Journal of
Clinical Pharmacy and Therapeutics

Journal of Clinical Pharmacy and Therapeutics, 2014, **39**, 475–484 doi: 10.1111/jcpt.12177

Review Article

Pharmacotherapy for weight loss: the cardiovascular effects of the old and new agents

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Received 2 October 2013, Accepted 23 April 2014

Keywords: **lorcaserin, obesity, phentermine/topiramate, weight loss**

SUMMARY

What is known and objective: **Obesity affects approximately one-third of the American population, and its prevalence continues to increase. It is a significant risk factor for cardiovascular diseases and contributes to increased healthcare costs and mortality. The objective is to review the current literature on the cardiovascular effects of weight loss pharmacotherapy agents.**
Methods: **Literature was accessed through MEDLINE/PubMed (up to April 2013) using the search terms obesity, weight loss, pharmacotherapy, cardiovascular adverse effects and cardiovascular side effects. References of the articles identified and www.clinicaltrials.gov were also reviewed. Relevant guidelines, review articles, clinical trials, meta-analyses, case series, FDA documentation and prescribing information were included and limited to English language articles.**
Results and discussion: **With the newly FDA-approved weight loss pharmacotherapy, treatment options for obesity are more diverse. However, safety concerns, including adverse cardiovascular effects, have played a significant role in the history of weight loss pharmacotherapy and will likely play a role in the future of the new agents, lorcaserin and phentermine/topiramate, as well.**
What is new and conclusion: **Long-term cardiovascular outcomes studies with and without high-risk cardiovascular patients are still needed for both lorcaserin and phentermine/topiramate before these agents can be recommended in these patient populations. It is yet to be determined whether modest weight loss benefit of these new agents outweighs the cardiovascular risks.**

WHAT IS KNOWN AND OBJECTIVE

The obesity epidemic affects a significant portion of Americans, and the prevalence of obesity continues to rise. In the early 1990s, 23% of Americans were considered obese; in 1999, the prevalence had risen to 30·5%.[1] Recent data suggest that approximately 36% of adult Americans are obese.[2] Obesity has been associated with coronary artery disease, stroke, peripheral arterial disease, venous thromboembolism, heart failure and hypertension.[3,4] In 1998, the American Heart Association reclassified obesity as a major, modifiable risk factor for coronary heart disease. With its high prevalence and associated risks, treatment of obesity is a significant healthcare target for intervention. Even modest weight loss of 5–10% is associated with improvements in cardiovascular (CV) outcomes including blood glucose, blood pressure, triglycerides and HDL.[5] A 5% weight loss reduced the risk of developing new type 2 diabetes mellitus by 58%.[6,7]

Medications are often used as adjunct therapy in the treatment of obesity, along with lifestyle interventions, counselling and surgery. The recently published AHA/ACC/TOS Guideline for the Management of Overweight and Obesity in Adults does not address options in pharmacotherapy for weight loss. At the time of guideline development, only orlistat was approved for weight loss. The guidelines state 'the provider should weigh the potential risks of the medication being considered against the potential benefits of successful weight loss for the individual patient. The rationale for use of medications is to help patients adhere to a lower calorie diet more consistently in order to achieve sufficient weight loss and health improvements when combined with increased physical activity. Medications work to reinforce lifestyle change and should be prescribed as an adjunct to lifestyle interventions' when needed.[8]

However, anti-obesity medications are often plagued by high rates of adverse effects, including adverse CV events. These events include valvular heart disease, pulmonary hypertension, myocardial infarctions and strokes. This review will examine the history of CV effects of weight loss pharmacotherapy and assess the newer, recently approved agents and the data on CV outcomes.

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METHODS

Literature was accessed through MEDLINE/PubMed (up to April 2013) using the search terms obesity, weight loss, pharmacotherapy, cardiovascular adverse effects and cardiovascular side effects. References of the articles identified and www.clinicaltrials.gov were also reviewed. Relevant guidelines, review articles, clinical trials, meta-analyses, case series, FDA documentation and prescribing information were included and limited to English language articles.

RESULTS

Mechanisms of action of weight loss pharmacotherapy

While the exact mechanisms of weight loss agents are often unknown, there are two proposed primary mechanisms of action

for anti-obesity medications: peripherally acting and centrally acting.[9,10] Peripherally acting agents reduce fat absorption from the gastrointestinal (GI) tract. For example, orlistat is a lipase inhibitor that impedes the absorption of dietary fat from the GI tract. Centrally acting agents may increase satiety through serotonergic, noradrenergic or dopaminergic targets by blocking reuptake or stimulating receptors in the satiety centre in the brain, including the hypothalamus and limbic system.[9,11] Agents may either work peripherally or centrally to increase energy expenditure by inducing thermogenesis or lipolysis as well.[9] It is hypothesized that sympathomimetic agents, such as phentermine, work mainly in the central nervous system by increasing norepinephrine in the synaptic cleft and directly stimulating receptors, but some may increase thermogenesis as well.[9,11] Ephedrine and herbal ephedra may work primarily through thermogenesis and lipolysis, but may work centrally as well.[9,11]

Many agents are often associated with adverse CV effects and have been removed from the market as will be discussed. However, a number of centrally acting sympathomimetic agents are still available for short-term use including phentermine, diethylpropion, benzphetamine and phendimetrazine.[9,10]

Pharmacotherapies withdrawn due to adverse cardiovascular effects

Fenfluramine/Dexfenfluramine. Fenfluramine came to the market in 1973, followed by dexfenfluramine in 1996. Fenfluramine and dexfenfluramine stimulate release of 5-hydroxytryptamine (5-HT) and inhibit reuptake in the synaptic cleft.[9] Dexfenfluramine was a more selective D-isomer of fenfluramine and was boasted to have fewer side effects than fenfluramine. Several randomized, controlled trials demonstrated the weight loss benefit of fenfluramine alone or in combination with phentermine or dexfenfluramine alone.[12,13] However, these benefits were marred by concerns for significant adverse effects, including valvular heart disease and pulmonary hypertension.[14–18] Prevalence estimates for valvular heart disease vary widely. A meta-analysis of observational studies indicated one in eight patients treated for more than 90 days with fenfluramine demonstrated valvular regurgitation.[16] In a case–control study comparing 95 patients with primary pulmonary hypertension to 355 controls, the use of anorexic drugs (mainly dexfenfluramine and fenfluramine) was associated with increased risk of developing primary pulmonary hypertension (OR 6·3; 95% CI 3·0–13·2).[17] These adverse events led to the withdrawal of both agents from the U.S. market in 1997.

