

## Review Article

# Pharmacotherapies for Obesity: Past, Current, and Future Therapies

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Past therapies for the treatment of obesity have typically involved pharmacological agents usually in combination with a calorie-controlled diet. This paper reviews the efficacy and safety of pharmacotherapies for obesity focusing on drugs approved for long-term therapy (orlistat), drugs approved for short-term use (amfepramone [diethylpropion], phentermine), recently withdrawn therapies (rimonabant, sibutramine) and drugs evaluated in Phase III studies (taranabant, pramlintide, lorcaserin and tesofensine and combination therapies of topiramate plus phentermine, bupropion plus naltrexone, and bupropion plus zonisamide). No current pharmacotherapy possesses the efficacy needed to produce substantial weight loss in morbidly obese patients. Meta-analyses support a significant though modest loss in bodyweight with a mean weight difference of 4.7 kg (95% CI 4.1 to 5.3 kg) for rimonabant, 4.2 kg (95% CI 3.6 to 4.8 kg) for sibutramine and 2.9 kg (95% CI 2.5 to 3.2 kg) for orlistat compared to placebo at  $\geq 12$  months. Of the Phase III pharmacotherapies, lorcaserin, taranabant, topiramate and bupropion with naltrexone have demonstrated significant weight loss compared to placebo at  $\geq 12$  months. Some pharmacotherapies have also demonstrated clinical benefits. Further studies are required in some populations such as younger and older people whilst the long term safety continues to be a major consideration and has led to the withdrawal of several drugs.

## 1. Introduction

Management strategies for weight reduction in obese individuals include physical interventions such as exercise, diet, and surgery, behavioural therapies, and pharmacological treatments. These strategies may be used alone or in combination for greater efficacy. Most randomized controlled trials (RCTs) evaluating pharmacotherapies include a calorie-controlled diet, and some also encourage participants to increase their physical activity.

Drugs used to induce weight loss may reduce appetite or increase satiety, reduce the absorption of nutrients, or increase energy expenditure. Weight loss with pharmacotherapies is generally modest, that is, usually 2 to 7.9 kg more than that achieved with placebo treatment [1]. In the past drug therapies available have included thyroid hormone, dinitrophenol and amphetamines, followed by amphetamine analogues, aminorex, and the fenfluramines [1]. More

recently a number of newer agents have been trialed though only orlistat and sibutramine were approved for long-term use ( $\geq 24$  weeks). Following the recent withdrawal of sibutramine this leaves only orlistat (Table 1).

Amongst the drugs marketed for weight loss there have been several instances of market withdrawal due to serious adverse events. The agents involved include dinitrophenol, aminorex, the fenfluramines, phenylpropanolamine and most recently rimonabant. Other drugs such as the amphetamines are severely restricted due to their abuse potential. Fenfluramine and dexfenfluramine were recalled from the world market in 1997 due to concerns of an increased prevalence of valvular heart disease, and the possible association with primary pulmonary hypertension [2–6]. In April 2000, the European Medicines Agency (EMA) recommended the withdrawal of several weight loss drugs from the market including phentermine, amfepramone (diethylpropion) and mazindol due to an unfavourable risk

TABLE 1: Drugs used for weight loss in obesity.

Drug	Introduced	Mechanism of action	Status
Dinitrophenol	1930s	Increases metabolic rate	Withdrawn—risk of neuropathy and cataracts
Amphetamines: dexamphetamine, methamphetamine	1936	Appetite suppression	Banned, restricted or discouraged—dependency and abuse potential, cardiovascular adverse effects
Amphetamine-like analogues: Phentermine, diethylpropion, phenylpropanolamine	1959-US	Appetite suppression	Diethylpropion—available for short-term use ( $\leq 12$ weeks) Phentermine—available for short-term use ( $\leq 12$ weeks) in some countries, withdrawn 2000 (UK) Phenylpropanolamine-withdrawn 2000—increased risk haemorrhagic stroke
Aminorex	1965	Appetite suppression	Withdrawn 1968—pulmonary hypertension
Mazindol	1970s	Appetite suppression	Discontinued 1993—Australia
Fenfluramine	1963-Europe 1973-US	Appetite suppression	Withdrawn 1997—valvular heart disease, pulmonary hypertension
Dexfenfluramine	1985-Europe 1996-US	Appetite suppression	Withdrawn 1997—valvular heart disease, pulmonary hypertension
Orlistat	1998-Europe and US	Decreased fat absorption	Also available <i>over-the-counter</i> in several countries
Sibutramine	1997-US 2001-Europe	Appetite suppression	Temporarily withdrawn 2002 Italy-concerns of raised risk of heart attacks and strokes Increase in contraindications 2010-US, Australia Suspension of market authorization 2010
Rimonabant	2006-Europe		Withdrawn 2009—potential of serious psychiatric disorders

to benefits ratio [7]. This was followed by the voluntary withdrawal of medications containing phenylpropanolamine due to reports of haemorrhagic stroke in women [8] (Table 1).

Rimonabant was approved as an adjunct to diet and exercise for the treatment of obese or overweight patients by the EMEA in 2006. However the FDA never approved its use in the US due to serious safety concerns. Then in January 2009, the EMEA withdrew market authorisation for rimonabant in all countries of the European Union due to an increased risk of psychiatric adverse events, including depressed mood disorders, anxiety, and suicidal ideation [9–11]. Concern was recently raised regarding the safety of sibutramine, following earlier reports of increased systolic and diastolic blood pressure and heart rate [10]. With this concern in mind, the safety was investigated in patients with a history of cardiovascular disease in the Sibutramine Cardiovascular Outcomes Trial (SCOUT). The release of preliminary results from SCOUT led to the compulsory inclusion of contraindications and precautions in the US and Australian product information, whilst the EMEA recommended total suspension of market authorisation for

the drug in Europe [12–16]. Following the subsequent publication of the SCOUT study [17] the FDA considered whether to severely restrict access to the sibutramine or remove it from the market. Sibutramine was subsequently withdrawn by the manufacturer.

Some drugs which had demonstrated positive weight loss potential such as taranabant have been abandoned during late phase clinical trials due to unacceptable adverse events. Whilst axokine, a ciliary neurotrophic factor that was administered as a daily subcutaneous injection, was abandoned due to the low percentage of responders as a result of the development of antibodies in the majority of patients taking the drug [18].

The efficacy and safety of long-term drug therapy is a very important consideration in the management obesity which often requires ongoing therapy to achieve and maintain the weight loss. This paper provides a review of the efficacy and safety of drug therapies for weight loss with at least six months of patient follow-up focusing on randomised controlled trials (RCTs) published over the last 4 years of recent past and current pharmacotherapies, as well as those in late phase clinical trials.

## 2. Measuring Effectiveness of Drug Therapy

There are some challenges in establishing the medium and longer-term efficacy of pharmacotherapies designed to induce weight loss. These include the continuance of patients throughout the entire study duration and the likelihood that patients who report more weight loss will be more likely to complete the study. In an effort to control bias from this source the use of last observation carried forward is commonly used to approximate weight loss for the patients withdrawing from a study [7, 19, 20].

There is also some controversy as to which primary outcome measures are best to evaluate the efficacy of drug therapies, that is, absolute weight loss (in excess of placebo), percentage weight loss, percentage of patients achieving  $\geq 5\%$  or  $\geq 10\%$  weight loss of initial weight, BMI, or waist circumference (WC). The length of time over which weight loss is sustained is also important which implies prolonged follow-up, at least twelve months or if possible longer. In studies involving children, the BMI appears to be the most appropriate measure of effectiveness [21]. Secondary efficacy endpoints are increasingly reported especially in more recent studies, and these include clinical measures such as blood pressure, glycaemic control (blood glucose or HbA1C levels) and cholesterol levels [14, 22, 23].

## 3. Past Drug Therapies and Current Approved Drugs

Drugs that have been prescribed or evaluated for obesity may reduce fat absorption or regulate satiety via their action on serotonin, noradrenergic or dopaminergic or the cannabinoid receptor systems in the brain (Table 2) [1, 3, 24–26].

