 of 866 (87%) eligible CONQUER participants (Table 1). The modified ITT analyses of SEQUEL data demonstrate that the weight loss and favourable metabolic effects of phentermine–topiramate CR are largely maintained over 2 years (Table 3). Although blood pressure decreased to a numerically similar extent in all three treatment groups (3–5 mmHg 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 versus placebo).13 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 had a higher probability than those on low-dose therapy to present with paraesthesia (~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, notably, patients receiving high-dose phentermine–topiramate CR had a fourfold to sevenfold higher probability 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 in patients 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. Nevertheless, the trials of phentermine–topiramate combination therapy, reported fewer adverse events and lower dropout rates than earlier studies of phentermine monotherapy for weight management. 24 The use of low doses and CR preparations might also have contributed to the reduction in adverse event rates observed in the 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 44 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, as well as special certification requirements for pharmacies that dispense the drug.

Naltrexone–bupropion

Bupropion

Bupropion is a noradrenaline and dopamine reuptake inhibitor that has been used in the treatment of depression for more than three decades 35 and 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 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 α-MSH 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 α-MSH. 39 This autoregulatory mechanism is believed to limit the antiobesity effect of bupropion monotherapy. 40

Naltrexone

Naltrexone is an opioid receptor antagonist that has been used since 1963 to treat opiate addiction and, since 2006, for alcohol addiction. 41 Naltrexone is almost fully absorbed after ingestion 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 elevated POMC levels and increasing and sustaining bupropion’s effect on energy intake and expenditure. 43 Moreover, some evidence suggests that the anti-opioid 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

Combination therapy

A total of 15 phase I and four phase II studies have investigated combinations of naltrexone and bupropion, which have been extensively reviewed elsewhere. 45 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. The producing company has addressed some of the regulatory concerns and provided additional analyses of their clinical data. 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 4).

Researchers of the Contrave Obesity Study Research (COR-1) 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 (Table 1). Although active treatments resulted in statistically significant placebo-adjusted weight change, (−3.7% in the low-dose group and −4.8% in the high-dose
group) this effect was rather modest and below the primary efficacy benchmark proposed by the FDA (a placebo-adjusted weight loss >5% of initial body weight). However, in this study, patients receiving active treatment exhibited a significant increase in the proportion of 5% weight loss achievers (39% in the low-dose group and 48% in the high-dose group versus 16% in the placebo group). Reaching the alternative efficacy benchmark proposed by the FDA—that is, ≥5% weight loss achieved by ≥35% of participants in the active-treatment groups, and approximately double the proportion of those who achieve this weight-loss target in the placebo-treated group. Patients in the active-treatment groups also had statistically significant, albeit rather modest, improvements in dyslipidaemia and hyperglycaemia (Table 4). 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.

Participants of the Naltrexone/Bupropion Combination Therapy as an Adjunct to Behaviour Modification (COR-BMOD) trial 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 programme (Table I). Completion rates were close to 60% in both groups, although the modified ITT 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...
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 mellitus in all phase II and III studies; Table 1).57 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)49—49–56% for naltrexone 32 mg–bupropion 360 mg daily versus 30–38% for placebo.62 Interestingly, despite significant improvements in diabetes control compared to placebo (fasting serum glucose −0.66 mmol/l versus −0.22 mmol/l, HbA₁c −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 mellitus.

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 4). Adverse events related to active treatment tended to occur within the first 4 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 aforementioned 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%).

**Obesity therapy in clinical practice**

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 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/m², or a BMI of 27–30 kg/m² and at least one weight-related comorbidity. FDA recommendations 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.

The approval of these two agents addresses an important therapeutic need in obesity management, however, 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 anti-obesity 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
Phentermine–topiramate CR

No specific haemodynamic effects reported

Urinary excretion

Renal impairment: mild, no dose adjustment required; moderate, use with caution; severe, use not recommended

