Current and emerging medications for overweight or obesity in people with comorbidities

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Recently, the recognition of obesity as a complex disease that requires chronic management has become more widespread. There has also been a movement away from a focus on body mass index alone, and toward the management of obesity-related comorbidities as well as excess weight. This article examines the current and emerging pharmacological options for weight management in people with overweight or obesity who have, or are at a high risk of, weight-related comorbidities. In the USA, the current options for pharmacological weight management are phentermine (indicated for short-term use only), orlistat, combined phentermine/topiramate extended release, lorcaserin, naltrexone/bupropion and liraglutide 3.0 mg. Currently, orlistat, naltrexone/bupropion and liraglutide 3.0 mg are approved in Europe. All of the above-mentioned medications have shown weight-loss efficacy versus placebo. Those approved for long-term weight management have also been associated with improvements in weight-related comorbidities, such as hypertension, prediabetes, diabetes or dyslipidaemia, or related biomarkers. As with all drugs, the safety and tolerability profiles of medications for weight management should be considered alongside their efficacy to ensure correct use. Additional medications for weight management that are in clinical development include bupropion/zonisamide and beloranib. The field of obesity treatment is advancing with a number of medications being recently approved, and with other pharmacological options emerging.

Keywords: comorbidities, medication, obese, overweight, pharmacological, weight management

Introduction

Global obesity rates have doubled since 1980 [1] and, in the USA, 70% of the population are now affected by excess weight or obesity. While overweight and obesity have traditionally been classified by body mass index (BMI) alone, the presence of related comorbidities is gaining importance as a diagnostic factor, as captured by the Edmonton Obesity Staging System (EOSS; Table S1) [2] and the Cardiometabolic Disease Staging (CMDS) system (Table S2) [3]. For some individuals, overweight or obesity has little apparent effect on health or daily living (stage 0–1 of the EOSS, stage 0 of the CMDS system) [2,3], with a proportion of these people having normal metabolic features despite increased adiposity ('metabolically healthy' overweight or obesity) [4]. For others, obesity is associated with chronic comorbidities (Figure 1) [5,6], physical or psychological symptoms and/or functional limitations, which can have a substantial, negative impact on quality of life (stages 2–4 EOSS) [2,8] and mortality (stages 2–4 CMDS system; Figure 2) [2,3]. Even apparently metabolically healthy obese people are at increased long-term risk of cardiovascular events and all-cause mortality compared with metabolically healthy, normal weight individuals [4].

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The most well-established weight-related comorbidities are prediabetes, type 2 diabetes (T2D) and cardiovascular disease, the risks of which are proportional to BMI [9–12]. For example, the Global Burden of Metabolic Risk Factors for Chronic Diseases Collaboration estimated a 27% increase in the risk of coronary heart disease and an 18% increase in the risk of stroke for each $5 \, kg/m^2$ higher BMI [12]. Other well-established complications associated with overweight and obesity include obstructive sleep apnoea, non-alcoholic fatty liver disease and polycystic ovary syndrome [2,5–7]. Obesity may also have psychological effects: obese individuals have a greater likelihood of experiencing depressive symptoms than non-obese individuals [odds ratio 1.26, 95% confidence interval (CI) 1.17–1.36], ($p \leq 0.001$) [13]. The sum of these negative health effects is reflected by a greater risk of all-cause mortality in those with a BMI $\geq 35 \, kg/m^2$ compared with those of a normal weight (hazard ratio 1.29, 95% CI 1.18–1.41) [14].

The American Association of Clinical Endocrinologists (AACE), American Medical Association, The Obesity Society (TOS) and the Endocrine Society all classify obesity as a disease and recognize that it requires treatment [15–18].

The present review examines the pharmacological options that are approved for the management of overweight and obesity in the USA and Europe, with a particular focus on people at a high risk of complications, who would benefit most from intervention. It also identifies treatment gaps in current weight loss strategies, and offers future perspectives. Detailed consideration of lifestyle modifications, counselling and bariatric surgery is beyond the scope of this article, but these topics have been reviewed elsewhere [19]. With the exception of low-dose
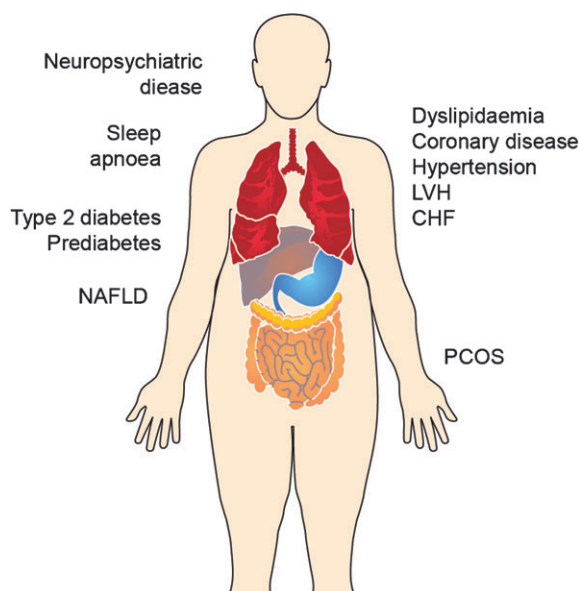
Figure 1. Chronic conditions linked with overweight or obesity. CHF, coronary heart failure; LVH, left ventricular hypertrophy; NAFLD, non-alcoholic fatty liver disease; PCOS, polycystic ovary syndrome [2,5–7]. Multiple comorbidities are associated with obesity, of which only a proportion are shown.

orlistat, over-the-counter medications are not considered in the present review because of a lack of evidence.

Managing Obesity/Overweight and Related Complications

Recent recommendations for addressing overweight and obesity with or without comorbidities have been presented by the Endocrine Society [18]; the American Heart Association (AHA), American College of Cardiology (ACC) and TOS (AHA/ACC/TOS) [19]; and by the AACE and American College of Endocrinology (Figure S1) [20]. The AHA/ACC/TOS recommend an initial weight loss target of 5–10% of baseline weight within 6 months [19].