**3.1. Amphetamines and Amphetamine-Like Analogues.** Amphetamines and amphetamine-like analogues (phentermine, diethylpropion, phenylpropanolamine) are indirect-acting sympathomimetic agents that act by releasing noradrenaline (NA) from presynaptic vesicles in the lateral hypothalamus [1]. Mazindol, a related but discontinued drug, blocks the reuptake of NA by presynaptic neurons (Table 2) [1]. The increase in NA concentration within the synaptic cleft results in the stimulation of  $\beta_2$ -adrenergic receptors and a resultant inhibition of appetite.

There is little data from large randomized controlled trials (RCTs) relating to the long-term efficacy or safety of amphetamines and amphetamine-like analogues, especially when used as monotherapy. These drugs have limited use in the routine management of obesity and are not currently approved for long-term use. *Phentermine* has been available since the late 1950s and is approved for short-term use in the US and Australia (Table 2). It has been evaluated as both monotherapy and as combination therapy though not in large-scale studies [27, 28]. A 36-week RCT in 108 overweight women demonstrated a mean weight loss of 12.2 kg (13%) with phentermine (30 mg daily) compared to 4.8 kg (5.2%) with placebo ( $P < .001$ ). Phentermine has been used in combination with fenfluramine and with fluoxetine [29].

Combination therapy with phentermine (15 mg) and fenfluramine (60 mg), demonstrated significantly more weight loss than placebo in a 28-week RCT (15.5% versus 4.9%,  $P < .001$ ) [28]. Phentermine is currently under evaluation in combination with topiramate and with pramlintide (*see Drug Monotherapies and Combination Therapies in Clinical Development*).

**3.1.1. Diethylpropion (amfepramone).** another amphetamine-like analogue has been available for weight loss since the early 1960s; however there are few if any RCTs of its long-term use especially with large sample sizes [30, 31]. Diethylpropion (75 mg daily) demonstrated significantly greater weight loss in a small 24-week study of 20 patients than placebo (11.6 kg versus 2.5 kg,  $P < .01$ ) [31]. Recently, diethylpropion (50 mg twice a day) was shown to be more effective than placebo in a small 6-month RCT with 69 obese adult patients (9.3 kg [95% CI 7–11.5 kg] versus 3.1 kg [95% CI 1.8–4.3 kg],  $P < .0001$ ) [32]. Greater than 5% weight loss was achieved in 67.6% of diethylpropion patients and 25.0% of those receiving placebo ( $P = .0005$ ). After further 6 months during an open label period of the study patients who were originally in the diethylpropion group lost a mean of 10.1 kg (95% CI 7.5–12.8). The most common side effects were dry mouth and insomnia ( $P = .02$  and  $P = .009$ , respectively). These were experienced in the first 3 months but become less apparent with continuing treatment [32].

**3.2. Fenfluramines.** Fenfluramine and dexfenfluramine elevate serum levels of serotonin (5HT) in the central nervous system by stimulating 5HT release and inhibiting its reuptake (Figure 1). Increased levels of 5HT appear to stimulate the hypothalamus, which controls satiation as well as mood, sleep, body temperature and other vital functions. These agents also activate melanocortin 4 receptors that in turn stimulate activation of 5-HT<sub>2C</sub> receptors, producing an increased release of 5HT within the hypothalamic-pituitary-adrenal axis which is claimed to lead to hypophagia and anorexia [33–36].

A meta-analysis of RCTs with fenfluramine and dexfenfluramine demonstrated higher weight loss than placebo following up to 12 months of treatment. The greatest efficacy was shown following 3 months treatment, 3.7 kg weight loss [37].

Although RCTs with fenfluramines (fenfluramine and dexfenfluramine), either alone [38, 39] or with phentermine [40], demonstrated significant weight-loss, they were withdrawn from the market due to increased reports of valvular heart disease and primary pulmonary hypertension [2, 3, 29, 41–43]. The prevalence rates of both valvular heart disease and primary pulmonary hypertension were higher following longer exposure to the fenfluramines [3].

### 3.3. Antidepressants

**3.3.1. Fluoxetine, Bupropion.** Fluoxetine, a selective serotonin reuptake inhibitor (SSRI) that augments 5HT within the central nervous system has been prescribed *off-label* for weight loss. Although significant weight loss was reported

TABLE 2: Central mechanisms of action of anti-obesity pharmacotherapies.

Central Subsystem	Drugs targets	Possible receptor subtypes involved
Monoamine system (indirect agonists and subtype selective receptor antagonists)	Single therapies	
	(i) Dex/fenfluramine (WD), fluoxetine	(i) 5HT
	(ii) Phentermine/Diethylpropion (ST)	(ii) DA, NA
	(iii) Sibutramine	(iii) $\alpha_1$ , $\beta_1$ , $\beta_3$ adrenergic and 5HT <sub>2B/C</sub>
	(iv) Bupropion	(iv) DA, NA
	(v) Tesofensine	(v) DA, NA, 5HT
Opioid system ( $\mu$ -opioid receptor antagonist)	(vi) Lorcaserin	(vi) 5HT <sub>2C</sub>
	(i) Naltrexone	(i) $\mu$ -opioid
	(ii) Topiramate	(ii) AMPA/kainite glutamate*
Cannabinoid system	(iii) Zonisamide	(iii) 5HT, DA*
	Single therapies:	
Monoamine/Opioid system	(i) Rimonabant (WD)	(i) CB <sub>1</sub>
	(ii) Taranabant (DC)	(ii) CB <sub>1</sub>
Neuropeptide Y/Agouti-related peptide system	Bupropion/naltrexone	(i) DA, NA/ $\mu$ -opioid
	Bupropion/zonisamide	(ii) DA, NA/5HT, DA*
	Pramlintide/metreleptin	(i) Calcitonin receptor*/Leptin receptor

5HT: serotonergic, DA: dopaminergic, NA: noradrenergic, WD:withdrawn; DC: phase III trials discontinued; ST: short term;\*: unknown; AMPA:  $\alpha$ -amino-3-hydroxyl-5-methyl-4-isoxazole-propionate.

with 60 mg of this agent in short-term studies of 6–8 weeks, with maximum weight loss achieved at 12–20-weeks, this is followed by a regain in bodyweight [44–47]. Most RCTs have not shown a significant difference when fluoxetine was compared to placebo at 52 weeks [46, 48]. Significantly greater weight loss has however been demonstrated at 8 months when fluoxetine was used in combination with dexfenfluramine (13.4 versus 6.2 kg with placebo) [49]. In clinical practice fluoxetine 10–20 mg has been used with phentermine (i.e., *phen-pro* or *phen-flu*) but there are no RCTs of either the long-term efficacy or safety of this combination [50]. A retrospective chart review suggested this combination is not as effective as fenfluramine with phentermine [51]. Fluoxetine generally has a tolerable safety profile with reported adverse events of headache, asthenia, nausea, diarrhoea, somnolence, insomnia, nervousness, sweating, and tremor [47].

3.3.2. *Bupropion*. is another antidepressant which inhibits reuptake of dopamine (DA) and noradrenaline (NA) resulting in a loss of appetite and decreased food intake [52] and modest weight loss in obese people [53–56]. The efficacy of bupropion as a sustained release (SR) formulation was demonstrated at 48 weeks in obese patients [53]. Weight loss was dose dependent with 7.5% initial weight loss for subjects taking 300 mg bupropion-SR and 8.6% with 400 mg [53]. Bupropion-SR was generally well tolerated, and weight loss was maintained at 48 weeks. A meta-analysis of weight loss treatments which included 5 bupropion studies reported a mean weight loss of 2.8 kg (95% CI, 1.1 to 4.5 kg) at 6 to 12 months with bupropion compared to

placebo [56] (Table 3). Although bupropion is not approved for weight loss, it has been used *off-label* and is currently under evaluation as combination therapy with naltrexone, a  $\mu$ -opioid receptor antagonist and zonisamide, a GABA receptor activator (see *Drug Monotherapies and Combination Therapies under Investigation*).