A possible mechanism for the valvular disease associated with appetite suppressants involves the stimulation of serotonin receptors.[19,20] The valve abnormalities seen with appetite suppressants are similar to patients with carcinoid tumours and ergot exposure. This occurs through stimulation of the 5-HT2b receptors on the interstitial cells of the mitral and aortic valves. There are ample numbers of these receptors on the valves, and they incite fibroblast mitogenesis. This leads to thickening of the heart valves and valvular insufficiency. However, 5-HT2a and 5-HT2c are not associated with valvulopathy. Fenfluramine binds weakly to 5-HT2a, 5-HT2b and 5-HT2c receptors, but norfenfluramine, the metabolite of fenfluramine, demonstrated high affinity for 5-HT2b and 5-HT2c receptors.[21] The possible mechanism for pulmonary hypertension related to appetite suppressant use is similar.[22] The 5-HT1b receptor subtype and the 5-HT transporter are associated with pulmonary hypertension and may be stimulated through the non-selectivity of fenfluramine and its metabolites.[23]

Sibutramine. The FDA approved sibutramine in 1997 for obesity after demonstrating significant weight loss benefits compared with placebo. Sibutramine is a norepinephrine and serotonin reuptake inhibitor[9,11]. These mechanisms are thought to reduce appetite and induce thermogenesis. The increase in sympathetic activity associated with its mechanism of action is thought to contribute to its effects on blood pressure and heart rate.[24] The product labeling contained a contraindication for patients with a history of coronary artery disease, heart failure, tachycardia, peripheral arterial occlusive disease, arrhythmia or cerebrovascular disease, or inadequately controlled hypertension due to a risk of CV events and substantial increases in blood pressure and heart rate.[25]

Due to concern for adverse CV events, the SCOUT trial was initiated to examine the long-term effects of sibutramine on CV outcomes in a high-risk population. Over 10 000 overweight or obese patients, with age >55 and pre-existing CV disease, type 2 diabetes or both, were randomized to receive sibutramine or placebo after a 6-week lead-in period. The primary outcome was a composite endpoint of non-fatal myocardial infarction (MI), non-fatal stroke, resuscitation after cardiac arrest or CV death. The incidence of the primary outcome was 11·4% in the sibutramine group vs. 10·0% in the placebo group (HR 1·16; 95% CI 1·03–1·31; $P = 0·02$). The incidence of non-fatal MI and non-fatal stroke were both significantly elevated in the sibutramine group compared with placebo, as well.[26] After review of the preliminary results of SCOUT, the FDA issued a safety alert that included a warning for patients with CV disease. However, after final publication of SCOUT, the FDA asked the manufacturer to withdraw sibutramine from the market completely.

Ephedrine and ephedra. Ephedrine and herbal ephedra may suppress appetite and stimulate thermogenesis by stimulating release of norepinephrine into the synaptic cleft and stimulating beta-adrenergic receptors.[9] However, adrenergic stimulation of both alpha- and beta-receptors is also associated with vasoconstriction and cardiac stimulation leading to increased blood pressure and heart rate.[27] In 2000, Haller and Benowitz published a review of 140 reports of adverse events associated with ephedra products. Of these reported, 31% were rated as definitely or probably related to ephedra, with another 31% were possibly related. Forty-seven per cent of these adverse effects were CV events including hypertension, palpitations, tachycardia, arrhythmias, MI, cardiac arrest or stroke. Twenty-three events involved death or permanent disability.[28] A meta-analysis of 50 trials assessed the safety of ephedra and ephedrine products. The pooled odds ratio for heart palpitations was 2·29 (95% CI 1·27–4·32) with a non-significant trend towards increased odds of hypertension among patients receiving ephedra or ephedrine products. The risk of adverse events increased with higher doses of ephedra/ephedrine, but was not significant.[29] In April 2004, the FDA declared ephedrine alkaloids as adulterated substances because of the health risks to the consumer and banned ephedra-containing dietary supplements from the United States market.[30]

Ma huang is a Chinese herb derived from *Ephedra* species, usually *E. sinica.* The herb is a source of ephedrine alkaloids, consisting mostly of ephedrine and pseudoephedrine.[27] The pharmacokinetic parameters of ma huang capsules are similar to ephedrine tablets and solution, with the exception of slower absorption for the ma huang capsules.[31]

Ephedra alkaloids have been associated with thermoregulatory dysfunction and have been involved in a number of deaths in athletes. In February 2003, Steve Bechler, a professional baseball

player, passed away during spring training due to heat stroke. The use of an ephedra-based supplement was implicated in his death.[32] The possible mechanisms for this thermodysregulation include increased metabolism, increased creation of heat and elevated core body temperature. Superficial vasoconstriction may decrease the capability of the body to redistribute heat sufficiently.[33]

Phenylpropanolamine. Phenylpropanolamine likely exhibits its effects through central alpha-receptor stimulation in the hypothalamus, thus reducing food intake.[11] Numerous published cases and reports to the FDA suggest an association between phenylpropanolamine and haemorrhagic stroke. A case–control study conducted in the 1990s revealed phenylpropanolamine as a possible risk factor for haemorrhagic stroke in women.[34] The odds ratio was 16·58 (95% CI, 1·51–182·21; $P = 0·02$) for the association between the use phenylpropanolamine in women and the risk of intracranial haemorrhage. Although the overall risk of intracranial haemorrhage was low, the FDA believed the risk did not outweigh the benefit of these agents. Based on this information, the FDA deemed phenylpropanolamine unsafe for use and requested all drug companies discontinue products containing phenylpropanolamine.

