

Cardiovascular effects of phentermine and topiramate: a new drug combination for the treatment of obesity

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Weight loss can reduce the increased cardiovascular risk associated with obesity. Pharmacotherapy is a recognized weight loss treatment option; however, cardiovascular safety issues with some previous weight loss drugs raise concerns for newly approved pharmacotherapies. Phentermine is approved for short-term obesity treatment in conjunction with lifestyle modifications, but is commonly used chronically. Topiramate, approved for treating epilepsy and preventing migraines, also induces weight loss. A single-dose combination of low-dose phentermine and topiramate extended-release was recently approved by the United States Food and Drug Administration as an adjunct to lifestyle intervention for the chronic treatment of overweight/obese adults. This review summarizes and evaluates the cardiovascular risk/benefit profile associated with phentermine and topiramate, individually and in combination. Cardiovascular data associated with long-term use of phentermine and topiramate extended-release indicate that this combination may be a safe and effective option for reducing weight in overweight/obese patients at low-to-intermediate cardiovascular risk.

Keywords: cardiovascular risk, obesity, phentermine, topiramate

Abbreviations: BP, blood pressure; b.p.m., beats per minute; C_{max} , mean plasma maximum concentration; CHMP, Committee for Medicinal Products for Human Use; CI, confidence interval; CNS, central nervous system; EMA, European Medicines Agency; FDA, Food and Drug Administration; GABA, γ -aminobutyric acid; HDL-C, high-density lipoprotein cholesterol; IC_{50} , half maximal inhibitory concentration; ITT-LOCF, intention-to-treat population with last observation carried forward; MACE, major adverse cardiac event; PHEN/TPM-ER, phentermine and topiramate extended-release; PNS, peripheral nervous system; T_{max} , time to mean plasma maximum concentration; T2DM, type 2 diabetes mellitus

INTRODUCTION

The prevalence of obesity, defined as a BMI at least 30 kg/m^2 , has increased substantially in many countries [1]. Obesity poses significant cardiovascular health risks, such as increased risk of hypertension and cardiovascular disease, and can cause or exacerbate arterial

hypertension; it is an important cause of treatment-resistant arterial hypertension [2,3]. Over the past decades, cardiovascular mortality has decreased in many countries, likely through use of statins, anti-hypertensives, and lifestyle modifications, including diet, exercise, and smoking cessation [4–7]. However, the rising prevalence of obesity and its related cardiovascular comorbidities could reduce, or even reverse, the impact of this achievement [8].

Modest weight loss of 5–10% in obese individuals improves cardiovascular risk markers, including blood pressure (BP) [9–11]. Consequently, the recently revised European Society of Hypertension guidelines recommend weight loss for obese hypertensive individuals [12]. The primary approach for the management of obesity and associated comorbidities is lifestyle intervention that includes energy restriction and increased physical activity; however, this approach is of modest efficacy and is associated with poor long-term patient adherence [13,14]. Additional interventions, such as bariatric surgery or pharmacotherapy, may be needed to achieve adequate sustained weight loss and cardiovascular risk reduction. Bariatric surgery effectively treats many weight-related comorbidities [15,16] and reduces all-cause mortality and mortality from myocardial infarction [15], but carries operative risks, and may not be appropriate for all patients [17].

Current licensed pharmacotherapies include phentermine hydrochloride (HCl), a sympathomimetic appetite-suppressant approved in the US for short-term (up to 12 weeks) treatment of obesity in conjunction with dietary and lifestyle modifications [18–20]; and orlistat, a gastric and pancreatic lipase inhibitor approved in the US and

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Europe for the long-term pharmacologic management of obesity [21–24]. Recently, the US Food and Drug Administration (FDA) has approved lorcaserin, a 5HT-2c agonist for chronic weight management in obese adult patients and overweight adult patients with at least one weight-related comorbidity as an adjunct to behavioural/lifestyle modifications [25]; and phentermine and topiramate extended-release (PHEN/TPM-ER), a once-daily combination therapy for chronic weight management in obese adult patients and overweight adult patients with at least one weight-related comorbidity as an adjunct to behavioural/lifestyle modifications [26].