3.4. *Orlistat*. Orlistat (a gastrointestinal lipase inhibitor) is a synthetic drug derived from a naturally occurring lipase inhibitor. It does not directly act on appetite as other obesity pharmacotherapies, rather it decreases fat absorption by binding to pancreatic lipase, the principle enzyme that hydrolyses triglyceride (Table 2) (Figure 1) [26]. A detailed review of the efficacy of orlistat treatment in obesity has previously been described [1]. The long-term efficacy of orlistat (120 mg three times daily) for weight loss has been demonstrated in several RCTs of 2- to 4- year therapy compared to placebo [61–64], as well as improvements in blood pressure, insulin resistance, and serum lipid levels [57, 64–66]. Several systematic reviews in adults [56, 57, 67–70] and a systematic review with 2 short-term studies in adolescents [71] demonstrated significantly more weight loss with orlistat than placebo, 6.2 kg (95% CI, 1.7 to 14.0 kg).

The most commonly experienced side effects of orlistat are gastrointestinal and include diarrhoea, flatulence, bloating, abdominal pain, and dyspepsia [25, 66, 70]. Recently, severe liver injury has been reported. The FDA received 32 reports of serious liver injury in patients using orlistat between 1999 and October 2008, including 6 cases of liver failure [72]. This prompted the FDA to undertake a review of the safety of orlistat treatment. The review identified a

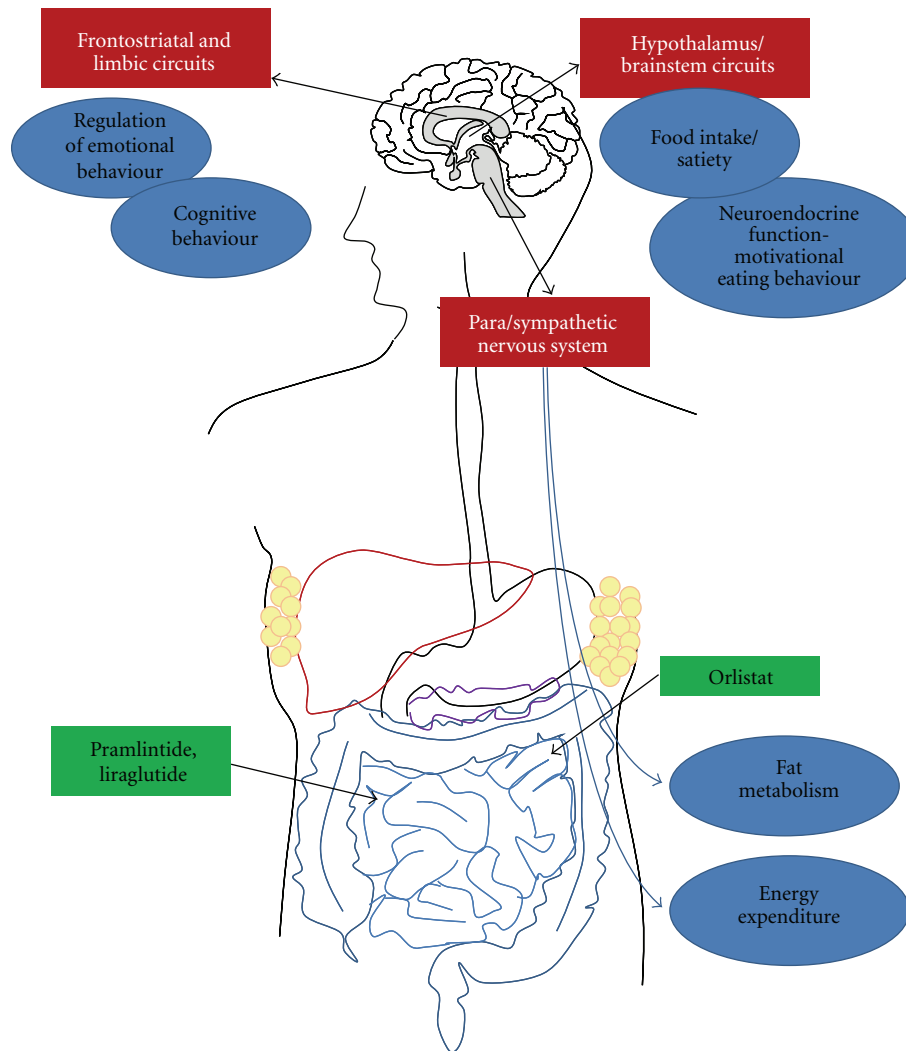


FIGURE 1: Overview of central and peripheral functions associated with anti-obesity pharmacotherapies.

total of 13 cases of severe liver injury (12 foreign reports with orlistat 120 mg and a US report with the lower dose *over-the-counter* product [orlistat 60 mg]) and in May 2010 led to a label revision and the addition of a warning of severe liver injury.

**3.5. Sibutramine.** Sibutramine, a 5HT and NA uptake inhibitor, was originally developed as an antidepressant and subsequently found to reduce appetite [26]. It has 2 active metabolites, which inhibit NA and 5HT uptake (and to a lesser extent DA) without any direct effect on neuronal NA, DA and 5HT release. It has been suggested that sibutramine has a dual action to facilitate weight loss, an anorectic effect suggested to be mediated through the central  $\alpha_1$  and  $\beta_1$  adrenergic receptors and thermogenic effects through  $\beta_3$  adrenergic receptors peripherally [73].

Maximal weight loss occurs by 6 months with sibutramine treatment [74, 75] and was dose related [74, 76, 77]. Sibutramine has consistently demonstrated significantly more weight loss than placebo in several RCTs with  $\geq 1$

year of therapy [1, 74, 75, 78–80]. Systematic reviews which included 7 sibutramine RCTs reported 4.3 kg (95% CI: 3.6 kg to 4.9 kg) or 4.6% (95% CI: 3.8% to 5.4%) greater weight loss than placebo [58, 70] (Table 3). There was  $\geq 10\%$  weight loss in 18% (95% CI: 11% to 25%) more sibutramine patients than placebo [58, 70]. Attrition rates in sibutramine studies were approximately 30%–40% [58]. In RCTs of 3 to 12 months that compared sibutramine and orlistat, the weighted mean difference in weight loss was 2.2 kg (95% CI 0.5–3.9) in favour of sibutramine [59]. A systematic review in adolescents which included 5 short-term studies has demonstrated significantly more weight loss with sibutramine than placebo, 5.3 kg (95% CI, 3.5 to 7.2 kg) [71].

Although treatment with sibutramine has resulted in lowered concentrations of cholesterol and triglycerides, blood pressure and pulse rate may be increased [57]. Increases in diastolic blood pressure (DBP) with sibutramine were reported in 2 meta-analyses, one in hypertensive patients which included 2 studies where the weighted mean difference was +3.2 mm Hg (95%CI +1.4 to +4.9 mm Hg)

TABLE 3: Comparative efficacy of pharmacotherapy from recent meta-analyses of long-term studies in adults (12 months or more).

Drug	No. of studies	Total subjects	Mean weight difference (kg) (95% CI)	Reference
Rimonabant	4	Placebo: ~1600 Rimonabant: ~2500	4.7 (4.1, 5.3)	[9, 57, 58]
Orlistat	14	Placebo: 4509 Orlistat: 4948	2.9 (2.5, 3.2)	[57, 58]
Sibutramine	7	Placebo: 699 Sibutramine: 837	4.2 (3.6, 4.8)	[57, 58]
Sibutramine Orlistat	5	Sibutramine: 229 Orlistat: 249	3.4 (2.3, 4.6)	[59]
Bupropion*	5	Bupropion: 618 Placebo: 344	2.8 kg (1.1 to 4.5 kg)	[56]

CI: confidence interval; \* 6 to 12 month studies.