Rimonabant. Although rimonabant was not withdrawn from the market due to adverse CV effects, it was determined that the risks outweighed the benefits of this medication and did not make it to the United States market. Rimonabant was an endocannabinoid-1 receptor antagonist. Potential mechanisms of weight loss included: decrease in food intake by inhibiting cannabinoid receptors in the CNS, increase in satiety signals, increased thermogenesis and decreased lipogenesis.[35] However, in June 2007, the FDA determined the risks of neurologic and psychiatric side effects outweighed the weight loss benefits of rimonabant and voted against approval.

Current FDA-approved therapies

As shown by the drugs withdrawn from the market, cardiovascular adverse effects are often a concern for new weight loss agents. In this section, the efficacy and cardiovascular safety of current FDA-approved pharmacotherapies for the treatment of obesity will be discussed.

Prior to recent FDA approvals, orlistat was the only weight loss medication approved for long-term use. It is a reversible inhibitor of both gastric and pancreatic lipases, which prevents the absorption of dietary fat.[9,11] At doses of 120 mg three times daily, dietary fat absorption is reduced by approximately 30%. Olistat is also available over-the-counter at a lower dose (60 mg three times daily). Two systematic reviews reported increased weight loss in patients receiving orlistat compared with placebo. Patients treated with orlistat lost 2·9 kg or 2·9% more weight than placebo. All trials demonstrated more orlistat patients achieving 5% weight loss (21% more patients in the orlistat group, 95% CI 18–24%) and 10% weight loss (12% more patients in the orlistat group, 95% CI 9–14%).[36,37] The longest trial to date spanned four years and included over 3000 patients. Patients in the orlistat group experienced significantly more weight loss than the control group (5·8 lb vs. 3·0 lb, $P < 0·001$) at 4 years. Significantly, more orlistat patients achieved at least 5% and at least 10% weight loss compared with placebo, respectively (≥5%: 52·8% vs. 37·3%, $P < 0·001$; ≥10%: 26·3% vs. 15·6%, $P < 0·001$).[38] Orlistat's side effect profile is largely associated with its effects on the gastrointestinal tract. Side effects include: abdominal pain, bloating, flatulence, diarrhoea and decreased absorption of fat-soluble vitamins. The CV profile of orlistat is generally favourable and lacks the adverse CV profile of other weight loss agents.

Phendimetrazine, phentermine, diethylpropion and benzphetamine are controlled amphetamine or amphetamine-like analogues available for short-term use, which is usually interpreted as up to 12 weeks. These sympathomimetic amines may stimulate the release of neurotransmitters acting centrally on the satiety centre of the brain and increase energy expenditure.[9,11] Limited information from large randomized controlled trials exists regarding long-term efficacy and safety of these medications. Because of this, the use of these agents is limited in the management of obese or overweight patients.[39] They are often associated with sympathomimetic CV adverse effects.[40,41] These include palpitations, tachycardia and elevations in blood pressure. It is recommended to use these agents with extreme caution in patients with hypertension and CV disease.

New agents

It had been over a decade since the FDA approved a medication for weight loss. Orlistat was approved for long-term weight loss in 1999. However, this changed in 2012 with the approval of two new agents for weight loss: lorcaserin and phentermine/topiramate.

Lorcaserin. Lorcaserin (Belviq®, Arena Pharmaceuticals, Zofingen, Switzerland) is a selective 5-HT2c receptor agonist. It is hypothesized lorcaserin selectively activates these receptors on anorexigenic pro-opiomelanocortin neurons in the hypothalamus, and activation of these receptors stimulates satiety and decrease food consumption.[42,43] The exact mechanism is unknown. Lorcaserin potency (EC50) and binding affinity (Ki) for human 5-HT2a, 5-HT2b and 5-HT2c receptor subtypes are as follows: EC50 = 5-HT2c 39 nM, 5-HT2b 2380 nM and 5-HT2a 553 nM; Ki = 5-HT2c 13 nM, 5-HT2b 147 nM, 5-HT2a 92 nM.[44] Lorcaserin is more potent and has a greater binding affinity for the 5-HT2c receptor. Based on these data, it is unlikely that lorcaserin would activate the 5-HT2b receptor at therapeutic doses. This selectivity differentiates lorcaserin from fenfluramine and dexfenfluramine. Whereas lorcaserin is selective in its agonism, fenfluramine and dexfenfluramine are non-specific agents. Their metabolites are potent 5-HT2b agonists associated with valvulopathy.[45] Theoretically, this selectivity allows for the weight loss benefit of 5-HT2c activation without the adverse effects of other serotonin receptor stimulation. Lorcaserin was studied in a series of trials in addition to diet and exercise counselling.