Previously approved pharmacotherapies for treating obesity, including fenfluramine, which was often used in combination with phentermine, were found to have unacceptable cardiovascular risks that outweighed their potential weight-loss benefits [27–39]. These cardiovascular risks included, but were not limited to, increased risk of valvulopathy and pulmonary hypertension, which resulted in withdrawal from the market (Table 1) [27–39]. As a result, the US FDA now requires weight-loss pharmacotherapies to show no excess cardiovascular health risks, similar to treatments for type 2 diabetes mellitus (T2DM), and frequently requires the drug's manufacturer to conduct post-marketing safety studies, including long-term cardiovascular outcome trials [39,40]. The European Medicines Agency (EMA) expects new T2DM agents to produce no excess cardiovascular risk, requiring cardiovascular outcomes studies of at least 18–24 months or sufficiently sized meta-analysis data prior to granting marketing approval [41]. A recent

concept paper from the Cardiovascular Working Party of the EMA Committee for Medicinal Products for Human Use (CHMP) indicates that the EMA is likely to adopt similar cardiovascular safety requirements for weight-loss pharmacotherapies in the near future [42]. This review aims to summarize and evaluate the cardiovascular benefit–risk profile associated with phentermine monotherapy, topiramate monotherapy, and their use in combination as PHEN/TPM-ER.

PHENTERMINE

Pharmacology and mechanism of action

Phentermine is an atypical amphetamine analogue that acts mainly to increase norepinephrine in the central nervous system (CNS), thereby suppressing appetite [43,44]. Phentermine potently releases norepinephrine [half maximal inhibitory concentration (IC₅₀) = 39.4 nmol/l], but shows weaker effects on the release of dopamine (IC₅₀ = 262 nmol/l) and serotonin (IC₅₀ = 3511 nmol/l) [44]. The drug is a weak substrate or uptake inhibitor of the serotonin transporter [43,44] and has minimal effects on plasma serotonin *in vivo* [45]. At plasma concentrations associated with low doses of phentermine (e.g. less than 20 mg), there is insufficient exposure to activate either dopamine or serotonin receptors [44]. Although increased catecholamine release may be perceived to increase the potential for adverse cardiovascular effects, norepinephrine released in the brain can act presynaptically to diminish sympathetic activity through a so-called clonidine-like effect [46–51].

TABLE 1. History of cardiovascular effects of drugs used for weight loss

Agent	Year(s)	History of cardiovascular effects
Dinitrophenol	1930s	Affected mitochondrial oxidative phosphorylation to induce weight loss, and was associated with elevated body temperature [27,39].
Amphetamines	1950s	Linked to increased risk of hypertension and pulmonary hypertension [29].
Phentermine	1959 till present	The European Commission withdrew marketing authorization for all weight-loss drugs (phentermine, amfepramone, and mazindol) from the market due to unfavourable risk-to-benefits ratio. The licence was withdrawn and then subsequently reinstated several times [38], but a decision in 2002 by the European Court of First Instance overturned previous decisions to withdraw marketing authorizations for phentermine [37]. Phentermine is eligible for marketing authorization, but would require an updated application to be submitted.
Fenfluramine and dexfenfluramine	Fenfluramine: 1973–1997; dexfenfluramine: 1996–1997	Fenfluramine or dexfenfluramine used in combination with phentermine until fenfluramine and dexfenfluramine were withdrawn from the market in September 1997 due to links to pulmonary hypertension and valvulopathy [28,30–33].
Aminorex	1965–1968	An amphetamine analogue, withdrawn due to risks of pulmonary hypertension [27].
Sibutramine	1997–2010	Norepinephrine and serotonin-reuptake inhibitor was approved for treating obesity in the US and in Europe. Due to increased SBP, DBP, and pulse, caution was recommended in people with poorly controlled hypertension or history of cardiovascular arterial disease, stroke, or arrhythmia hyperthermia [27,39]. Findings from the Sibutramine cardiovascular Outcomes Trial (SCOUT) of 10 000 overweight/obese patients with a history of coronary or peripheral vascular disease or stroke, and other risk factors, showed: 16% increase in risk of non-fatal myocardial infarction or non-fatal stroke, cardiovascular death, or resuscitated cardiac arrest with sibutramine vs. placebo, which caused US and European market withdrawal in October 2010 [35]; modest weight loss in patients participating in the SCOUT study was associated with reductions in cardiovascular mortality over 4–5 years of follow-up [10].
Phenylpropanolamine	2000	Withdrawn from the US market due to increased risk of haemorrhagic stroke [27].
Ephedrine	2004	Withdrawn from the US market due to adverse cardiovascular effects [27].
Rimonabant	2006–2008	Oral cannabinoid receptor antagonist/inverse agonist, gained approval in Europe in 2006 (but not in the US due to psychiatric safety concerns), was studied for possible long-term benefits for reducing cardiovascular risk in people with cardiovascular disease [34]. The Comprehensive Rimonabant Evaluation Study of CV Endpoints and Outcomes (CRESCENDO) trial was prematurely discontinued due to European Health Authorities withdrawing rimonabant from the market (due to psychiatric risks) [27].