Note: another meta-analysis of 5 studies with rimonabant compared to placebo, did not provide mean weight difference in kg, however the odds ratio was 1.07 (95% CI 0.9, 1.3) [60].

[66], whilst another reported a placebo-controlled change in DBP of +1.7 (95% CI 0.7, 2.6) and a small nonsignificant change in systolic BP (+0.5 mm Hg, 95% CI -1.1, 2.1) [81]. Although sibutramine may reduce body weight by a similar amount as orlistat in hypertensive patients, it does not have the same beneficial effects on BP [65].

Weight loss was significantly greater at 1 year when sibutramine was combined with lifestyle modification ( $10.8\% \pm 10.2\%$ , mean  $\pm$  SD,  $P < .05$ ) and diet ( $16.5\% \pm 8.0\%$ ,  $P < .05$ ) than when sibutramine was used alone ( $4.1\% \pm 6.3\%$ ) [82]. Although the addition of orlistat to sibutramine therapy does not appear to enhance weight loss [83, 84], combination therapy with the amylin analogue pramlintide is producing promising results [85] (see Titled *Drug Monotherapies and Combination Therapies under Investigation*).

Apart from increases in BP and heart rate the most common side-effects reported with sibutramine are dry mouth, constipation, and headache [57, 66].

Following the report of two sibutramine-related deaths in Britain and serious side effects in France, the EMEA demanded a long-term trial in patients at high risk of cardiovascular disease hence the Sibutramine Cardiovascular Outcome trial (SCOUT) was initiated [86, 87]. SCOUT is a double-blind, randomized, placebo-controlled outcome trial in 10,742 overweight or obese patients at high-risk for cardiovascular disease that commenced recruitment in December 2002. Of the total patients 97% had cardiovascular disease, 88% had hypertension, and 84% had type 2 diabetes [88]. Until recently the only published results from SCOUT were from the 4–6-week lead in period [13–15, 87, 89]. At 6 weeks there was a significant reduction in body weight (2.2 kg), waist circumference (2.0 cm), systolic (3.0 mm Hg) and diastolic blood pressure (1.0 mm Hg) with sibutramine treatment, however pulse rate was increased by 1.5 bpm (all  $P < .001$ ) [89]. Results were similar for the diabetic patients in the study, that is, a 2.1 kg decrease in weight and decrease in blood pressure by 3.5/1.0 mm Hg with sibutramine compared to placebo [14]. A total of 9,800 patients were followed up for six years. The preliminary data released in late 2009, suggested that sibutramine was

associated with a higher rate of CV events than placebo [90], whilst data from a FDA early communication indicated that there was an increased rate of CV events (heart attacks, strokes, resuscitated cardiac arrest, CV death) in patients with cardiovascular disease and diabetes (11.9% placebo, 13.9% sibutramine, hazard ratio 1.18, 95% CI 1.02–1.35,  $P = .023$ ) [91]. The EMEA concluded that the benefits of sibutramine did not outweigh the risks and recommended that all marketing authorisations for medicines containing sibutramine should be suspended throughout Europe [10]. The FDA initially allowed sibutramine to be available, but asked for stronger warnings on the product labels [92]. The warning recommended that sibutramine should not be used by people who have a history of stroke or heart attacks and uncontrolled high blood pressure. The recent publication of the SCOUT study which had a mean follow-up period of 3.4 years reported a large number of patients that discontinued treatment (40.2% sibutramine, 42.3% placebo), a higher risk of cardiovascular outcome with sibutramine (11.4% versus 10%, hazard ratio 1.16 95% CI 1.03–1.31,  $P = .02$ ). [17] In particular there was a higher rate of nonfatal MI and nonfatal stroke for sibutramine (4.1% and 2.6%, resp.) than placebo (3.2% and 1.9%).

A 3-year prospective observational study of 15,686 patients prescribed sibutramine in New Zealand has not demonstrated a higher risk of death from a cardiovascular event [93]. The FDA is currently reviewing the potential benefits and risks of sibutramine [94].

**3.6. Rimonabant.** Rimonabant, an endocannabinoid receptor (subtype 1) blocker, was developed as a result of observations on the appetite stimulation associated with recreational cannabis use (Table 2). The drug has a range of both central and metabolic peripheral effects and had also been investigated for smoking cessation [26, 95].

Attrition rates in a pooled study of 5,580 patients without diabetes and 1,047 patients with diabetes taking rimonabant 20 mg daily for one year and a hypocaloric diet were approximately 40% [96]. In the nondiabetic patient subgroup, rimonabant reduced body weight by 6.5 kg compared to

placebo ( $P < .001$ ). Weight-loss of  $\geq 5\%$  was achieved in 50.8% of the treatment group, and waist circumference was reduced by 6.4 cm compared to placebo ( $P < .001$ ) (Table 4) [96]. There was an improvement in glycaemic control in diabetic patients with a reduction in mean HbA1C levels of 0.6% ( $P < .001$ ) [96]. Discontinuation due to side-effects occurred in 13.8% of rimonabant patients and in 7.2% of placebo patients. The most commonly experienced adverse events were gastrointestinal disorders, mood alterations with depressive symptoms, anxiety, dizziness, nausea, and upper respiratory tract infections.

Four large Rimonabant in Obesity and Related Metabolic Disorders (RIO) Phase III studies (*RIO-Europe*, *RIO-North America*, *RIO-Diabetes*, *RIO-Lipids*) were included in two meta-analyses and a systematic review to investigate the efficacy and safety of rimonabant in improving cardiovascular and metabolic risk factors in overweight patients [9, 60] (Table 3). Compared with placebo, rimonabant (20 mg) produced a 4.9 kg (95% CI 4.3, 5.0) greater reduction in body weight as well as improvements in waist circumference ( $-3.84$  cm, 95% CI  $-4.26$ ,  $-3.42$ ), high-density lipoprotein cholesterol, triglyceride levels, and systolic and diastolic BP [60]. A subsequent meta-analysis which included the 4 RIO studies provided evidence of the likelihood of experiencing serious side effects with rimonabant [9]. The odds ratio (OR) for depression was 2.51 (95% CI, 1.23–5.12) and 3.03 (95%, 1.09–8.42) for anxiety [9]. A systematic review and meta-analysis reported that the 20 mg rimonabant dose was associated with an increased risk of adverse events (RR 1.35; 95% CI 1.17–1.56), increased discontinuation rate (RR 1.79; 95% CI 1.35–2.38), and psychiatric (RR 2.35; 95% CI 1.66–3.34), and nervous system adverse events (RR 2.35; 95% CI 1.49–3.70) [100]. The number needed to harm (NNH) for psychiatric adverse events was 30 [100]. In a comparison with other pharmacotherapies the risk ratios for discontinuation in RCTs due to adverse events were significantly elevated for rimonabant (2.00; 95% CI 1.66–2.41) and orlistat (1.59; 95% CI 1.21–2.08), but not sibutramine (0.98, 95% CI 0.68–1.41) [20]. The risk difference was largest for rimonabant (7%, 95% CI: 5%–9%; NNH 14, 95% CI: 11–19) compared with placebo, followed by orlistat (3%, 1%–4%; NNH 39, 95% CI: 25–83), while no significant difference was seen for sibutramine (0.2%, 95% CI:  $-3\%$  to 4%; NNH 500).

In late 2008, the manufacturers of rimonabant announced that all clinical research studies would be stopped permanently. This announcement followed a decision by the EMEA to withdraw marketing of the drug as the risks especially of psychiatric side effects were considered to outweigh the drug's benefits [101].