The BLOOM trial was a 2-year, randomized, placebo-controlled, double-blind trial that examined the efficacy and safety of lorcaserin for weight loss. This study randomized 3182 obese or overweight adults [BMI 30–45 or BMI 27–45 with at least one coexisting condition (hypertension, dyslipidemia, CV disease, impaired glucose tolerance or sleep apnoea)] to receive lorcaserin 10 mg twice daily plus diet and exercise counselling or placebo plus diet and exercise counselling for 52 weeks. At 52 weeks, the treatment group was further randomized to continue lorcaserin or initiate placebo. At one year, significantly more patients in the lorcaserin group, compared with the placebo group, achieved ≥5% weight loss than in the placebo group (47·5% vs. 20·3%, $P < 0·001$), lost a higher percentage of the baseline weight (5·81% vs. 2·16%, $P < 0·001$) and achieved ≥10% weight loss from baseline (22·6% vs. 7·7%, $P < 0·001$). At one year, patients in the lorcaserin group lost a mean of 5·8 kilograms (kg), compared with a mean of 2·2 kg in

Table 1. Efficacy endpoints (1-year results, *P*-value vs. placebo)[46,47,51]

	Lorcaserin					Phentermine/Topiramate		
	BLOOM		BLOSSOM			CONQUER		
	Placebo	10 mg BID	Placebo	10 mg BID	10 mg QD	Placebo	7·5 mg/46 mg	15 mg/92 mg
Absolute weight change (kg)	−2·2	−5·8 $P < 0·001$	−2·9	−5·8 $P < 0·001$	−4·7 $P < 0·001$	−1·4	−8·1 $P < 0·0001$	−10·2 $P < 0·0001$
Per cent weight change from baseline (%)	−2·16	−5·81 $P < 0·001$	−2·8	−5·8 $P < 0·001$	−4·7 $P < 0·001$	−1·2	−7·8 $P < 0·0001$	−9·8 $P < 0·0001$
Patients with ≥5% weight loss (%)	20·3	47·5 $P < 0·001$	25	47·2 $P < 0·001$	40·2 $P < 0·001$	21	62 $P < 0·0001$	70 $P < 0·0001$
Patients with ≥10% weight loss (%)	7·7	22·6 $P < 0·001$	9·7	22·6 $P < 0·001$	17·4 $P < 0·001$	7	37 $P < 0·0001$	48 $P < 0·0001$

the placebo group ($P < 0·001$). More patients who continued lorcaserin for the second year maintained weight loss (67·9% vs. 50·3%, $P < 0·001$).[46] (Table 1)

Overall, there were no significant differences between lorcaserin and placebo for adverse CV outcomes. At one year, there was no statistical difference between the rates of valvulopathy between the two groups (2·7% vs. 2·3%, $P = 0·70$). This continued at year 2 as well (2·6% vs. 2·7%). Valvular insufficiency scores (mitral and aortic valves) and change in mean pulmonary-artery systolic pressure were not statistically different between the study groups as well. However, power was not met for FDA-defined valvulopathy due to an overestimation of effect size. This decreased the statistical power to rule out relative risk of FDA-defined valvulopathy for lorcaserin to 60%, below the required 80%. This limits the ability to draw conclusions regarding valvulopathy from this trial.[46]

Blood pressure, total cholesterol, triglycerides, fasting glucose, glycated haemoglobin, CRP and fibrinogen improved significantly from baseline to one year in the lorcaserin group compared with placebo.[46] (Table 2)

A follow-up trial to BLOOM, the BLOSSOM trial, was conducted in 4008 patients to determine the optimal dose of lorcaserin for both efficacy and safety. Patients received either lorcaserin 10 mg daily, lorcaserin 10 mg twice daily or placebo. All patients received diet and exercise counselling. The results of this trial paralleled the results of the BLOOM trial. They found the weight loss associated with lorcaserin appeared to be dose-dependent. The patients receiving lorcaserin achieved significantly more weight loss than placebo with a trend towards increased weight loss with the twice daily dose. Mean weight loss in patients treated with lorcaserin 10 mg twice daily was similar to that in BLOOM. Percentage of patients achieving ≥5% weight loss, ≥10% weight

Table 2. Change in metabolic and cardiovascular endpoints (1-year results)[46,47,51]

	Lorcaserin					Phentermine/Topiramate		
	BLOOM		BLOSSOM			CONQUER		
	Placebo	10 mg BID	Placebo	10 mg BID	10 mg QD	Placebo	7·5 mg/46 mg	15 mg/92 mg
Waist circumference (cm)	−3·9 ± 0·2	−6·8 ± 0·2*	−4·1 ± 0·2	−6·3 ± 0·2*	−5·8 ± 0·3*	−2·4 ± 0·3	−7·6 ± 0·4*	−9·2 ± 0·3*
BMI	−0·8 ± 0·1	−2·1 ± 0·1*	−1·0 ± 0·1	−2·1 ± 0·1*	−1·7 ± 0·1*			
Blood Pressure (mm Hg)								
Systolic	−0·8 ± 0·3	−1·4 ± 0·3*	−1·2 ± 0·3	−1·9 ± 0·3	−1·3 ± 0·4	−2·4 ± 0·5	−4·7 ± 0·4*	−5·6 ± 0·5*
Diastolic	−0·6 ± 0·2	−1·1 ± 0·2*	−1·4 ± 0·2	−1·9 ± 0·2	−1·1 ± 0·3	−2·7 ± 0·3	−3·4 ± 0·4	−3·8 ± 0·3*
Cholesterol (%)								
Total	0·6 ± 0·3	−0·9 ± 0·3*	0·0 ± 0·3	−0·7 ± 0·3	−1·3 ± 0·5*	−3·3 ± 0·5	−4·9 ± 0·7*	−6·3 ± 0·5*
LDL	4·0 ± 0·6	2·9 ± 0·6*	1·7 ± 0·5	0·3 ± 0·5	−0·1 ± 0·7	−4·1 ± 0·9	−3·7 ± 1·1	−6·9 ± 0·9*
HDL	−0·2 ± 0·3	0·1 ± 0·3	1·3 ± 0·4	3·7 ± 0·4*	3·5 ± 0·6*	1·2 ± 0·7	5·2 ± 0·9*	6·8 ± 0·7*
Triglycerides (%)	−0·1 ± 1·0	−6·2 ± 1·0*	−0·9 ± 0·9	−4·3 ± 0·9*	−5·5 ± 1·3*	4·7 ± 1·7	−8·6 ± 2·2*	−10·6 ± 1·7*
Fasting glucose (mg/dL)	1·1 ± 0·3	−0·8 ± 0·3*				0·13 ± 0·03	−0·01 ± 0·04*	−0·07 ± 0·03*
Glycated hemoglobin (%)	0·03 ± 0·01	−0·04 ± 0·01*	−0·14 ± 0·01	−0·19 ± 0·01	−0·17 ± 0·01	0·1 ± 0·03	0 ± 0·03*	−0·1 ± 0·03*
Heart rate (beats/min)	−1·6 ± 0·4	−2·0 ± 0·3*	−1·6 ± 0·2	−2·3 ± 0·2	−1·1 ± 0·3			