Modest weight loss with lifestyle modification programmes can have long-term health benefits, including improved lipid and glycaemic control, and reduced risk of T2D [21–25]; however, attrition rates from these programmes are generally high, and low adherence can severely impair their long-term weight loss efficacy [26]. Bariatric procedures are thought to be more effective than non-surgical interventions in terms of weight loss and may reduce the long-term risk of diabetes, cardiovascular events and cancer, as well as overall mortality [27]; however, bariatric surgery is not suitable or feasible for all people with obesity: indeed, <1% of eligible people undergo bariatric surgery [28]. Pharmacological options have the potential to bridge the treatment gap between lifestyle modifications and bariatric surgical procedures [19].

Medications for long-term weight management were not selected for comprehensive evaluation in the 2013 AHA/ACC/TOS guidelines, as only orlistat was approved at the time of review [19]. Rather than providing extensive guidelines,
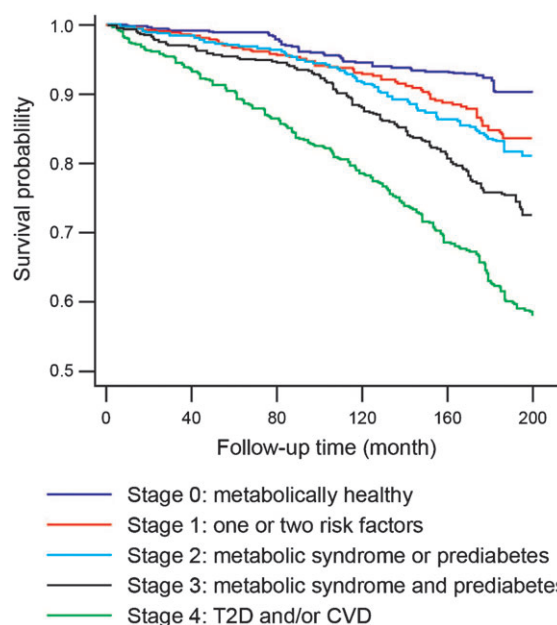
Figure 2. Kaplan–Meier plots for all-cause mortality according to the Cardiometabolic Disease Staging system. Stage 0, metabolically healthy (no risk factors); stage 1, one or two cardiovascular risk factors present; stage 2, metabolic syndrome or prediabetes present; stage 3, metabolic syndrome and prediabetes present; stage 4, type 2 diabetes (T2D) or cardiovascular disease present. © The Obesity Society 2013, reproduced with permission from Guo F, Moellering DR, Garvey WT. *Obesity* (Silver Spring) 2014; **22**: 110–118 [3].

the AHA/ACC/TOS recommendation by expert opinion was that US Food and Drug Administration (FDA)-approved pharmacotherapy can be considered as an adjunct to comprehensive lifestyle intervention in individuals with a BMI ≥30 or ≥27 kg/m² with at least one obesity-associated comorbidity, who are motivated to lose weight [19]. Meanwhile, the most recent AACE guidelines recommend basing the selection of treatment method and intensity for those with a BMI of ≥27 kg/m² on the presence of obesity-related complications, such as diabetes (Figure S1) [20]. The Endocrine Society also recommends diet, exercise and behavioural modification with the addition of pharmacotherapy in individuals with a BMI ≥27 kg/m² with comorbidity or a BMI ≥30 kg/m² without comorbidity [18]. This comorbidity-centric view supports the approach of using medications for weight loss as first-line treatment [20]. It also emphasizes the benefit of weight loss in those with obesity-related disease.

Targeting individual complications may result in problematic poly-pharmacy (which increases the odds of side effects, drug–drug interactions and non-adherence, as well as cost) [29]. When treating obesity-related comorbidities, the preference is for therapy options that target the specific comorbidity without increasing body weight, a common problem with several medications used for the treatment of T2D. For example, the optimum approach for the management of hyperglycaemia would be the use of a weight-neutral, or even weight-reducing, agent, such as metformin [18,30], a glucagon-like peptide 1 (GLP-1) receptor agonist [18,31] or a sodium-glucose transporter-2 (SGLT2) inhibitor [32].

As for all prescription drugs, doctor–patient discussions about on the potential benefits and risks of a particular weight loss medication are encouraged, along with appropriate monitoring of individual responses [33,34].

Current Status of Pharmacological Weight Management in the USA and Europe

As of the second quarter of 2015, the pharmacological options for overweight and obesity treatment approved in the USA are phentermine, orlistat, phentermine/topiramate extended release (ER) combination therapy, lorcaserin, naltrexone/bupropion and the recently approved liraglutide 3.0 mg [35] (Figure S2).

Currently, orlistat, naltrexone/bupropion and liraglutide 3.0 mg are approved in Europe [36]. Sibutramine was withdrawn (from the USA and Europe) on the basis of concerns regarding cardiovascular risk, and marketing approval received for rimonabant in Europe was withdrawn because of concerns regarding depression/suicidality [36]. The European marketing authorization application for phentermine/topiramate ER has been rejected twice, and the corresponding application for lorcaserin withdrawn [36].

The 1-year weight loss efficacy data and 1-year weight loss maintenance data for medications approved in the USA are shown in Tables 1–3. The weight loss data presented are as described in the medication US Prescribing Information or individual trial, with last observation carried forward (LOCF) if available.