CV, cardiovascular.

This mechanism may explain the observation that norepinephrine-uptake inhibitors, such as sibutramine, reboxetine, and desipramine, paradoxically decrease sensitivity to sympathetic stimuli [46–51].

Treatment of obesity and associated cardiovascular effects

Phentermine is the most widely used weight-loss pharmacotherapy in the US [52]; phentermine HCl, an immediate-release formulation that undergoes rapid dissolution and absorption in the gastrointestinal tract, is currently approved for use at a dose of 15.0–37.5 mg/day (adjusted to the patient's need) for the short-term (up to 12 weeks) treatment of obesity (Table 2) [19,20]. A phentermine resin that slowly releases active drug into the gastrointestinal system is also approved in the US for the short-term treatment of obesity (Table 2) [18]. Phentermine (either

phentermine HCl 37.5 mg/day or phentermine resin 15–30 mg/day) has been evaluated as a monotherapy in several studies up to 36 weeks, and demonstrated reductions in body weight and waist circumference, and improved achievement of at least 5 or 10% weight loss relative to placebo [53–56]. Munro *et al.* [55] in 1968 studied weight loss with phentermine monotherapy (30 mg/day) in a 36-week, double-blind trial of overweight and obese women, and found significant weight loss with both continuous and intermittent regimens of phentermine treatment (12.2 and 13.0 kg, respectively) vs. a dummy vehicle (4.8 kg). Although no published studies describing long-term, randomized, controlled weight-loss trial data for phentermine are currently available, Hendricks *et al.* [57] in 2011 observed that patients ($n=300$) treated with phentermine monotherapy, at doses ranging from 15 to 37.5 mg/day (mean dose 33.6 mg/day), showed significantly

TABLE 2. Indications and contraindications of approved phentermine and topiramate agents