*P-value <0·05 compared to placebo.

loss and mean weight change in kilograms were significantly improved with the twice daily dosing scheme compared with daily dosing ($P < 0{\cdot}01$).[47] (Table 1)

The significant differences in cardiometabolic endpoints seen in the BLOOM trial were not significant in BLOSSOM. Total cholesterol and LDL-C were not statistically different from placebo. However, both triglycerides and HDL-C were significantly improved compared with placebo for both dosing schemes, with blood pressure significantly improved with the twice daily dosing scheme. The incidence of cardiac valvulopathy was not statistically different between the treatment and placebo groups. This trial was not powered to detect a difference with cardiac valvulopathy, and more data are needed before major conclusions can be drawn regarding valvulopathy.[47] (Table 2)

BLOOM-DM examined the weight loss efficacy and safety of lorcaserin in patients with type 2 diabetes mellitus. Patients were eligible if they had a diagnosis of type 2 diabetes treated with metformin, a sulfonylurea, or both, had glycated haemoglobin of 7–10% at screening and had a BMI between 27 and 45 kg/m^2. In this study, 604 patients were randomized to receive placebo, lorcaserin 10 mg daily or lorcaserin 10 mg twice daily. All patients received diet and exercise counselling. Significantly, more patients achieved ≥5% weight loss in the lorcaserin twice daily or the lorcaserin daily groups compared with placebo (37·5% vs. 44·7% vs. 16·1%, $P < 0{\cdot}001$ compared to placebo). Per cent weight change in the lorcaserin twice daily, lorcaserin daily and placebo was $-4{\cdot}5 \pm 0{\cdot}35\%$, $-5{\cdot}0 \pm 0{\cdot}5\%$ and $-1{\cdot}5 \pm 0{\cdot}36\%$, respectively, ($P < 0{\cdot}001$ compared with placebo for each). Glycated haemoglobin decreased $0{\cdot}9 \pm 0{\cdot}06$ for lorcaserin twice daily, $1{\cdot}0 \pm 0{\cdot}09$ for lorcaserin daily and $0{\cdot}4 \pm 0{\cdot}06$ for placebo ($P < 0{\cdot}001$ compared to placebo for each). There was a non-significant increase is valvulopathy based on echocardiogram in the lorcaserin groups; however, the study was not powered to detect significant difference with this outcome. At 24 weeks, 1·9% of placebo patients had new valvulopathy whereas 3·9% ($P = 0{\cdot}395$, compared to placebo) in the lorcaserin daily group and 2·5% ($P = 0{\cdot}750$ compared to placebo) in the lorcaserin twice daily groups had new valvulopathy. At 52 weeks, 0·5% experienced new valvulopathy in the placebo group, whereas 2·5% ($P = 0{\cdot}187$, compared with placebo) in the lorcaserin daily group and 2·9% ($P = 0{\cdot}122$, compared with placebo) in the lorcaserin twice daily group had these findings.[48]

Like most weight loss trials, these studies included high rates of study drug discontinuation. This requires imputation methods to account for the missing data, and it is unclear which statistical method to account for this missing data is most accurate to predict the efficacy of lorcaserin clinically. Also, patients with depression or treated with selective serotonin reuptake inhibitors were excluded in these trials and the majority of the population was female. In BLOOM and BLOSSOM, the male participants were <20%. These studies do not address the effects of lorcaserin in a general population, and further clinical experience will be necessary. Lastly, to fully assess the risk cardiac valvulopathy in patients receiving lorcaserin, larger trials will be needed.

In September 2010, the FDA's Endocrinologic and Metabolic Drugs Advisory Committee voted against approval because of preclinical carcinogenicity concerns with minimal weight loss found in the clinical trials. The FDA required more information regarding these concerns. In December 2011, Arena Pharmaceuticals, the manufacturer of Belviq®, submitted data in response to these concerns that included official consensus on the preclinical data and final analysis included the final data from BLOOM-DM.[49]

This report provided a pooled analysis of the valvulopathy data from the three clinical, phase 3 trials. At 52 weeks, the proportion of patients with an increase from baseline valvular regurgitation was significantly increased in mitral and tricuspid regurgitation and in all valves combined. Another pooled analysis of FDA-defined valvulopathy included data from the three, phase 3, clinical trials. The pooled relative risk was 1·16 (95% CI 0·81 to 1·67) based on these three trials.[49] (Tables 3 and 4)

Based on the results of these studies, the FDA granted approval for lorcaserin for chronic weight loss management in addition to diet and exercise. Because the effect of lorcaserin on adverse CV outcomes, specifically valvulopathy, has yet to be extensively

Table 3. Patients with increase in valvular regurgitation from baseline (excluding absent to trace) (1-year results with last observation carried forward)[49]

	Lorcaserin 10 mg BID (%)	Placebo (%)	Relative risk (95% CI)	*P*-value
Aortic	1·34	1·45	0·92 (0·59–1·44)	0·71
Mitral	9·92	8·19	1·21 (1·02–1·43)	0·03
Pulmonic	17·00	15·51	1·10 (0·97–1·24)	0·14
Tricuspid	12·18	9·88	1·23 (1·06–1·44)	0·008
Any valve	32·37	28·24	1·15 (1·06–1·24)	0·001

Adapted from Belviq FDA documentation.