**3.7. Systematic Reviews Comparing Several Drug Therapies.** Several meta-analyses and systematic reviews have demonstrated that pharmacotherapy in combination with a low calorie diet and in some cases exercise generally results in a maximum weight reduction at six months of 1–9.6 kg, maintenance of weight loss with continued therapy, and a regain in weight after drug therapy is discontinued [7, 30]. The largest mean effect sizes were demonstrated with amphetamines, fenfluramines and sibutramine, though no

drug demonstrated clear superiority [30, 58] and most of the drugs have been prescribed for a limited duration. A systematic review which included 14 RCTs with orlistat, 7 RCTs of sibutramine and 4 RCTs with rimonabant compared to placebo, reported 2.9 kg greater weight loss with orlistat than placebo, 4.2 kg for sibutramine and 4.7 kg for rimonabant (Table 3). Patients on active drug therapy were significantly more likely to achieve  $\geq 5\%$  and  $\geq 10\%$  weight loss [57]. Continuation on treatment was a problem with attrition rates averaging 30%–40% within 12 months [57].

In adolescents a meta-analyses of RCTs with orlistat and sibutramine demonstrated a mean decrease in weight between the intervention and control groups of 5.25 kg (95% CI: 3.03–7.48) after a minimum follow-up of 6 months [71]. Systemic reviews of pharmacotherapy for overweight and obese children, adolescents, and older adults only include a limited number of mainly short-term studies [21, 102–104] hence, there is a lack of high-quality evidence to support the efficacy and safety of drug therapy in these populations.

## 4. Drug Monotherapies and Combination Therapies under Investigation

Some already marketed drugs (that are approved for other indications) and several new agents are currently being evaluated for the management of obesity [25, 105, 106]. These include tesofensine, a pharmacological agent that targets the inhibition of NA, DA, and 5HT reuptake and, liraglutide a glucagon-like peptide-1 analog and lorcaserin the selective serotonin 2C (5-HT<sub>2C</sub>) receptor agonist (Table 2). There are also several combination drug therapies in Phase III trials including bupropion and naltrexone, bupropion and zonisamide, phentermine and topiramate, and pramlintide and metreleptin. Some drugs that were in late phase trials such as axokine, a naturally occurring re-engineered human protein known as ciliary neurotrophic factor, taranabant a CB<sub>1R</sub> inverse agonist, and ecopipam a selective dopamine D<sub>1</sub>/D<sub>5</sub> antagonist have been abandoned, the latter two due to an increase in psychiatric adverse events. There are also some weight loss medications that have previously been used in the management of diabetes that are being evaluated for weight loss, that is, pramlintide, liraglutide, and exenatide.

**4.1. Pramlintide.** Pramlintide, a synthetic analog of the pancreatic hormone amylin, was originally used for the treatment of type 1 and 2 diabetes. It has been associated with reduced, appetite, food intake and enhanced satiety through delayed gastrointestinal motility and is currently under investigation as a potential treatment for obesity [25, 105]. In a 16-week dose escalation RCT 3.7% mean weight loss was demonstrated with pramlintide 240  $\mu$ g given as a subcutaneous (SC) injection compared to placebo ( $P < .001$ ) and  $\geq 5\%$  weight loss was achieved in 31% of patients ( $P < .001$ ) [107]. In obese patients participating in a 4-month RCT of pramlintide at doses of 120, 240, and 360  $\mu$ g administered two or three times a day, followed by a single blind extension to 1 year, weight loss was regained in the placebo group but maintained or continued in all but the

TABLE 4: Recent randomised controlled trials of weight loss therapies with 6-month followup.

Drug	No. subjects	Absolute weight loss (kg) (95% CI)	≥5% weight loss	≥10% weight loss	Change in WC (cm)	Serious adverse events	Reference
Bupropion (400 mg) plus Naltrexone	Placebo-85	0.9 ± 0.5	15%	2%	-0.9 ± 0.9		[22]
	N 48 mg-56 B-60	1.1 ± 0.7	10%	2%	-3.8 ± 1.2	Nausea: 3.5% P, 28.1% BN16, 39.7% BN32, 41% BN48	
	BN16 mg-64	2.6 ± 0.6	26%	7%	-2.9 ± 1.1		
		5.1 ± 0.6 <sup>P</sup> < .05	52%, <sup>P</sup> < .05	17%, <sup>P</sup> < .05	-3.7 ± 1.1, <sup>P</sup> < .05		
	BN 32 mg-63	5.1 ± 0.6 <sup>P</sup> < .05	51%, <sup>P</sup> < .05	19%, <sup>P</sup> < .05	-4.6 ± 1.0, <sup>P</sup> < .05		
BN 48 mg-61	4.0 ± 0.6 <sup>P</sup> < .05	39%, <sup>P</sup> < .05	15%, <sup>P</sup> < .05	-4.7 ± 1.2, <sup>P</sup> < .05			
Bupropion (120 mg/360 mg) + Zonisamide (360 mg/360 mg)	729 (total)	1.4 <sup>^</sup> P	15% <sup>^</sup> P	4% <sup>^</sup> P	NA	NA	[97]
		3.2 <sup>^</sup> Z120	27% <sup>^</sup> Z120	9% <sup>^</sup> Z120			
		5.3 <sup>^</sup> Z360	44% <sup>^</sup> Z360	18% <sup>^</sup> Z360			
		2.3 <sup>^</sup> B360	21% <sup>^</sup> B360	11% <sup>^</sup> B360			
		6.1 <sup>^</sup> ZB120	47% <sup>^</sup> ZB120	25% <sup>^</sup> ZB120			
	<sup>P</sup> < .001	( <sup>P</sup> < .05) 60% <sup>^</sup>	<sup>P</sup> < .05				
	7.5 <sup>^</sup> ZB360	ZB360 ( <sup>P</sup> < .05)	32% <sup>^</sup> ZB360				
	<sup>P</sup> < .001		<sup>P</sup> < .05				
Rimonabant	P-417	0.5 (0.3, 1.3)	NR	NR	1.0 (-0.2, 1.9)	Psychiatric: 28.4% P, 43.4% R, <sup>P</sup> < .001	[98]
	R-422	4.3 (3.5, 5.1)			4.5 (-3.7, -5.4), <sup>P</sup> < .001	Severe psychiatric: 3.5% P, 4.8% R, <sup>P</sup> = .52	
Rimonabant*	3165 (total)	Placebo 1.6	19.7%	7.8%	6.4	Depression: 0.8% P, 1.9% R, NS	[96]
		R 6.5	50.8%, <sup>P</sup> < .001	27%, <sup>P</sup> < .001	2.5	NS Anxiety: 0.3 P, 1.0% R, NS	
Tesofensine	Placebo-52	2.2 (0.9, 3.5)	13 (29%)	3 (7%)	-2.4 (0.7, 4.2)	Anger and hostility: 4% P, 14.3% T 1 mg, <sup>P</sup> = .018	[99]
	T 0.25 mg-52	6.7 (5.4, 8.0), <sup>P</sup> < .0001	29 (59%)	17 (35%)	-5.9 (4.0, 7.8), <sup>P</sup> = .007	Increased confusion: P-NA,	
	T 0.5 mg-50	11.3 (9.9, 12.7), <sup>P</sup> < .0001	41 (87%)	25 (53%)	-9.4 (7.7, 11.0), <sup>P</sup> < .0001	T 0.5 mg <sup>P</sup> = .015,	
	T 1.0 mg-49	12.8 (11.6, 14.1), <sup>P</sup> < .0001	42 (91%)	34 (74%)	-9.3 (7.6, 11.0), <sup>P</sup> < .0001	T 1 mg <sup>P</sup> = .0003	

Absolute weight loss: weight loss from baseline; NS: not significant; NR: not recorded; WC: waist circumference; P: placebo; B: bupropion; N: naltrexone; Z: zonisamide; R: rimonabant; T: tesofensine; NA: not available; \* pooled non-diabetic patients; #mean ± standard deviation; ^ estimated absolute weight based on mean baseline weight of 100 kg.

pramlintide 120  $\mu$ g twice daily arm [108]. Nausea was the most common adverse event.