Phentermine Monotherapy

Phentermine is a sympathomimetic amine anorectic [45]. Having received initial approval in 1959, it is indicated in the USA for short-term weight management (the label states 'a few weeks', which is commonly taken to mean up to 12 weeks [45,46]), as an adjunct to caloric restriction and lifestyle modifications, in those with a BMI $\geq$30 or $\geq$27 kg/m^2 and weight-related comorbidities [45]. The usual maximum adult dose of phentermine hydrochloride (brand name ADIPEX-P®) is 37.5 mg (30 mg base phentermine) once daily, but an individualized dose should be used to obtain an adequate response with the lowest possible dose [45]. In clinical practice, it is common for physicians to prescribe the generic 37.5 mg tablet and advise the recipient to take a half tablet (18.75 mg) once daily in the mid-morning. According to the phentermine label, increased weight loss with 'anorectic drugs' compared with placebo is modest ('a fraction of a pound per week') and occurs during the first few weeks of therapy, tending to decrease in succeeding weeks [45]. A meta-analysis of six 2–24-week randomized clinical trials found that participants who received phentermine lost an additional 3.6 kg of their body weight compared with those who received placebo (imputation method for missing values not stated) [47].

People with overweight or obesity and comorbid diabetes who are treated with phentermine may require reductions in concomitant antihyperglycaemic medication [45]. Phentermine monotherapy should be used with caution in those with hypertension because of the risk of an increase in blood pressure [45], although statistically significant increases have not been universally observed [48]. Phentermine is contraindicated in those with a history of cardiovascular disease and in pregnancy (category X) [45].

Orlistat

Orlistat (brand name Xenical®) is a reversible gastric and pancreatic lipase inhibitor that reduces fat absorption by ~30% at the recommended therapeutic dose of 120 mg three times daily [37]. In the prospective XENDOS clinical trial, orlistat (120 mg three times daily) produced significantly greater weight loss compared with placebo after 4 years (5.2% vs 2.8%; p < 0.001) [37,49]. Orlistat therapy was accompanied by an ~50% risk reduction in progression to T2D in those with impaired glucose tolerance at baseline, although it did not significantly decrease the rate of progression to impaired glucose tolerance or T2D in those with normal glucose tolerance at baseline [49]. Improvements in blood pressure, waist circumference, total cholesterol and LDL cholesterol were also greater with orlistat than with placebo [49]. Even at the over-the-counter dose of 60 mg three times daily (brand name Alli®), improvements in body composition, lipid profiles and blood pressure may be observed [50]. Orlistat has well-known gastrointestinal adverse events, including faecal leakage [37]. It is also associated with a decrease in the absorption of fat-soluble vitamins, which can be addressed by taking a daily multivitamin containing vitamins A, D, E, K and beta-carotene [32,37,49]. Orlistat is contraindicated in pregnancy (category X) [37].

Phentermine/Topiramate Extended Release

The combination of phentermine and topiramate ER (topiramate is an antiepileptic drug used for the treatment of seizures and migraines) received FDA approval for weight management in 2012 (for people with a BMI $\geq$30 or $\geq$27 kg/m^2 and with weight-related comorbidities), as an adjunct to diet and exercise (brand name Qsymia®) [38]. In a randomized controlled trial of topiramate monotherapy (64–384 mg daily) for weight loss in obesity, adverse events related to the central or peripheral nervous system were observed, including paresthaesia, somnolence and difficulty with memory, concentration and attention [51]. Most events were dose-related [51], and topiramate monotherapy has not been pursued further for weight management.

There are four separate doses available for phentermine/topiramate ER combination therapy, but only two are recommended for long-term treatment (7.5 mg phentermine/46 mg topiramate ER once daily and 15 mg/92 mg once daily). The remaining two doses of 3.75 mg/23 mg and 11.25 mg/69 mg once daily are titration doses [38]. When prescribing this drug, a 2-week course of 3.75 mg/23 mg is recommended before the recipient is placed on a 'mid-range' maintenance dose of 7.5 mg/46 mg. It is recommended that the drug is either discontinued or escalated where people have not lost 3% of their body weight after 3 months on 7.5 mg/46 mg. At the mid-dose of 7.5 mg/46 mg, the medication can simply be stopped without titration. At the maximum dose of 15 mg/92 mg, drug discontinuation should be tapered by

Table 1. Change in weight from baseline observed after 1 year of treatment with medications approved for long-term weight management in the USA.

Medication and dose	Clinical data	Baseline characteristics of trial population	Mean weight change from baseline after 1 year	Proportion of participants who achieved ≥5% weight loss after 1 year
Orlistat 120 mg three times daily [37]	Clinical data from five trials	17–78 years (n ≥ 2665)	[−6.0 Kg vs −2.6 Kg] with placebo; placebo-subtracted weight loss 3%	36–55% vs 16–27% with placebo
Phentermine/topiramate ER 15 mg/92 mg [38]	1-year trial, people with obesity (BMI ≥35 kg/m²)	43 years, 83% female, 42 kg/m², 116 kg (n = 1267)	−10.9% vs −1.6% with placebo	67% vs 17% with placebo
	1-year trial, people with overweight or obesity and ≥2 comorbidities	51 years, 70% female, 37 kg/m², 103 kg (n = 2487)	−9.8% vs −1.2% with placebo	70% vs 21% with placebo
Lorcaserin 10 mg twice daily [39]	2-year trial, people with obesity or overweight and ≥1 comorbidity	44 years, 84% female, 36 kg/m², 100 kg, n = 3182	−5.8% vs −2.5% with placebo*	47% vs 23% with placebo*
	1-year trial, people with obesity or overweight and ≥1 comorbidity	44 years, 80% female, 36 kg/m², 100 kg (n = 4008)	—	—
Naltrexone/bupropion 32 mg/360 mg [40]	Four 56-week trials, people with obesity or overweight and ≥1 comorbidity	46 years, 83% female, 36 kg/m² (n = 4536)*	−5.4% vs −1.3% with placebo (COR-I)	42% vs 17% with placebo (COR I)
			−8.1% vs −4.9% with placebo (COR-BMOD)	57% vs 43% with placebo (COR-BMOD)
Liraglutide 3.0 mg [41]	56-week trial, people with obesity or overweight and ≥1 comorbidity	45 years, 79% female, 38 kg/m², 106 kg (n = 3731)	−7.4% vs −3.0% with placebo	62% vs 34% with placebo

Data are from the relevant USA prescribing information: those in square brackets have been calculated using information from the USA label. Doses are once daily unless otherwise stated. Because of differences in study designs and populations, these data are not directly comparable. BMI, body mass index; ER, extended release; NA, not available.
*Pooled data.