Table 4. FDA-defined valvulopathy (1-year results)[49]

	BLOOM		BLOSSOM		BLOOM-DM	
	Lorcaserin 10 mg BID *n* = 1278	Placebo *n* = 1191	Lorcaserin 10 mg BID *n* = 1208	Placebo *n* = 1153	Lorcaserin 10 mg BID *n* = 210	Placebo *n* = 209
FDA-defined valvulopathy[a], *n* (%)	34 (2·66)	28 (2·35)	24 (1·99)	23 (1·99)	6 (2·86)	1 (0·48)
Relative risk (95% CI)	1·13 (0·69 to 1·85)		1·00 (0·57 to 1·75)		5·97 (0·73 to 49·17)	
Pooled relative risk (95% CI)	1·16 (0·81 to 1·67)					

Adapted from Belviq FDA documentation.
[a]FDA-defined valvulopathy is defined as mild or greater aortic insufficiency and/or moderate or greater mitral insufficiency.

examined, the FDA will require post-marketing studies involving CV outcomes to determine the risk of major adverse CV events.

The prescribing information includes warnings and precautions regarding specific patient populations. It recommends using lorcaserin with caution in patients with congestive heart failure (CHF), valvular disease and pulmonary hypertension because studies did not include these patient populations. Data also suggest 5HT2b serotonin receptors may be overexpressed in CHF.[44,50] The high affinity of lorcaserin for the 5-HT2c receptor compared with the other 5-HT2 receptors may be lost if the 5-HT2 receptor ratio is altered. Due to the potential risk of adverse CV outcomes in these populations, use of lorcaserin is not recommended.

Phentermine/Topiramate. Phentermine/Topiramate (Qsymia™, VIVUS Inc., Mountain View, CA, USA) is a low-dose, controlled release, combination product. Phentermine is a centrally acting sympathomimetic, similar to amphetamine, which stimulates release of norepinephrine from the hypothalamus.[51,52] It was first approved for the short-term treatment of obesity in 1959. Topiramate is approved for the treatment of epilepsy and migraine prophylaxis. Topiramate was initially studied for weight loss as a single agent; however, the dose-dependent neuropsychiatric effects, such as memory and mood effects, prevented the realization of this indication. Topiramate blocks neuronal voltage-dependent sodium channels, boosts GABA activity, antagonizes glutamate receptors and inhibits carbonic anhydrase.[53] However, the exact mechanism in weight loss is largely unknown. A possible mechanism associated with topiramate includes decreased caloric intake, as indicated by human studies, but other mechanisms may contribute. Animal studies indicate other mechanisms may include increased energy expenditure, decreased food intake, decreased energetic efficiency, increased thermogenesis and/or increased insulin sensitivity.[53–55] There appears to be a possible synergistic effect when combined. However, this has not been examined clinically. The combination is formulated to achieve peak exposure to each drug separately. The peak exposure of the immediate-release phentermine occurs in the morning, whereas the peak exposure to the extended-release topiramate occurs in the late afternoon or evening to coincide with late afternoon/evening hunger.[56]

CONQUER was a randomized, double-blind, placebo-controlled trial that examined the efficacy and safety of phentermine/topiramate controlled release combination for weight loss in overweight and obese individuals with two or more risk factors (hypertension, dyslipidemia, diabetes or prediabetes, or abdominal obesity). In this 1-year trial, 2487 patients were randomized to receive phentermine 7·5 mg/topiramate 46 mg once daily (P/T 7·5/46), phentermine 15 mg/topiramate 92 mg once daily (P/T 15/92) or placebo. Both doses of phentermine/topiramate had significantly improved weight loss compared with placebo. At the end of the study, patients receiving placebo lost significantly less weight than either the lower dose phentermine/topiramate combination or the higher-dose combination, respectively (−1·4 kg vs. −8·4 kg vs. −10·2 kg, $P < 0·0001$ for each compared to placebo). Significantly, more patients achieved ≥5% weight loss compared with placebo (21%) in both treatment groups (lower dose 62%, $P < 0·0001$; higher dose 70%, $P < 0·0001$) (Table 1). In terms of the cardiometabolic endpoints, both treatment groups demonstrated significantly reduced waist circumference, blood pressure, total cholesterol, triglycerides, fasting glucose, glycated haemoglobin and C-reactive protein (CRP) compared with placebo (Table 2). These reductions were more evident in patients with pre-existing risk factors. Average heart rate was increased in the high-dose treatment group compared with baseline (1·7 beats per minute; 95% CI 0·9 to 2·4; $P < 0·0001$). More patients in the treatment groups experienced increases of more than 10 beats per minute at consecutive visits as well.[51]

The SEQUEL trial was a 52-week extension of the CONQUER study. In this trial, 866 patients continued their originally randomized treatment for a total of 108 weeks. The results from the CONQUER trial were sustained in SEQUEL. Both doses of phentermine/topiramate significantly improved weight loss compared with placebo, as well as cardiometabolic markers with decreased utilization of medications to treat the cardiometabolic disease states. Percentage change from baseline body weight was −1·8%, −9·3% and −10·5% for placebo, P/T 7·5/46 and P/T 15/92, respectively ($P < 0·0001$ for each compared with placebo). Absolute mean weight loss was −2·1 kg, −9·6 kg and −10·9 kg for placebo, P/T 7·5/46 and P/T 15/92, respectively ($P < 0·0001$ for each compared with placebo).[57]