Generic name	Indication(s)	Contraindications
Phentermine HCl [19,20] (15 mg, 30 mg, 37.5 mg)	Short-term adjunct (a few weeks) in a regimen of weight reduction based on exercise, behavioural modification and caloric restriction in the management of exogenous obesity for patients with an initial BMI ≥ 30 kg/m ² , or ≥ 27 kg/m ² in the presence of other risk factors (e.g. hypertension, diabetes, hyperlipidaemia)	<ul style="list-style-type: none"> • History of cardiovascular disease (e.g. coronary artery disease, stroke, arrhythmias, congestive heart failure, uncontrolled hypertension) • During or within 14 days following the administration of monoamine oxidase inhibitors • Hyperthyroidism • Glaucoma • Agitated states • History of drug abuse • Pregnancy • Nursing • Known hypersensitivity, or idiosyncrasy to the sympathomimetic amines • Advanced arteriosclerosis, cardiovascular disease, moderate-to-severe hypertension
Phentermine resin [18] (15 mg, 30 mg)	Short-term adjunct (a few weeks) in a regimen of weight reduction based on exercise, behavioural modification and caloric restriction in the management of exogenous obesity for patients with an initial BMI ≥ 30 kg/m ² or ≥ 27 kg/m ² in the presence of other risk factors (e.g. hypertension, diabetes, hyperlipidaemia)	<ul style="list-style-type: none"> • During or within 14 days following the administration of monoamine oxidase inhibitors • Hyperthyroidism • Glaucoma • Agitated states • History of drug abuse • Known hypersensitivity, or idiosyncrasy to the sympathomimetic amines • Hypersensitivity to the active substance or to any of the excipients^a
Topiramate immediate-release (tablets: 25 mg, 50 mg, 100 mg, and 200 mg; Sprinkle capsules: 15 mg and 25 mg) [65,66]	<ul style="list-style-type: none"> • Monotherapy epilepsy: Initial monotherapy in patients ≥ 2 years of age with partial onset or primary generalized tonic-clonic seizures • Adjunctive therapy epilepsy: Adjunctive therapy for adults and pediatric patients (2 to 16 years of age) with partial onset seizures or primary generalized tonic-clonic seizures, and in patients ≥ 2 years of age with seizures associated with Lennox-Gastaut syndrome • Migraine: Treatment for adults for prophylaxis of migraine headache 	<ul style="list-style-type: none"> • Migraine prophylaxis in pregnancy and in women of childbearing potential if not using effective methods of contraception^a
Phentermine and topiramate extended-release [26]	Adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial BMI ≥ 30 kg/m ² or ≥ 27 kg/m ² in the presence of ≥ 1 weight-related comorbidity (hypertension, type 2 diabetes mellitus or dyslipidaemia)	<ul style="list-style-type: none"> • Pregnancy • Glaucoma • Hyperthyroidism • During or within 14 days of taking monoamine oxidase inhibitors • Known hypersensitivity or idiosyncrasy to sympathomimetic amines

^aContraindications listed for topiramate immediate-release apply to the product's European package leaflet. The US package insert lists the contraindications as 'none'.

greater weight loss for 1 through 104 weeks of treatment (12.7%) compared with those on a low-carbohydrate ketogenic diet alone (8.4%; $P=0.0144$).

The belief that phentermine increases heart rate and BP may be due to the assumption of amphetamine-like side effects based on similarities in drug pharmacology. However, in the observational study by Hendricks *et al.* [57], normotensive (14%), prehypertensive (52%), and hypertensive (34%) patients treated for a long term with phentermine (mean time on therapy of 92 weeks) demonstrated no significant increase in heart rate, as well as reductions in SBP and DBP that were similar to those in patients losing weight on a low-carbohydrate ketogenic diet alone. Furthermore, clinical studies using short-term (12 weeks) phentermine monotherapy have shown either reductions in heart rate and BP with phentermine treatment, perhaps linked to weight loss [56], or no significant changes in BP with phentermine treatment [53,54]. A study of patients taking phentermine for weight loss ($n=269$) found no abuse potential or amphetamine-like withdrawal upon abrupt cessation of long-term treatment, even at doses higher than that commonly recommended and after treatment duration of up to 21 years [58]. Common side effects, as described in the phentermine-prescribing information, for short-term (12–14 weeks) use include dry mouth, insomnia, headache, dizziness, fatigue, tachycardia, and palpitations [18–20].

It should be noted that there were reports of valvular heart disease when phentermine was used in combination with fenfluramine or dexfenfluramine [28,30–33,59]. Of the 132 spontaneous reports with complete information, 113 (86%) met the cardiac valvulopathy case definition [59]. Of these 113 cases, 2 (2%) used fenfluramine alone, 16 (14%) dexfenfluramine alone, 89 (79%) a combination of fenfluramine and phentermine, and 6 (5%) a combination of all three drugs. There were no cases reported with phentermine monotherapy use [59]. Since none of these cases of cardiac valvulopathy was linked directly with phentermine treatment, the US FDA required the removal of fenfluramine and dexfenfluramine from the market, while maintaining its approval of phentermine as a monotherapy [39]. Ultimately, activity on the 5-HT_{2b} receptor on heart valves was implicated as the primary mechanism associated with fenfluramine/dexfenfluramine-related valvulopathy [60]. Phentermine has no affinity for the 5-HT_{2b} receptor and does not increase circulating serotonin [60,61]. Two case reports have described a temporal association between phentermine monotherapy and valvular heart disease or pulmonary arterial hypertension [62,63], but numerous pre-existing and concomitant morbidities in these cases have precluded any definitive conclusion about whether these were linked to treatment [64].