**4.2. Glucagon-Like Peptide-1 (GLP1) Analogues: Liraglutide, Exenatide.** Liraglutide and exenatide are glucagon-like peptide-1 (GLP1) analogues developed and approved for the treatment of type 2 diabetes (Table 2) [109]. Phase III trials of liraglutide have demonstrated beneficial weight loss in obese patients. These analogues have a dual mechanism of action, that is, on the gastrointestinal (GI) tract and the brain. Signals from the GI tract are sent to the brain to increase the secretion of leptin, resulting in suppressed appetite, energy intake and a delay in gastric emptying. A key benefit with long-term use of liraglutide and exenatide is a decrease in HbA1c levels and systolic BP [110, 111]. A recent 20 week dose-ranging RCT of liraglutide (1.2, 1.8 mg, 2.4 mg, 3.0 mg) in comparison with orlistat (120 mg) treatment in 564 nondiabetic obese patients demonstrated a mean weight loss of 4.8 kg, 5.5 kg, 6.3 kg, and 7.2 kg, resp. compared with 2.8 kg with placebo and 4.1 kg with orlistat ( $P = .003$  for 1.2 mg,  $P < .0001$  for 1.8–3.0 mg liraglutide) [112]. Higher doses of liraglutide (2.4 and 3.0 mg) demonstrated significantly greater mean weight loss than orlistat. The most common adverse events with liraglutide were nausea and vomiting, but these were not significantly different to the placebo group. Patients treated with liraglutide also showed a significant reduction in blood pressure and the prevalence of prediabetes (84%–96%).

Exenatide is currently only in Phase II trials [113] for obesity but early results from an open-label study have demonstrated weight loss as well as an improvement in glycemic control [114].

**4.3. Taranabant.** Taranabant a cannabinoid CB-1 receptor (CB1R) inverse agonist which reduces appetite and increases energy expenditure has been evaluated for the treatment of obesity [115]. It demonstrated greater weight loss with higher doses in a 12 week RCT that assessed its safety and efficacy. Four Phase III trials have been published, two assessed the risk/benefit profile of low and high doses and one included patients with type 2 diabetes [23, 116–118]. Mean weight loss after 1 year of taranabant was 5.0 kg with the 0.5 mg dose, 5.2 kg with the 1mg, 6.4 kg with the 2 mg compared to 1.4 kg for placebo (all  $P < .001$ ) [118]. Significantly more patients achieved  $\geq 5\%$  and  $\geq 10\%$  loss of baseline body weight with taranabant than placebo ( $P < .001$  for all doses) (Table 5). Approximately 80% of patients from each taranabant dose group experienced one or more adverse events [118].

A study using higher doses (2 mg, 4 mg, and 6 mg) achieved greater mean weight loss at 1 year of treatment which persisted to 2 years (Table 5) [23]. Although weight loss with the highest dose of 6 mg proved to be the most efficacious after 1 year of treatment, the adverse events were significantly increased with increasing doses particularly serious psychiatric events which included depression, depressive mood, anxiety, anger, and aggression [23]. The odds ratios for suicidality with increasing doses of taranabant after 1 year treatment were 1.74 (95% CI 0.87–3.51) with the 2 mg dose,

2.16 (95% CI 1.10–4.25) for 4 mg, and 2.34 (95% CI 1.11–4.96) with the 6 mg. Hence, only the lower doses (2 mg and 4 mg) were used for the remainder of the study.

The overall safety and efficacy profile of taranabant from the Phase III trials did not support its further development in the treatment of obesity, and clinical trials were ceased [23, 117, 119].

**4.4. Lorcaserin.** Lorcaserin is a selective serotonin 2C receptor agonist (5-HT<sub>2C</sub>), sharing characteristics similar to fenfluramines, which acts through another serotonin receptor (5-HT<sub>2B</sub>) that has been associated with cardiac valvular disease [124] (Table 2).

Recent clinical trials with lorcaserin have demonstrated effective weight loss compared to placebo along with a good safety profile [125, 126]. Results from two recently presented pivotal Phase III trials, BLOOM (Behavioral modification and Lorcaserin for Overweight and Obesity Management) and BLOSSOM (Behavioral modification and Lorcaserin Second Study for Obesity Management) indicated greater weight loss with lorcaserin than with placebo (Table 5) [120, 127, 128]. In these RCTs, 6380 non-diabetic patients aged 18–66 years with a BMI 27–45 kg/m<sup>2</sup> were treated for 52 weeks with lorcaserin 10 mg twice daily or with placebo. Using the pooled data from these two trials, weight loss at 52 weeks decreased by 5.8% in the lorcaserin group and 2.5% in the placebo group ( $P < .0001$ ) [127]. Weight loss was similar amongst males and females but was higher in Caucasian patients than African American patients or Hispanic patients and patients >50 years lost more weight than younger patients. Average weight loss at 1 year in the BLOOM study was 5.8  $\pm$  0.2 kg with lorcaserin and 2.2  $\pm$  0.1 kg with placebo ones ( $P < .001$ ) with 47.5% and 20.3% losing  $\geq 5\%$  of their body weight (Table 5) [120]. Weight loss was maintained in 67.9% of lorcaserin patients in year 2 and 50.3% of placebo ( $P < .001$ ) (Table 6) [120]. After 52 weeks of lorcaserin treatment, changes in lipid and glucose values were more favourable in responders than nonresponders, and twice as many patients responded to lorcaserin as placebo (i.e.,  $\geq 5\%$  body weight loss in 47.1% lorcaserin patients and 22.6% placebo) [128]. The most frequent adverse events reported were headache, dizziness and nausea, but these were not significantly different between treatment groups (Table 5). There was no increase in the rate of cardiac valvulopathy after 2-year treatment with lorcaserin [120].

Although the recently published study indicated lorcaserin was safe and moderately effective, there was a high dropout rate [120]. Lorcaserin was submitted for FDA approval however in September 2010 the advisors recommended against approval as they did not consider that the potential benefits of the drug outweighed the risks. In particular they claimed that patients on lorcaserin did not achieve the percentage point criterion set by the FDA. The FDA which usually takes the advice of its committees is expected to decide in October whether to approve lorcaserin.

**4.5. Tesofensine.** Tesofensine is another novel pharmacological agent which inhibits the uptake of presynaptic NA, DA, and 5HT (Table 2, Figure 1). Tesofensine was discovered

TABLE 5: Recent randomised controlled trials of weight loss therapies with 12-month followup.