EQUIP examined the efficacy and safety of phentermine/topiramate in patients with class II or class III obesity (BMI ≥35). Patients were randomized to receive placebo, phentermine/topiramate 3·75 mg/23 mg (P/T 3·75/23) or P/T 15/92 in addition to a reduced calorie diet. Both treatment groups lost significantly more body weight compared with placebo at 56 weeks ($P < 0·0001$ for each), as well as significantly more patients achieving a weight loss of >5% ($P < 0·0001$ for each). Both the low-dose and high-dose combination demonstrated improved waist circumference and blood pressure compared to placebo, with the high-dose treatment demonstrating improved total cholesterol, LDL-c, HDL, triglycerides and fasting serum glucose. The high-dose treatment increased heart rate from baseline by 1·2 beats per minute ($P = 0·0830$), which may be ascribed to the sympathomimetic activity of phentermine.[52]

Table 5. Mean changes in surrogate cardiovascular endpoints (1-year results)[56]

	Placebo $n = 1532$	P/T 3·75 mg/23 mg $n = 234$	P/T 7·5 mg/46 mg $n = 488$	P/T 15 mg/92 mg $n = 1553$
Systolic BP (mm Hg)	−2·1 (14·01)	−3·3 (11·95) $P = 0·2322$	−5·2 (14·77) $P < 0·0001$	−5·2 (14·48) $P < 0·0001$
Diastolic BP (mm Hg)	−1·9 (9·61)	−0·9 (8·29) $P = 0·1362$	−3·3 (9·87) $P = 0·0044$	−2·9 (9·40) $P = 0·0023$
Heart rate (beats/minute)	0·0 (10·19)	1·3 (10·32) $P = 0·0688$	0·6 (10·18) $P = 0·2933$	1·6 (10·28) $P < 0·0001$
Rate-pressure product	−0·15 (1·67)	−0·09 (1·54) $P = 0·5470$	−0·30 (1·73) $P = 0·1686$	−0·19 (1·69) $P = 0·3306$

Mean change (SD), *P*-value compared with placebo.
Adapted from Qsymia FDA documentation.

Like lorcaserin, phentermine/topiramate trials also had high dropout rates, lack of population diversity and high numbers of female participants.

Initially, in 2010, the FDA rejected phentermine/topiramate due to concerns for adverse effects. The FDA required more information regarding the elevations in heart rate and its relation to adverse CV events. In response to the FDA's request, VIVUS, the drug's manufacturer, evaluated pooled data from the original studies to examine adverse CV events related to the increase in heart rate associated with phentermine/topiramate. (Table 5)

The report included analysis of heart rate, cardiac arrhythmias, rate-pressure product, major CV outcomes and mortality risk scores. The predictor of increased heart rate was baseline heart rate. Patients with lower baseline heart rates experienced the largest increase in heart rates. Cardiac arrhythmic effects occurred more frequently in the P/T 15/92 (4·7%) and P/T 7·5/46 (4·2%) groups compared with placebo (1·8%). The majority of these events were palpitations, increased heart rate and tachycardia. The change in rate-pressure product (RPP) was not statistically different when comparing treatment groups with placebo. Increase in RPP is associated with an increase in myocardial oxygen demand, which may lead to adverse cardiac events. Treatment groups were associated with a decrease in RPP.[56]

Additionally, VIVUS used risk models, including Cooper Clinic Mortality Risk Index, to assess the overall all-cause mortality effects of phentermine/topiramate. The Cooper Clinic Mortality Risk Index accounts for the following factors: age, heart rate, blood pressure, diabetic status, smoking status and body mass index (BMI). A drawback to this risk model is that validation occurred in a population that consisted only of men. When applied separately to the male and female patients of the 1-year cohort, it demonstrated a significant reduction in mortality risk scores in the higher-dose groups in both male and female patients. However, our ability to draw conclusions from these data is limited because a risk model was utilized instead of a randomized, controlled trial powered to detect differences in mortality.[56]

Lastly, they analysed a variety of major CV outcomes. These included composite of CV death, MI and stroke; composite of CV death, stroke, coronary revascularization and unstable angina (Jupiter MACE); and other composite major adverse CV events. Hazard ratios were less than one for all composite CV outcomes examined; however, due to the low number of events, the 95% confidence intervals were wide. There were a limited number of adverse CV events in the studies making it difficult to draw conclusions regarding the effect of phentermine/topiramate on these outcomes. The authors were unable to find a connection between heart rate and adverse CV events.[56] (Table 6)

In July 2012, after review of the new analysis, the FDA approved phentermine/topiramate for chronic weight management in addition to diet and exercise. However, like lorcaserin, the FDA will require post-marketing studies to assess long-term CV outcomes and risk of major adverse CV events. The prescribing information includes a warning for increased heart rate and advises monitoring for patients with cardiac or cerebrovascular disease. If palpitations, high heart rates at rest or significant increases in heart rate are noted, it is recommended to decrease dose or discontinue therapy. Because phentermine/topiramate has not been studied in patients with recent or unstable cardiac or cerebrovascular disease, use is not recommended in these patient populations.

Pipeline agents

Naltrexone/Bupropion was submitted to the FDA for approval in 2010. In the FDA's response letter, they asked the company for a randomized, double-blind, placebo-controlled trail to assess the risk of major adverse CV events.