Table 2. Change in weight from baseline observed after 1 year of treatment with medications approved for long-term weight management in the USA, in overweight or obese participants with type 2 diabetes.

Medication and dose	Trial	Baseline characteristics of trial population	Mean weight change from baseline after 1 year (%)	Proportion of participants who achieved ≥5% weight loss after 1 year (%)
Lorcaserin 10 mg twice daily [39]	1-year study, people with BMI ≥27 kg/m² and T2D	53 years, 54% female, 36 kg/m², n = 604		**38%** vs 16% with placebo
			−4.5% vs −1.5% with placebo	
Naltrexone/bupropion 32 mg/360 mg [40]	56-week study, people with BMI ≥27 kg/m² and T2D (n = 505)	46 years, 83% female, 36 kg/m² (data pooled across four studies n = 4536)	**−3.7% vs** −1.7% with placebo	**36%** vs 18% with placebo
Liraglutide 3.0 mg [41]	56-week study, people with BMI ≥27 kg/m² and T2D	55 years, 50% female, 37 kg/m², 106 kg, n = 635	**−5.4%** vs −1.7% with placebo	**49%** vs 16% with placebo

Data are from the relevant USA prescribing information. Doses are once daily unless otherwise stated. Because of differences in study designs and populations, these data are not directly comparable. BMI, body mass index; NA, not available; T2D, type 2 diabetes.

Table 3. Change in weight after 1 year of treatment with medications approved for long-term weight management in the USA in people who had previously lost ≥5% of initial body weight.

Medication and dose	Trial	Baseline characteristics of participants (age, gender, BMI and weight before ≥5% weight loss)	Weight after ≥5% initial weight loss	Weight change 1 year after losing ≥5% of initial body weight	Proportion of participants who maintained ≥5% weight loss 1 year after losing ≥5% of initial body weight
Lorcaserin 10 mg twice daily [39,42]	2-year trial, people with obesity or overweight and ≥1 comorbidity (BLOOM)	44 years, 84% female, 36 kg/m², 100 kg	[94.6 kg vs 97.5 kg with placebo]	NA	**68%** vs 50% with placebo
Liraglutide 3.0 mg once daily [41,43]	56-week trial, people with obesity or overweight and ≥1 comorbidity (SCALE Maintenance) [44]	46 years, 81% female, 38 kg/m², 105.9 kg	100.4 kg vs 98.7 kg with placebo	**−4.9%** vs −0.3% with placebo	**44%** vs 22% with placebo

Mean data are presented: those in square brackets have been calculated using information from the relevant publications. Weight loss data are for the intention to treat, modified intention to treat populations or full analysis set, last observation carried forward. Because of differences in study designs and populations, these data are not directly comparable. Initial weight loss in the BLOOM trial was associated with lorcaserin therapy in combination with diet and exercise counselling. Initial weight loss in the SCALE Maintenance trial was associated with a low calorie diet and exercise counselling. BMI, body mass index; NA, not available.

taking a dose every other day for ≥1 week before stopping treatment (in those who have not lost 5% body weight with the maximum dose [38]). The concept of identifying responders and non-responders and acting accordingly is relatively new in the obesity field, and phentermine/topiramate ER was the first obesity medication for which the FDA incorporated non-responder recommendations into the package insert. The Endocrine Society guidelines also include recommendations that alternative weight loss treatments are considered for non-responders or in the case of safety or tolerability issues [18].

The two major pivotal trials of phentermine/topiramate ER (EQUIP and CONQUER) [52,53] were completed in overweight or obese populations with, or at a high risk of, weight-related complications.

In the EQUIP study, in which weight loss in subjects with a BMI ≥35 kg/m² was evaluated, the dose of 15 mg/92 mg produced a weight loss of 10.9% (vs 1.6% with placebo; p < 0.0001)

after 1 year (Table 1) [38,52]. Participants in the CONQUER trial had a BMI of 27–45 kg/m² and ≥2 obesity-related comorbidities. In that study, 1-year weight loss was 7.8% with the 'mid-range' dose of phentermine/topiramate ER (7.5 mg/46 mg once daily) and 9.8% with the maximum dose (15 mg/92 mg once daily; compared with 1.2% with placebo; p < 0.0001 for both doses) [38,53]. Among those participants who entered an extension phase of the CONQUER study (the SEQUEL trial) [54], weight loss was sustained after a total of 108 weeks of phentermine/topiramate ER therapy (−9.3% with 7.5 mg/46 mg; −10.5% with 15 mg/92 mg; compared with 1.8% with placebo; p < 0.0001 for both doses).

In people with a BMI ≥35 kg/m² (EQUIP trial), phentermine/topiramate ER was also associated with significant improvements in waist circumference, blood pressure, lipid profiles and fasting serum glucose compared with placebo [52]. Similar improvements accompanied weight loss with

phentermine/topiramate ER in the CONQUER trial [53]. In the SEQUEL study, the decreases in blood pressure of 3–5 mmHg did not significantly differ across arms; however, phentermine/topiramate ER reduced concomitant antihypertensive and lipid-lowering medication use [54]. Phentermine/topiramate ER also impeded progression to T2D over 108 weeks (up to 76 and 79% in those without diabetes or those with prediabetes and/or metabolic syndrome at baseline, respectively, with the maximum dose of 15 mg/92 mg once daily) compared with placebo [54,55]. In another study of obese adults with severe sleep apnoea, phentermine/topiramate ER 15 mg/92 mg produced greater weight loss and improvements in apnoea-hypopnea index and sleep apnoea symptoms than placebo [56].