TOPIRAMATE

Pharmacology and mechanism of action

Topiramate immediate-release is a sulfamate-substituted monosaccharide used to treat epilepsy and to prevent migraines [65,66]. It is suggested that topiramate acts on kainate/alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid glutamate receptors. Moreover, topiramate

appears to block voltage-dependent sodium channels, augment γ -aminobutyric acid activity (GABA-A), and inhibit carbonic anhydrase isoenzymes II and IV, although the mechanism of action for topiramate's effects on weight is unknown [65,66]. Topiramate may decrease food intake via effects of carbonic-anhydrase inhibition on taste [67,68], or through its effects on GABA transmission, since GABA-A receptor activation [69] and the interaction between GABA and leptin pathways [70] are known to mediate effects on appetite and metabolism. Topiramate may also affect energy expenditure (based on preclinical data) [71].

Current indications, treatment of obesity, and cardiovascular effects

Topiramate immediate-release is currently approved at doses of 100–400 mg/day (titrated over 6 weeks) as monotherapy for treating seizures in adults and children over age 6, with other medicines to treat seizures in adults and children aged at least 2 years, or for preventing migraines in adults (Table 2) [65,66]. Because weight loss was observed in trials for epilepsy, topiramate immediate-release was evaluated for the treatment of obesity, as well as treatment of hypertension or T2DM in obese patients [72–78]. A 6-month, placebo-controlled, randomized trial of 385 obese patients demonstrated weight loss of 2.6% with placebo, and 5.0, 4.8, 6.3, and 6.3% in patients randomized to topiramate immediate-release 64, 96, 192, or 384 mg/day along with lifestyle intervention, respectively [73]. Doses were gradually increased over 12 weeks and tapered at the end of trial [73]. All topiramate immediate-release doses elicited greater weight loss than placebo [73]. A long-term study (up to 60 weeks) evaluated the safety and efficacy of topiramate immediate-release for weight maintenance in obese patients who had lost at least 8% body weight after 8 weeks on a low-calorie diet [72]. After 44 weeks of treatment, patients treated with topiramate immediate-release had lost 15.4 and 16.5% of their enrolment body weight at 96 and 192 mg/day doses, respectively (vs. 8.9% with placebo), and more patients treated with topiramate immediate-release lost at least 15% body weight than those treated with placebo [72]. In another placebo-controlled, randomized clinical trial of 531 obese patients with hypertension, patients treated with topiramate immediate-release experienced weight loss of 5.9 and 6.5% at 96 and 192 mg/day, respectively (vs. 1.9% with placebo), as well as reductions in BP after 28 weeks of treatment [SBP: -8.6 and -9.7 mmHg, respectively, vs. -4.9 mmHg with placebo ($P=NS$); DBP: -5.5 and -6.3 mmHg, respectively, vs. -2.1 mmHg with placebo ($P<0.015$)] [76]. Subsequent to these studies of topiramate immediate-release, an extended-release formulation of topiramate was developed potentially to enhance tolerability while simplifying dosing [78], but this formulation was never submitted for regulatory approval.