Drug	No. subjects	Outcomes		Change in WC (cm)	Serious adverse events	Reference
		Absolute weight loss (kg) (95% CI)	≥10% weight loss			
Lorcaserin	Placebo-716	2.16 ± 0.14 <sup>^</sup>	20.3%	3.9 ± 0.2	Headache 2% P, 0.8% L	[120]
	L-883	5.81 ± 0.16 P < .001	47.5% P < .001	6.8 ± 0.2 P < .001	Dizziness 0.8% P, 0.1% L	
Taranabant	Placebo-417	2.6 (1.8, 3.3)	27.2%	-3.1 (2.3, 3.9)	Nausea 6.5% P, 16.7% TB 2 mg, 21.4% TB 4 mg, P < .001	[31]
	TB 2 mg-415	6.6 (5.9, 7.4), P < .001	56.5%, P < .001	-7.0 (6.1, 8.1), P < .001	Vomiting 3.4% P, 8.4 TB 4 mg, P < .01	
	TB 4 mg-414	8.1 (7.4, 8.9), P < .001	64.2%, P < .001	-7.5 (6.7, 8.3), P < .001	Diarrhoea 7.2% P, 12.3 TB 2 mg, P < .05, 13.7% TB 4 mg, P < .01 Anxiety 3.4 P, 9.9 TB 4 mg, P < .01	
Taranabant	Placebo-196	+1.7 (0.8, 2.7)	62.2%	-0.7 (-0.3, 1.8)	Irritability TB 1 mg and 2 mg, P ≤ .038	[116]
	TB 0.5 mg-196	0.1 (-1.0, 0.8), P < .007	71.8%	-1.5 (-2.6, -0.5)		
	TB 1 mg-196	0.6 (-1.5, 0.4), P < .007	78%, P < .05	-2.3 (-3.4, -1.3)		
	TB 2 mg-196	1.2 (-2.1, -0.3), P < .007	83.3%, P < .001	-2.4 (-3.4, -1.3)		
Bupropion/naltrexone*	Placebo-137	1.4 (-0.5, -2.4)	24.3%	-3.0 (-1.9, -4.1)	Psychiatric-17.7% P, 28.8% TB1mg, 29%TB 2 mg, P ≤ .038	[118]
	TB 0.5 mg-141	5.0 (-4.0, -5.9), P < .001	44.2%, P < .001	-5.6 (-4.5, -6.6), P < .001		
	TB 1 mg-138	5.2 (-4.2, -6.2), P < .001	45.3%, P < .001	-5.7 (-4.6, -6.7), P < .001		
	TB 2 mg-277	6.4 (-5.7, -7.2), P < .001	53%, P < .001	-6.9 (-6.1, -7.7), P < .001		
Bupropion/naltrexone	Placebo-202	7.3% ± 0.9%	60.4%	-6.8 (5.3, 8.3)	Nausea 10.5% P, 34.1% BN P < .001	[121]
	BN 360/32-591	11.5% ± 0.6%, P < .001	80.4%, P < .001	-10.0 (9.0, 10.9), P < .001	Dizziness 4.5% P, 14.6% BN, P < .001	
	BN 16 mg-64	2.7 ± 0.9	33%	NA	NA	[22]
	BN 32 mg-63	5.0 ± 0.9	50%			
	BN 48 mg-61	6.1 ± 0.8, P < .05	51%			
		4.6 ± 0.9	39%			
Pramlintide	Placebo-63Pramlintide-61	2.1 ± 0.9	3%	NR	Nausea 0% P, 30% Pramlintide	[85]
		3.6 ± 0.7	28%			
Topiramate	Placebo-55	2.5 ± 3.1	19%	-2.3 ± 4.7	Paraesthesia -0% P, 28% TPsychiatric -11% P, 33% T	[122]
	T-54	6.0 ± 5.2, P < .001	50%, P < .001	-4.2 ± 5.7, P = .078		
Topiramate/phentermine	P-498	1.6	17%	NA	NA	[123]
	TP 3.75/23 mg-234	5.1, P < .0001	45%, P < .0001			
	TP15/92 mg-498	11, P < .0001	67%, P < .0001			
Topiramate/phentermine	P-979	1.8	21%	NA	NA	[123]
	TP 7.5/46 mg-488	8.4, P < .0001	62%, P < .0001			
	TP15/92 mg-981	10.4, P < .0001	70%, P < .0001			

Absolute weight loss: weight loss from baseline; NS: not significant; NA: not available; L: lorcaserin; NB: naltrexone/bupropion, TB: taranabant; T: topiramate controlled release; TP: topiramate/phentermine; ^ mean ± standard error; \* both groups also received intensive behavior modification.

TABLE 6: Recent randomised controlled trials of weight loss therapies with 2-years followup.

Drug	No subjects	Outcomes			Change in WC (cm)	Serious adverse events	Reference
		Absolute weight loss (kg) (95% CI)	≥5% weight loss	≥10% weight loss			
Lorcaserin	P-684	3.0% ± 0.2%	50.3%	7.7%	4.3 ± 0.2	NS	[120]
	L-564	7.0% ± 0.2%	67.9%	22.6%	8.1 ± 0.2		
		<i>P</i> < .001	<i>P</i> < .001	<i>P</i> < .001	<i>P</i> < .001		
Taranabant	P-244	1.4 (0.3, 2.5)	30.3%	13.4	-2.7 (1.5, 3.8)	NS	[23]
	TB 2 mg-264	6.4 (5.3, 7.4), <i>P</i> < .001	59.6, <i>P</i> < .001	33, <i>P</i> < .001	-6.3 (5.2, 7.4) <i>P</i> < .05		
	TB 4 mg-260	7.6 (6.5, 8.7), <i>P</i> < .001	64.8, <i>P</i> < .001	37.9, <i>P</i> < .001	-7.0 (5.9, 8.1), <i>P</i> < .01		

Absolute weight loss = weight loss from baseline; WC: waist circumference, NR: not recorded, TB: taranabant, NS: not significant; P: placebo; L: lorcaserin.

to decrease weight in patients receiving the drug for the treatment of Alzheimer's and Parkinson's disease [129]. Investigators performed a dose-dependent analysis in obese patients for 14 weeks, demonstrating a mean change in weight loss for tesofensine doses of 0.125 mg, 0.25 mg, 0.5 mg and 1 mg of 2.1%, 8.2%, 14.1%, and 20.9%, resp. [129]. Of the total obese patients in the study, 32.1% achieved a ≥5% weight loss with tesofensine, (*P* < .001 for 0.25, 0.5, and 1.0 mg versus placebo). No effect on blood pressure was observed, but there were increases in heart rate with increasing dose.

Further evidence was demonstrated in another 24-week Phase IIb randomised dose-dependent tesofensine trial in 203 obese individuals, with 79% of participants completing the study [99]. Weight loss was dose dependant with 4.5% weight loss (0.25 mg), 9.2% (0.5 mg), and 10.6% (1.0 mg) and was greater than that achieved with diet and placebo (*P* < .0001) (Table 4). The drug was well tolerated with no significant increases in systolic or diastolic blood pressure however, heart rate was increased by 7.4 beats/min in the middose group (*P* = .0001).

**4.6. Naltrexone.** Naltrexone, a high affinity and long-acting opioid receptor antagonist which was originally produced for the treatment of opioid and alcohol dependence, decreased food intake and led to weight loss in former narcotic addicts. The role of opioid receptors in eating behaviour was initially demonstrated following the administration of naloxone to rats resulting in a significant reduction in short-term food intake by blocking β-endorphin (Table 2) [130]. In RCTs naltrexone (an analogue of naloxone) has not consistently demonstrated statistically significant weight loss in obese and lean subjects [131–134].

**4.7. Bupropion Plus Naltrexone (Contrave).** Bupropion was combined with the naltrexone following the recognition that naltrexone blocks β-endorphin mediated pro-opiomelanocortin (POMC) autoinhibition to sustain α-MSH release, whilst bupropion (through DA receptors) activates POMC neurons and enhances the release of the anorexiatic neuropeptide α-MSH in the hypothalamus [22,

135, 136]. The bupropion-naltrexone combination is said to tackle the motivation/reinforcement that food brings (DA effect) and the pleasure/palatability of eating (opioid effect) [137].

A 24 week dose ranging study of naltrexone/bupropion-SR did not demonstrate increased weight loss with increasing doses of naltrexone (weight loss for 16 mg dose was 4.62% [95% CI: -6.24 to -2.99, *P* < .001], for 32 mg dose 4.65% [95% CI: -6.20 to -3.09, *P* < .001], and for the 48 mg dose 3.53% [95% CI: -5.15 to -1.90, *P* < .001]) (Table 4) [22]. Nevertheless, weight-loss was maintained in a 24-week extended period.

An open-label 24-week study demonstrated that naltrexone 32 mg SR/bupropion-SR 360 mg resulted in significant improvements in depressive symptoms in addition to weight loss and improved control of eating in overweight and obese women with major depression [138]. Depression scores as measured with the Montgomery-Asberg Depression Rating Scale decreased from an average of 23.7 at baseline to 10.5 (consistent with mild depression) at week 12 (*P* < .001) and 8.4 (consistent with remission) at week 24 (*P* < .001).