The most common adverse reactions associated with phentermine/topiramate ER are paresthaesia (19.9% with phentermine/topiramate ER 15 mg/92 mg, 13.7% with 7.5 mg/46 mg, 4.2% with 3.75 mg/23 mg vs 1.9% with placebo over 1 year), dry mouth (19.1%, 13.5%, 6.7% vs 2.8%, respectively), constipation (16.1%, 15.1%, 7.9% vs 6.1%, respectively), dysgeusia (9.4%, 7.4%, 1.3% vs 1.1%, respectively), insomnia (9.4%, 5.8%, 5.0% vs 4.7%, respectively) and dizziness (8.6%, 7.2%, 2.9% vs 3.4%, respectively) [38]. The occurrence of these events, along with a number of others, is apparently dose-dependent [38]. It is therefore prudent to use the lowest dose that provides adequate weight loss to minimize the occurrence of side effects.

Along with guidelines on how to titrate and when to stop using phentermine/topiramate ER, the FDA also impose a Risk Evaluation Management Strategy programme, intended to help ensure that the medication is used properly [38]. This is because of the teratogenic risk associated with topiramate: foetuses exposed to topiramate in the first trimester have an increased risk of oral clefts (cleft lip with or without cleft palate) [38]. Phentermine/topiramate ER is contraindicated in pregnancy (category X) [38]. It is only available through certified pharmacies, which ensure recipients are aware of the risk and take appropriate precaution.

The European Medicines Agency (EMA) has raised concerns regarding the long-term safety of phentermine/topiramate ER because of potential adverse cardiovascular, psychiatric, cognitive and teratogenic effects [36].

Lorcaserin

In 2012, lorcaserin (brand name Belviq®), a 5-hydroxytriptamine (serotonin; 5-HT)$_{2C}$ receptor agonist, was also approved for weight management in the USA. Lorcaserin is used at a dose of 10 mg twice daily and taken independently of meals [39]. In contrast to phentermine/topiramate ER, no dose titration of lorcaserin is required and no Risk Evaluation Management Strategy programme is in place for this medication. There is a recommended time point in clinical management to discontinue the medication if it has not been effective for an individual. If the recipient has not lost ≥5% of their weight 3 months after having initiated lorcaserin, they are considered a non-responder and the medication should be stopped, as it is unlikely they will achieve and sustain clinically meaningful weight loss with continued treatment [39].

After a 1-year period in the BLOOM and BLOSSOM studies, lorcaserin (10 mg twice daily), in conjunction with a diet and exercise programme, was associated with weight loss of 5.8% (compared with weight loss of 2.5% with placebo; p < 0.001) (Table 1) [39,42,57]. As expected, slightly less weight loss was observed in people with overweight or obesity and T2D in the BLOOM-DM trial of lorcaserin: 4.5% with lorcaserin 10 mg twice daily, versus 1.5% in the placebo group (p < 0.001) after 1 year (Table 2) [39,58].

The proportion of patients achieving ≥5% weight loss after 1 year in the BLOOM trial was significantly higher with lorcaserin 10 mg twice daily than placebo (48% vs 20% p < 0.001) [42]. Among individuals who received lorcaserin and lost ≥5% of their body weight after 1 year, 68% maintained the weight loss after a further year of lorcaserin treatment, compared with 50% of those who were reassigned to receive placebo (p < 0.001; Table 3) [42].

In the BLOOM trial, improvement in blood pressure and lipid levels was observed with lorcaserin versus placebo [39], and in the BLOSSOM study, lorcaserin was associated with a decrease in the concomitant use of medications to treat hypertension and dyslipidaemia [57]. In the BLOOM-DM trial of individuals with T2D, O'Neil et al. [58] noted significant improvements in glycaemic control with lorcaserin 10 mg twice daily compared with placebo [glycated haemoglobin (HbA1c) −0.9% (10 mmol/mol) vs −0.4% (4 mmol/mol) with placebo; p < 0.001] [39,58]. Fasting plasma glucose decreased by 1.5 and 0.7 mmol/l with lorcaserin 10 mg twice daily and placebo, respectively (p < 0.001) [39,58].

Overall, reported discontinuation rates associated with this medication were relatively low and similar to placebo in clinical trials of at least 1 year in duration (8.6% with lorcaserin vs 6.7% with placebo) [39]. Adverse events reported as occurring in ≥5% of people without diabetes with lorcaserin include headache (16.8% vs 10.1%), dizziness (8.5% vs 3.8%), nausea (8.3% vs 5.3%), fatigue (7.2% vs 3.6%), constipation (5.8% vs 3.9%) and dry mouth (5.3% vs 2.3%) [39]. Of the adverse reactions occurring in <5% of people, cognitive impairment (e.g. difficulty with concentration/attention/memory, confusion) was noted in 2.3% of those treated with lorcaserin (vs 0.7% with placebo) [39]. In people with diabetes receiving lorcaserin, the most common adverse reactions were hypoglycaemia (29.3% vs 21.0%), headache (14.5% vs 7.1%), back pain (11.7% vs 7.9%), cough (8.2% vs 4.4%) and fatigue (7.4% vs 4.0%) [39]. In the BLOOM-DM (T2D) trial, symptomatic hypoglycaemia occurred in 7.4% of participants receiving lorcaserin 10 mg twice daily, 10.5% of those receiving lorcaserin once daily and 6.3% in the placebo group [58]. Noting the close to 1.4 mmol/l drop in fasting plasma glucose during the first 2 weeks of treatment [58], it would be important to consider dose adjustments to diabetes medications associated with hypoglycaemia after initiating lorcaserin in a person with controlled diabetes.