Renal failure

Increased incidence of orofacial clefts and hypospadias

Risk evaluation and mitigation strategy in place

Effective contraception methods required

Phentermine–topiramate CR

No dependency or abuse potential

Use with caution if Child–Turcotte–Pugh score >9

Increased incidence of cognitive impairment

Glaucoma, hyperthyroidism, kidney stones, oligohydrosis

Hepatic failure

No studies in patients taking insulin

Increased risk of hypoglycaemia

No studies in patients taking insulin

Type 2 diabetes mellitus

Potential improvement of hepatic glucose sensitivity

Increased risk of hypoglycaemia

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

Avoid if history of suicidal attempts or active suicidal ideation

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

Can cause dose-related impairment of concentration, attention, memory and speech

Increased incidence of cognitive impairment

No adequate safety or efficacy studies in this population

Other contraindications

None

Recommended considerations for special populations

<table>
<thead>
<tr>
<th>Special population</th>
<th>Lorcanerin</th>
<th>Phentermine–topiramate CR</th>
<th>Naltrexone SR–bupropion SR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women of reproductive age*</td>
<td>No teratogenesis reported in preclinical studies</td>
<td>Increased incidence of orofacial clefts and hypospadias</td>
<td>No teratogenesis reported with either individual agent</td>
</tr>
<tr>
<td>Renal failure</td>
<td>Urinary excretion</td>
<td>Urinary excretion</td>
<td>Urinary excretion</td>
</tr>
<tr>
<td></td>
<td>Renal impairment: mild, no dose adjustment required; moderate, use with caution; severe, use not recommended</td>
<td>Renal impairment: mild, no dose adjustment required; moderate/severe, do not exceed phentermine 7.5mg–topiramate 46mg daily</td>
<td>Renal impairment: mild, no dose adjustment required; moderate/severe, use with caution</td>
</tr>
<tr>
<td>Hepatic failure</td>
<td>Use with caution if Child–Turcotte–Pugh score &gt;9</td>
<td>If Child–Turcotte–Pugh score &gt;7 do not exceed phentermine 7.5mg–topiramate 46mg daily</td>
<td>No hepatotoxicity reported with naltrexone at low doses</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Reduced clearance in patients with severe hepatic impairment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Contraindicated in severe hepatic failure</td>
</tr>
<tr>
<td>Bradycardia or arrhythmia‡</td>
<td>Slight reduction in heart rate, use carefully in patients with bradycardia or greater than first-degree heart block</td>
<td>Might increase heart rate</td>
<td>Small (1–3 bpm) transient increase in heart rate</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No effect on incidence of arrhythmia reported</td>
</tr>
<tr>
<td>Hypertension</td>
<td>No specific haemodynamic effects reported</td>
<td>Might increase blood pressure</td>
<td>Transient (in first 8 weeks) increases in blood pressure (1 mmHg)</td>
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<td>Type 2 diabetes mellitus</td>
<td>Potential improvement of hepatic glucose sensitivity</td>
<td>Increased risk of hypoglycaemia</td>
<td>No increased risk of hypoglycaemia</td>
</tr>
<tr>
<td></td>
<td>Increased risk of hypoglycaemia</td>
<td>No studies in patients taking insulin</td>
<td>No studies in patients taking insulin</td>
</tr>
<tr>
<td>Depression and/or at risk of suicide</td>
<td>Close monitoring of depression required</td>
<td>Co-administration with monoamine oxidase inhibitors contraindicated</td>
<td>Risk of 5-hydroxytryptamine syndrome or reactions resembling neuroleptic malignant syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Close monitoring of depression required</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Avoid if history of suicidal attempts or active suicidal ideation</td>
<td></td>
</tr>
<tr>
<td>Psychotic disorders</td>
<td>Might increase incidence of hallucination, euphoria or dissociative episodes</td>
<td>Phentermine has dose-related effects on psychosis, hallucination, euphoria or dissociative episodes</td>
<td>No increased risk of psychosis or psychotic episodes reported</td>
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<tr>
<td>Previous or current addiction</td>
<td>No dependency or risk of abuse reported</td>
<td>Potential for tolerance, dependency and abuse</td>
<td>No dependency or abuse potential reported</td>
</tr>
<tr>
<td>Cancer</td>
<td>Safety still to be determined in large studies</td>
<td>No increased cancer incidence has been reported with any component in this preparation</td>
<td>No increased cancer incidence has been reported with any component in this preparation</td>
</tr>
<tr>
<td>Age &gt;65 years</td>
<td>Increase incidence of cognitive impairment</td>
<td>Can cause dose-related impairment of concentration, attention, memory and speech</td>
<td>Increased incidence of cognitive impairment</td>
</tr>
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<td></td>
<td>No adequate safety or efficacy studies in this population</td>
<td>No adequate safety or efficacy studies in this population</td>
<td>No adequate safety or efficacy studies in this population</td>
</tr>
<tr>
<td>Other contraindications</td>
<td>None</td>
<td>Glaucoma, hyperthyroidism, kidney stones, oligohydrosis</td>
<td>None</td>
</tr>
</tbody>
</table>

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.


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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.