Several Phase III trials have been conducted in both diabetic and non-diabetic patients including COR-I, COR-II, COR-BMOD and COR-Diabetes [105, 121, 139–141]. COR-Diabetes was a 56-week RCT of 505 overweight or obese patients with type 2 diabetes (Hb A1C levels 7% to 10%, mean 8.0%) randomized to naltrexone 32 mg SR/bupropion 360 mg SR or placebo [140]. The naltrexone/bupropion patients lost significantly more weight (5.0% versus 1.8%, *P* < .001) at 56 weeks [140] with 44.5% of patients achieving ≥5% loss of body weight compared to 18.9% on placebo. Greater improvement in glycemic control was achieved in the treatment group with average baseline HbA1C reduced by 0.6% compared to 0.1% for placebo. The investigators noted that over 44% of treated patients achieved the American Diabetes Association treatment target of <7% for HbA1C compared to 26% of placebo patients (*P* < .001).

This drug combination has generally been welltolerated in most patients (Table 5). Nausea was the most frequent adverse event, and this occurred more frequently with higher naltrexone doses. A new drug application has been submitted

for review by the FDA with the outcome expected in December 2010.

**4.8. Bupropion Plus Zonisamide.** The combination of bupropion with the epilepsy agent, zonisamide has been evaluated in three Phase II trials [97, 142–144]. The mechanism of action for zonisamide has not been fully characterised, however it has demonstrated biphasic DA and 5HT activity [142, 145]. The potential of zonisamide in the management of obesity was demonstrated in a small RCT where zonisamide patients experienced significantly more weight lost than those on placebo [145]. A 24-week RCT of bupropion 300 mg combined with zonisamide 400 mg achieved greater weight loss (9.2%) than either drugs alone (bupropion 6.6%, zonisamide 3.6%) or placebo (0.4%) [143]. Similar results were observed in a randomised open-label study [142]. Weight loss in a 24 week multicentre RCT with either drug alone and different combinations of zonisamide SR with bupropion SR were 1.4% with placebo, 3.2% with zonisamide SR 120 mg, 5.3% with zonisamide SR 360 mg, 2.3% with bupropion SR 360 mg, 6.1% with zonisamide SR 120 mg/bupropion SR 360 mg, and 7.5% for zonisamide SR 360 mg/bupropion SR 360 mg with  $\geq 5\%$  weight loss in 15%, 27%, 44%, 21%, 47%, 60%, respectively, [97]. The most frequent adverse events reported were headache, nausea and insomnia.

Weight loss with zonisamide and bupropion appears to be greater than that observed with the bupropion/naltrexone combination over the same period of treatment [22].

**4.9. Topiramate Plus Phentermine (Qnexa).** Topiramate is a GABA agonist and an approved antiepileptic drug which has been trialed as monotherapy for weight loss [1]. It acts as an appetite suppressant that has been suggested to influence kainate/ $\alpha$ -amino-3-hydroxy-5-methylisoxazole-4-propionic acid glutamate receptors, voltage-gated sodium channels, and  $\gamma$ -aminobutyric acid-A activity [146], however the exact mechanism of action for weight loss is not known (Table 2). Several RCTs demonstrated greater weight loss with topiramate monotherapy than placebo with continued weight loss throughout the duration of the study [1]. However concerns regarding central and peripheral nervous system adverse effects led to Phase III trials of topiramate being halted and topiramate being reformulated. As the sustained release formulation did not have better tolerability trials were discontinued in December 2004.

The combination of controlled release low dose topiramate with low dose phentermine has recently been shown to be effective for weight loss treatment [147]. A 28-week RCT using phentermine with topiramate (92 mg/15 mg and 46 mg/7.5 mg doses) demonstrated a 9.2% weight loss compared to a 6.4% weight loss with topiramate alone, 6.1% for phentermine alone and 1.7% for placebo [123]. The tolerance and safety of this drug combination are being evaluated in several Phase III trials (EQUATE, EQUIP, CONQUER). In July 2010 an FDA advisory committee agreed that the phentermine/topiramate combination was effective in reducing weight loss however it refused to endorse a recommendation for the treatment of obesity

due to safety concerns which included increased heart rate, possible birth defects, and psychiatric problems (depression, suicidal thoughts, impaired memory and concentration) [148]. The final FDA determination on the drug combination is expected in late October 2010.

**4.10. Pramlintide Combination Therapies.** Pramlintide has been combined with recombinant methyl human leptin (metreleptin), an adipocyte-derived hormone involved in long-term signalling of adiposity and energy intake [149]. In early trials this combination of an amylin and a leptin agonist has demonstrated greater weight loss than either drug alone [148, 149]. Weight loss with pramlintide/metreleptin was  $12.7\% \pm 0.9\%$  (mean  $\pm$  SE) to week 20 compared with  $8.4\% \pm 0.9\%$  for pramlintide ( $P < .001$ ) and  $8.2\% \pm 1.3\%$  for metreleptin ( $P < .01$ ) [149]. Pramlintide is also being evaluated in combination with sibutramine and phentermine [85]. In a 24-week open-label study weight loss was in subjects taking pramlintide and sibutramine was  $11.1\% \pm 1.1\%$  (mean  $\pm$  SE),  $11.3\% \pm 0.9\%$  for those taking pramlintide plus phentermine,  $3.7\% \pm 0.7\%$  with pramlintide alone, and  $2.2\% \pm 0.7\%$  with placebo ( $P < .001$ ) [85]. Common side effects experienced with combination treatments were nausea and increased heart rate [85]. There was a significant increase in heart rate and blood pressure with the combination of pramlintide and sibutramine ( $3.1 \pm 1.2$  beats/min,  $P < .05$ ;  $2.7 \pm 0.9$  mm Hg,  $P < .01$ ) and pramlintide with phentermine ( $4.5 \pm 1.3$  beats/min,  $P < .01$ ;  $3.5 \pm 1.2$  mm Hg,  $P < .001$ ). Pramlintide is also being investigated with exenatide, the GLP-1 agonist used for the treatment of obesity in diabetic and non-diabetic patients [113].

## 5. Conclusion

Pharmacological interventions in addition to lifestyle changes (diet and physical activity) and in some cases behavioural modifications are used to promote weight loss. At present, only two drugs are currently approved and available for the long-term treatment of obesity—orlistat and sibutramine. However, there are several drugs and combination drug therapies undergoing Phase III trials that may be approved in the next few years. Pharmacotherapies have demonstrated a significant though modest decrease in weight compared to placebo over 1-2 years. Unfortunately weight loss following pharmacological intervention is not sustained when therapy is discontinued with individuals regaining some or all of the weight that was originally lost.

Obesity is often considered a chronic disease, hence it requires long-term therapy. Currently, there is a lack of high quality evidence from long-term studies of both the efficacy and safety of pharmacological interventions for obesity. Serious safety concerns have resulted in the withdrawal of some drugs that had originally received market approval whilst other drugs have been abandoned during Phase III evaluation. An increase in psychiatric disorders following Phase III studies (RIO-Europe, RIO-North America, RIO-Diabetes and RIO-Lipids) with rimonabant treatment resulted in its withdrawal from the European market two

years after its approval. Orlistat treatment is associated with troublesome side effects such as diarrhoea, flatulence, bloating, abdominal pain, and dyspepsia which may not be acceptable to some patients on long-term treatment whilst the recent concerns of severe liver disease have led to a review of its safety. Long-term treatment with sibutramine is associated with a positive though modest efficacy profile and a low risk profile for neuropsychiatric adverse events; however we will need to wait for the publication of the full results of the SCOUT study to determine if there is an increase rate of CV events in patients with cardiovascular disease and diabetes.

Among the drugs in late phase trials, lorcaserin appears to be a potential candidate for long-term treatment in obesity due to its demonstrated efficacy and tolerable safety profile. Treatment with topiramate and taranabant result in significant weight loss in long-term studies, however both of these drugs have serious adverse effects. In the case of taranabant the psychiatric adverse events have led to the discontinuation of Phase III trials. Amongst the combination therapies both bupropion with naltrexone and bupropion with zonisamide have demonstrated effective weight loss and appear to be generally well tolerated based on published results from RCTs whereas there appears to be concerns regarding the safety of combination therapy using topiramate with phentermine.

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