The COR-I (Contrave Obesity Research I) trial assessed the efficacy and safety of sustained-release naltrexone/bupropion for weight loss in 1742 overweight and obese patients (BMI 30–45 kg/m2 or BMI 27–45 with dyslipidemia or hypertension). Exclusion criteria included type 1 or 2 diabetes, and cerebrovascular, CV, hepatic or renal disease. Patients were randomized to receive SR naltrexone/bupropion 16 mg/180 mg twice daily, SR naltrexone/bupropion 8 mg/180 mg twice daily or placebo twice daily for 56 weeks. Compared with placebo, patients who received SR naltrexone/bupropion achieved significantly more weight loss. This was evident in both the high-dose group (6·1% vs. 1·3%, $P < 0·0001$ compared with placebo) and the low-dose group (5·0% vs. 1·3%, $P < 0·0001$ compared with placebo). Patients who achieved a weight loss of ≥5% were also significantly higher in both treatment groups compared to placebo. In the high-dose group, 48% of patients attained this endpoint compared to 16% in the placebo arm ($P < 0·0001$). In the low-dose group, 39% of patients lost ≥5% of their baseline weight ($P < 0·0001$ compared with placebo). Patients in both treatment groups had a significant increase in HDL and decrease in triglycerides and CRP compared with placebo with no significant difference in LDL at 56 weeks. However, there was a transient increase in mean blood pressure

Table 6. Incidence rates per year for cardiovascular outcomes[56]

	Placebo $n = 1742$	P/T 3·75/23 mg $n = 240$	P/T 7·5/46 mg $n = 604$	P/T 15/92 mg $n = 1737$	P/T Total $n = 2581$	Hazard ratio[d]	95% CI
CV death, MI, stroke	0·3	0·5	0·3	0·2	0·3	0·84	0·26–2·64
Jupiter MACE[a]	0·6	0·5	0·3	0·3	0·3	0·55	0·21–1·42
FDA MACE[b]	0·6	0·5	0·3	0·3	0·3	0·49	0·19–1·25
Modified FDA MACE[c]	0·8	0·5	0·6	0·5	0·5	0·62	0·29–1·33

Adapted from Qsymia FDA documentation. MACE = major adverse cardiovascular events.
[a]CV death, MI, stroke, coronary revascularization and unstable angina.
[b]CV death, MI, stroke, coronary revascularization, unstable angina and congestive heart failure.
[c]CV death, ACS, cerebrovascular events, coronary revascularization, hospitalization for heart failure, stent thrombosis, hospitalization for other CV causes, carotid artery revascularization, peripheral vascular revascularization, lower extremity amputation, hospitalization for cardiac arrhythmia.
[d]Hazard ratio is from a univariate Cox proportional hazards regression analysis comparing P/T Total to placebo.

from baseline in the treatment groups, and blood pressure was increased compared with placebo in both treatment groups.[58] A trial investigating cardiovascular outcomes of naltrexone–bupropion in obese and overweight patients with cardiovascular risk factors is currently ongoing.[59]

There are medications indicated for type 2 diabetes that are associated with the potential for weight loss as well. These medications include glucagon-like peptide-1 (GLP-1) receptor agonists (liraglutide and exenatide), amylinomimetic (pramlintide) and metformin. Several of these agents are either undergoing or have recently completed clinical trials in obese patients without diabetes.[59]

Small studies have demonstrated GLP-1 receptor agonists have the potential to increase satiety, decrease food intake, and induce weight loss.[60,61] However, emerging evidence suggests these agents have potential for cardiovascular benets beyond blood glucose control and weight loss as well.[62] However, this evidence is preliminary and requires further investigation in large clinical trials.

Other agents currently in clinical trials include: bupropion/zonisamide, pramlintide/metreleptin, canagliflozin, cetilistat and velneperit.[59]

WHAT IS NEW AND CONCLUSION

Obesity continues to adversely affect a large portion of the population, and its prevalence continues to rise. It is also a risk factor for CV disease, and new treatment options are needed. However, safety issues, specifically adverse CV events, have significantly influenced the ability of weight loss pharmacotherapies to make it to or remain on the market. This was evident in the decade long gap between FDA approvals of new weight loss medications. The market drought ended with the approval of lorcaserin and phentermine/topiramate. In Table 1, we compare the efficacy outcomes across the main trials for each medication. It appears phentermine/topiramate may be a slightly more potent weight loss agent when comparing efficacy outcomes across the trials. Numerically, phentermine/topiramate had a greater absolute weight loss and per cent weight loss from baseline, and more patients achieved ≥5% weight loss and ≥10% weight loss than lorcaserin. However, it is unclear whether this comparison would continue in a clinical trial. The differences in the methodology of the trials, patient populations, and diet and exercise interventions limit the ability to make comparisons across the studies. It is important to note that there is no head-to-head comparison trial for these two agents and any comparison made in this paper of the two agents is only hypothesis generating.

The new weight loss medications potentially have serious risks associated with their use. If these agents are used, it is important they are used as indicated in the product labelling. One major concern is these medications may be used inappropriately, including use for minor cosmetic weight loss in patients with a BMI that does not meet the criteria for use. Also, patients who receive these medications need to be monitored appropriately for efficacy. If these efficacy criteria (as indicated in product labelling) are not met, discontinuation of the medication should occur, as it is unlikely the patient will achieve weight loss if continued. In both these situations, the risks likely outweigh the benefits of use, or continued use, of the medications.

Each new agent has unique cardiovascular concerns, and it is difficult to determine, based on adverse effects, which agent would be preferred. There are major concerns regarding use in patients with cardiovascular disease, and there are still many issues that need to be addressed. These include long-term CV outcomes studies with and without high-risk CV patients, before these agents can be recommended in these patient populations. It is yet to be determined whether modest weight loss benefit of these new agents outweighs the CV risks.

CONFLICT OF INTEREST

There are no actual or potential conflict of interests to disclose by any authors of this manuscript.

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