Fenfluramine, a discontinued appetite suppressant drug, stimulates both the 5-HT$_{2C}$ receptor (involved in the regulation of satiety) and the 5-HT$_{2B}$ receptor (expressed on the heart valves) in vitro [42]. In 1997, fenfluramine was found to be associated with cardiac valvular abnormalities, in particular thickening of the mitral and aortic valve causing regurgitation,

leading to its withdrawal [42,59]. Lorcaserin clearly differs, as it is highly selective for the 5-HT$_{2C}$ receptor ($\sim$100 times more functionally selective for the 5-HT$_{2C}$ receptor vs the 5-HT$_{2Bs}$ receptor) [42]. In all of the major, FDA-mandated clinical trials of lorcaserin, multiple ECGs of the heart were carried out to examine the possibility of thickening of heart valves. On the basis of 1- and 2-year data from the BLOOM and BLOSSOM studies, respectively, it was determined that lorcaserin was not associated with any significant changes in heart valves relative to placebo [42,57].

Several warnings are included in the package insert for lorcaserin [39], and because of its serotonin-related mechanism of action, caution should be used if combining this medication with other agents that may affect the serotonergic neurotransmitter system [39]. Lorcaserin is contraindicated in pregnancy (category X) [39].

In agreement with Endocrine Society clinical practice guidelines [18], lorcaserin may be a suitable weight loss option for individuals with a history of cardiac arrhythmia or hypertension, as it is not associated with mean increases in blood pressure or pulse [39].

Naltrexone/Bupropion

A sustained-release combination of naltrexone, an opioid receptor antagonist and bupropion, a catecholamine reuptake inhibitor, was approved in September 2014 by the FDA for weight loss in people with overweight or obesity (brand name Contrave®) [40]. Naltrexone/bupropion also received marketing authorization from the EMA in March 2015 (under its European trade name, Mysimba) [60]. Naltrexone and bupropion synergistically stimulate central melanocortin pathways and antagonize inhibitory feedback loops that limit weight reduction, leading to improved energy expenditure and reduced appetite [61]. In a substudy of a phase II trial, naltrexone/bupropion combination therapy was associated with weight loss and with greater reductions in body fat and visceral adipose tissue mass than placebo or either component alone, over 24 weeks [62]. The maximum recommended treatment dose of naltrexone/bupropion is two 8 mg naltrexone/90 mg bupropion tablets taken twice daily, to give a total daily dose of 32 mg naltrexone/360 mg bupropion [40,60]. The weight loss effects of naltrexone/bupropion should be assessed after 12 weeks at the maintenance dose (FDA) or 16 weeks (EMA) and the drug should be discontinued if individuals have not lost at least 5% of their baseline body weight [40,60].

In two phase III trials in obese/overweight participants without diabetes (the COR-I and COR-BMOD studies), this dose was associated with a mean weight loss at week 56 of 5.4% (COR-I) and 8.1% (COR-BMOD) from baseline [40]. Compared with placebo, significant reductions in weight (COR-I: 5.4% vs 1.3%; COR-BMOD: 8.1% vs 4.9%; p < 0.001 in each case) and significant increases in the proportions of individuals achieving ≥5% weight loss (COR-I: 42% vs 17%; COR-BMOD: 57% vs 43%; p < 0.001 in each case) were observed (Table 1) [40]. Similar findings were made in a phase III trial in people with T2D (COR-Diabetes), with a significant reduction in weight (3.7% vs 1.7%; p < 0.001) and a significant increase in the proportion of participants achieving ≥5% weight loss

(36% vs 18%; p < 0.001) at week 56, compared with placebo (Table 2) [40,63]. Naltrexone/bupropion also improved certain cardiovascular risk markers vs placebo (HbA1c, weight circumference, HDL cholesterol and triglycerides) in people with diabetes [63]. Mean weight loss with naltrexone/bupropion was not generally accompanied by a decrease in blood pressure or pulse, which increased by $\sim$1–2 mmHg and 2 beats per min (bpm), respectively, relative to placebo [40]. Thus, the FDA requested a long-term, pre-approval cardiovascular outcomes trial of the drug, the Light Study (ClinicalTrials.gov, NCT01601704). The Light Study was terminated early for reasons other than superiority or harm, with final data yet to be reported [64]. The FDA requires a second, post-marketing clinical trial to evaluate the effect of naltrexone/bupropion on cardiovascular outcomes [64]: this is planned to begin in 2015, with a target completion date of 2022 [64].

The most common treatment-emergent adverse events with naltrexone/bupropion in clinical trials were nausea (32.5% vs 6.7% with placebo), constipation (19.2% vs 7.2%), headache (17.6% vs 10.4%), vomiting (10.7% vs 2.9%) and dizziness (9.9% vs 3.4%); nausea, headache and vomiting were the most common adverse events leading to treatment discontinuation [40]. In clinical practice, nausea and vomiting are common but can be easily controlled by slowing the upward titration of naltrexone/bupropion (note: this recommendation is not included in the medication label). In the present author's experience, many patients do well on lower doses of the medication and do not require full doses to achieve significant weight loss. Naltrexone/bupropion did not appear to be associated with increased risk of depression or suicidality, and in one study [65], depression was reported more frequently with placebo than naltrexone/bupropion (2.5% vs 0.3%; p = 0.014) [65–67], therefore, naltrexone/bupropion could potentially be beneficial for overweight or obese individuals with depression. Close monitoring for clinical worsening of depression, unusual changes in behaviour or suicidal thoughts is recommended, however, in those being treated with antidepressants for any indication [40]. Naltrexone/bupropion is contraindicated in pregnancy (category X) [40].