Topiramate, like other carbonic anhydrase inhibitors, may produce CNS and peripheral nervous system (PNS) effects, such as paraesthesias, acute myopia, blurred vision, redness of the sclera, photophobia, and eye discomfort resulting from secondary angle-closure glaucoma, as well as psychiatric and neurologic disturbances, including fatigue, somnolence, depression, and difficulties with concentration and memory [65,66]. Although in-vitro evidence

has suggested the potential for topiramate to be arrhythmogenic [79], data indicate that topiramate does not increase the risk of sudden unexpected death due to cardiac arrhythmia in epilepsy patients [80]. Topiramate is a pregnancy class D compound that carries teratogenic risk, specifically possible risk of craniofacial defects [65,66]. Data from patients (mostly adults with partial-onset seizures) in double-blind, placebo-controlled studies receiving doses of 200–1000 mg/day ($N=360$) and long-term studies (up to approximately 5 years; $N=1001$) showed CNS treatment-related adverse events that were dose-dependent, with a greater frequency at topiramate dosages greater than 200–600 mg/day, and occurring early in treatment [81]. The most common adverse events in weight-loss trials of obese/overweight patients were dose-related and in the PNS, CNS, or psychiatric categories (including paraesthesia, hypoaesthesia, memory/attentional difficulties, dizziness, neuropathy, anxiety, depression, headache, fatigue, insomnia, and somnolence) [72–78]. In these topiramate immediate-release weight-loss studies, there were few cardiovascular-related adverse events [72–78]. Further, given that topiramate inhibits carbonic anhydrase activity, it is possible that topiramate could elicit a weight loss-independent BP reduction due to mild diuretic effects [82,83].

PHENTERMINE AND TOPIRAMATE EXTENDED-RELEASE FOR THE TREATMENT OF OBESITY

Pharmacology and mechanism of action

On the basis of the weight loss achieved with phentermine and topiramate as individual agents, and the notion that a combination of these agents at low doses might have additive or synergistic effects, thereby providing improved efficacy and safety over the products individually, a combination of PHEN/TPM-ER was developed for once-daily oral dosing to enhance weight loss and to improve weight-related comorbidities in overweight and/or obese patients [84–89]. In this low-dose formulation, phentermine [mean plasma maximum concentration (C_{max}) 49.1 ng/ml; time to median plasma maximum concentration (T_{max}) 6 h] is readily absorbed and immediately released to provide effects early in the day, whereas topiramate extended-release (C_{max} 1020 ng/ml; T_{max} 9 h) is released later and provides effects through later periods of the day [26,90]. PHEN/TPM-ER is currently approved at doses of 3.75 mg/23 mg, 7.5 mg/46 mg and 15 mg/92 mg for chronic weight management in obese and overweight adults with at least one weight-related comorbidity (Table 2) [26].

Clinical trials

The efficacy, safety, and tolerability of PHEN/TPM-ER were assessed in overweight and obese patients with comorbidities in two 1-year, randomized, double-blind, placebo-controlled phase 3 studies [84,86]. EQUIP included 1267 severely obese adults (≤ 70 years of age and BMI ≥ 35 kg/m²; patients with T2DM were excluded) [84]. CONQUER included 2487 overweight and obese adults (≤ 70 years of age; BMI ≥ 27 kg/m² and ≤ 45 kg/m²) with at least two weight-related comorbidities, including

hypertension and T2DM [86]. An extension study was also performed, which evaluated patients from select CONQUER sites who elected to continue their blinded, randomized treatments in the study for an additional 52 weeks (SEQUEL) [87]. In a fourth study, adults with T2DM were evaluated in a 28-week extension of a 28-week double-blind, placebo-controlled phase 2 trial (DM-230; 56 weeks total) [88]. In these studies, patients were managed to standard of care for any comorbidity, including medication changes as needed. All patients received dietary and lifestyle counselling based on the Lifestyle, Exercise, Attitudes, Relationships, Nutrition (LEARN) programme [91], including guidance to reduce daily caloric intake by 500 kilocalories, increase water consumption, and increase physical activity [84,86,87]. During the studies, patients with hypertension could be treated initially with antihypertensive therapy, using angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers; if patients were already taking these agents, calcium channel blockers, beta blockers, or thiazide diuretics could be added [92]. Patients whose BP exceeded 160/100 mmHg on three consecutive visits or who underwent increases in either dose or number of antihypertensives on each of these visits were discontinued from the study and referred back to their primary care physician [92]. Similarly, patients with T2DM or dyslipidaemia could also have their medications adjusted to achieve standard of care [92]. Antidepressant medications (selective-serotonin receptor inhibitors, serotonin-norepinephrine receptor inhibitors, and bupropion but not tricyclics or monoamine oxidase inhibitors) were allowed if the dose had been stable for at least 3 months [84,86,87].