Liraglutide

Liraglutide 3.0 mg is the first GLP-1 analogue to be approved for long-term weight management in individuals with overweight or obesity. Liraglutide, which has 97% homology to native GLP-1, has been indicated for glycaemic management in adults with T2D at doses of up to 1.8 mg once daily (brand name Victoza®) since 2009 in Europe and 2010 in the USA [35,36]. In phase III trials with liraglutide 1.2 and 1.8 mg, reductions in body weight that accompanied robust improvements in HbA1c profiles [44] led to the clinical development of liraglutide at the higher dose of 3.0 mg for weight management in people with overweight or obesity, with or without diabetes (ClinicalTrials.gov, NCT01272232) [41,43,68]. Liraglutide 3.0 mg (brand name Saxenda®) was approved for chronic weight management in the USA in December 2014 and in Europe in March 2015, as an adjunct to a reduced-calorie diet and increased physical activity, in adults with BMI ≥30 or ≥27 kg/m^2 and ≥1

weight-related comorbidity [41,69]. The FDA recommends that liraglutide 3.0 mg is discontinued after 16 weeks if the recipient has not lost at least 4% of baseline body weight [41]. The EMA recommends its discontinuation if 5% weight loss has not been achieved after 12 weeks at the 3.0 mg dose [69].

GLP-1 is a physiological regulator of appetite and energy intake via GLP-1 receptors in the periphery and brain, and liraglutide-induced weight loss is mediated by its effects on appetite regulation (increases satiety, reduces hunger) and reduced energy intake [70].

The liraglutide 3.0 mg weight management dose identified during phase II development [68] was assessed further in the phase III SCALE Maintenance trial [43]. SCALE Maintenance evaluated the effects of liraglutide 3.0 mg (dose escalated in 0.6 mg increments over 4 weeks) in individuals with overweight or obesity and without diabetes, who had already lost ≥5% weight through low-calorie diet and exercise counselling during a 12-week run-in period. Individuals in both arms continued to receive extensive diet and exercise counselling after randomization. Participants were prescribed a diet with a 500 kcal/day deficit based on their estimated daily energy expenditure and were advised to continue with regular physical activity (150 min/week of brisk walking). Those who were randomized to liraglutide 3.0 mg averaged a further 6.2% reduction in body weight over 56 weeks, while weight in the placebo arm remained relatively unchanged over the same period [mean −0.2%; estimated treatment difference for liraglutide vs placebo, −6.1% (full analysis set, LOCF), −5.2% (all randomized subjects who had a baseline body weight measurement, weighted regression analysis) p < 0.0001] [41,43,69]. Significant improvements in cardiovascular risk markers (waist circumference, HbA1c, systolic blood pressure, triglycerides, high-sensitivity C-reactive protein) were also observed; therefore, liraglutide 3.0 mg may be considered a suitable option for overweight or obese people with comorbid dysglycaemia and/or other cardiovascular risk factors. The long-term glycaemic efficacy and safety of liraglutide 1.8 mg in people with T2D and cardiovascular risk factors is currently under evaluation in the LEADER trial [71].

Gastrointestinal disorders were reported in 73.6% vs 45.2% of participants in the SCALE Maintenance trial treated with liraglutide 3.0 mg or placebo, respectively, but most events were transient and mild to moderate in severity [43]. It has been the present author's experience that slowing titration when necessary and even using a lower target dose, although not part of the label, can greatly reduce nausea and vomiting in susceptible individuals. Consistent with previous observations made in people with T2D [72], liraglutide was also associated with increases in mean pulse rate of +3.6 bpm vs +2.4 bpm with placebo after 56 weeks in SCALE Maintenance, p = 0.2, with the maximum mean increase of 6.6 bpm after 6 weeks of liraglutide therapy [43]. After initial increases, pulse subsequently decreased over the course of the trial, with the level at the end of the trial close to those observed at randomization (baseline) or with placebo [43]. The mechanisms underlying this increase in heart rate have not yet been fully elucidated.

The most common adverse events reported by ≥5% of people receiving liraglutide 3.0 mg vs placebo are nausea (39.3% vs 13.8% with placebo), hypoglycaemia in T2D (23.0% vs 12.7%), diarrhoea (20.9% vs 9.9%), constipation (19.4% vs 8.5%), vomiting (15.7% vs 3.9%), headache (13.6% vs 12.6%), decreased appetite (10.0% vs 2.3%), dyspepsia (9.6% vs 2.7%), fatigue (7.5% vs 4.6%), dizziness (6.9% vs 5.0%), abdominal pain (5.4% vs 3.1%) and increased lipase (5.3% vs 2.2%) [41].

GLP-1 receptor agonists and other incretin-based therapies carry label warnings concerning pancreatitis. In the clinical development programme for liraglutide 3.0 mg, there was a higher incidence of confirmed acute pancreatitis in individuals treated with liraglutide 3.0 mg than with placebo [0.4%, 0.26 events/100 patient-years of risk (PYR) vs <0.1%, <0.1 events/100 PYR]; there were no cases of chronic pancreatitis [73]. The events of acute pancreatitis observed with liraglutide 3.0 mg were generally uncomplicated, and there was no increased risk of pancreatitis with prolonged exposure [73]. Monitoring for signs and symptoms after initiation of liraglutide 3.0 mg is recommended, and liraglutide should be discontinued promptly if pancreatitis is suspected [41,69].

A higher incidence of acute gallbladder disease has been observed with liraglutide 3.0 mg compared with placebo (cholelithiasis: 1.5% vs 0.5%; cholecystitis: 0.6% vs 0.2%) [41].

Certain GLP-1 receptor agonists (liraglutide, exenatide once weekly) carry label warnings regarding thyroid tumours [41,74]. An increased incidence of thyroid tumours was reported in some rodent safety studies of liraglutide and other GLP-1 receptor agonists [41,69,73,74]. In the clinical development programme for liraglutide 3.0 mg, the incidence of malignant thyroid neoplasms was low, occurring in four people (four events, 0.09 events/100 PYR) with liraglutide 3.0 mg and one individual (one event, 0.04 events/100 PYR) with placebo, respectively [73]. The package insert recommends counselling people prescribed liraglutide 3.0 mg regarding the risk of medullary thyroid carcinoma and the symptoms of thyroid tumours [41].

Liraglutide 3.0 mg is contraindicated in those with a personal or family history of medullary thyroid carcinoma, people with multiple endocrine neoplasia syndrome type 2 [41]. It is also contraindicated in pregnancy (category X) [41,69].

Other drugs in this class (e.g. exenatide, lixisenatide) are also associated with body weight reductions [31,75,76], and could emerge for weight management in due course [77]. GLP-1 analogues could represent a new treatment paradigm in anti-obesity therapy, treating obesity and dysglycaemia with a single agent. SGLT2 inhibitors also improve glycaemic control and promote weight loss [78], and have been investigated in overweight or obese individuals without diabetes [79].

Novel Weight–loss Medications in Clinical Development

Until recently, there have been few well-tolerated medications available for effective management of obesity and related comorbidities. With the recent approvals of phentermine/topiramate ER, lorcaserin, naltrexone/bupropion and liraglutide 3.0 mg, and with other medications in the

pipeline, future prospects for pharmacological options are promising, and it is anticipated that this pharmaceutical gap in treatment options will improve. This section considers pharmacotherapies that may emerge shortly in the USA and Europe.

Bupropion/Zonisamide

Bupropion is also under evaluation for weight reduction in combination with zonisamide (planned trade name Empathic™), an anticonvulsant drug. In a phase IIb trial, subjects who received bupropion/zonisamide treatment (360 mg/360 mg) lost 7.5% of their baseline body weight, while those who received placebo lost 1.4% of their baseline weight (p ≤ 0.001). The most common adverse events were headache, insomnia and nausea [80].

Beloranib

Beloranib is from a novel class of weight loss medications that influence metabolism as a result of selective methionine aminopeptidase 2 inhibition. Specifically, methionine aminopeptidase 2 inhibitors reduce fat biosynthesis and increase fat oxidation and lipolysis [81]. In a short (4-week) feasibility trial of 31 obese women, intravenous beloranib 0.1–0.9 mg twice weekly reduced hunger, produced weight loss of 0.8–3.5% (vs 0.6% with placebo; per protocol population), and improved certain cardiovascular risk markers (triglycerides, LDL, C-reactive protein) [81]. Adverse events reported with beloranib include headache, infusion site injury, nausea and diarrhoea [81]. A phase II trial indicated weight loss of 5.5–10.9 kg (5.3–10.6%) with subcutaneous beloranib 0.6–2.4 mg twice weekly over 12 weeks, versus 0.4 kg (0.3%) with placebo (all p < 0.0001 vs placebo; per protocol population) [82]. In this particular study, adverse events of sleep disturbance, nausea and vomiting were noted [82]. Medications of this class are unique in their dual effect to increase fat metabolism and reduce hunger sensations; however, their long-term efficacy and safety remain to be demonstrated.

Possible Implications of Having Multiple Pharmacological Options for Weight Management Approved in Clinical Practice

The availability of a relatively large pharmacological armamentarium for long-term weight management, including drugs with different mechanisms of action, will increase the options for those in whom other weight management medications are contraindicated. There will be more options for alternative medications if the first drug prescribed has been associated with adverse events or has not been effective (weight loss had been insufficient or tapered). Where supported by clinical evidence and within regulatory approvals, it could also provide additional options for combining weight management drugs. Finally, a wider pool of medications from which to select will provide more scope for individualizing weight loss programmes, with clinicians able to select from multiple diet, exercise, surgical and pharmacological treatment combinations to tailor therapy.

Conclusions

Obesity is a heterogeneous disease, and therefore individualizing therapy is important. Treatment approaches should take into account the underlying causes of obesity. If a complication from obesity exists, targeting both the excess weight and the comorbid disease would be advisable to improve benefit. Pharmacological therapies have their place, as well as limitations, in obesity treatment. Promising medications for long-term weight management have recently emerged, adding to the possibilities for bespoke weight loss programmes.

Conflict of Interest

The author has received consulting fees and participation in speakers' bureaus for Eisai, Novo Nordisk, NPS and Takeda; consulting fees for Isis Pharmaceuticals Inc, NaZura, Novo Nordisk, Zafgen, Orexigen and Enteromedics, and grant support from Eisai, Novo Nordisk, NPS, Orexigen, Enteromedics, Shire and Weight Watchers. The author determined the content and scope, and critically revised drafts of the article, had final approval of the published version and accepts accountability for all aspects of the work.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Description of the Edmonton Obesity Staging System classification. © Nature Publishing Group 2009, reproduced with permission from Sharma & Kushner. *Int J Obes (Lond)* 2009; 33: 289–95 [2].

Table S2. Description of the Cardiometabolic Disease Staging System classification. © The Obesity Society 2013, reproduced with permission from Guo F, Moellering DR, Garvey WT. *Obesity (Silver Spring)* 2014; 22: 110–118 [3].

Figure S1. Recommendations for managing overweight or obesity by complications and staging. © Reprinted with permission from the American Association of Clinical Endocrinologists. Garber AJ, Abrahamson, MJ, Barzilay JI, et al. AACE/ACE comprehensive diabetes management algorithm 2015. Endocr Pract 2015; 21: 438–447 [20].

Figure S2. Timeline of availability of different pharmacotherapies for overweight/obesity treatment in the USA. Fenfluramine, serotonin receptor (5-HT$_{2B}$ and 5-HT$_{2C}$) agonist; sibutramine, serotonin-norepinephrine-dopamine reuptake inhibitor; orlistat, gastric and pancreatic lipase inhibitor; phentermine, sympathomimetic amine; topiramate extended release (ER), extended release formulation

of an antiepileptic drug; lorcaserin, serotonin receptor (5-HT$_{2C}$) agonist; naltrexone/bupropion, opioid receptor antagonist (naltrexone) combined with catecholamine reuptake inhibitor (bupropion); liraglutide 3.0 mg (once daily), GLP-1 analogue. Phentermine monotherapy is approved for short-term weight management in the US. Currently, orlistat, naltrexone/bupropion and liraglutide 3.0 mg are approved in Europe.

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