Weight loss (1-year and 2-year studies)

In the 1-year pooled analysis of the EQUIP ($n=1267$) [84] and CONQUER ($n=2487$) [86] studies, and in DM-230 ($n=130$), PHEN/TPM-ER was associated with significant and sustained percentage weight loss in overweight and obese patients when compared with placebo [intention-to-treat population with last observation carried forward (ITT-LOCF); Fig. 1] [88,92]. A significantly greater proportion of patients receiving PHEN/TPM-ER also achieved at least 5% weight loss after 56 weeks of treatment in the phase 2 and 3 studies when compared with placebo [92]. Similarly, patients showed significant, sustained percentage and categorical weight loss through 108 weeks in the 2-year cohort of the SEQUEL extension study [87].

Changes in heart rate and blood pressure (1-year and 2-year cohorts, safety set)

In the 1-year cohort, weight loss induced by PHEN/TPM-ER was associated with significant reductions in SBP ($P<0.0001$ for PHEN/TPM-ER 7.5/46 and 15/92 doses vs. placebo; not significant for PHEN/TPM-ER 3.75/23 vs. placebo) and DBP ($P<0.005$ for PHEN/TPM-ER 7.5/46 and 15/92 doses vs. placebo; not significant for PHEN/TPM-ER 3.75/23 vs. placebo; Fig. 2) [88,89]. Reductions in BP occurred in parallel with slight increases in heart rate in all PHEN/TPM-ER groups [mean change \pm SD) of 1.3 ± 10.3 beats per minute (b.p.m.), 0.6 ± 10.2 b.p.m. and 1.6 ± 10.3 b.p.m. for PHEN/TPM-ER 3.75/23, 7.5/46,

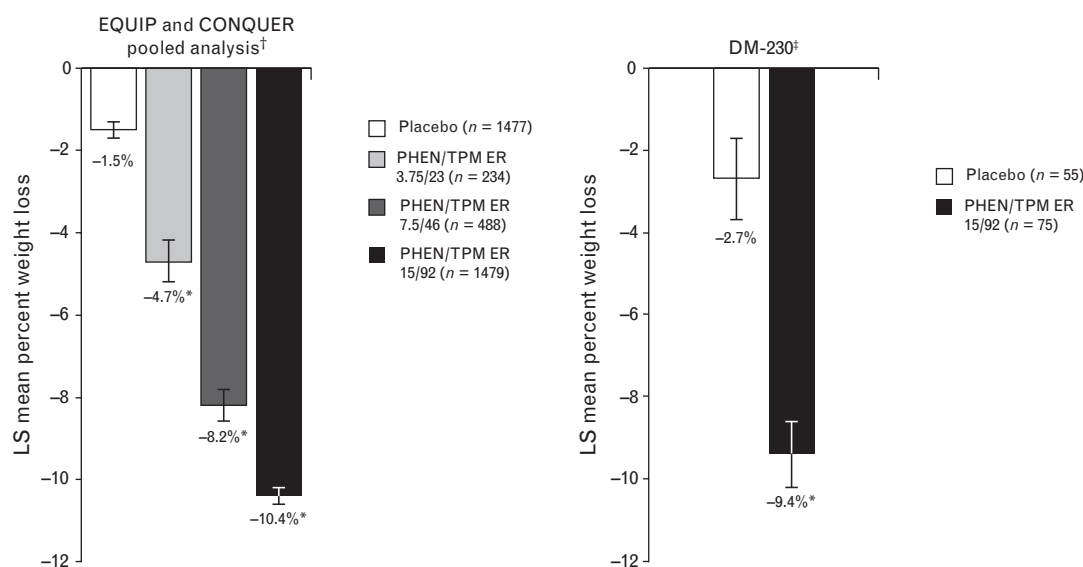


FIGURE 1 Weight loss from baseline to week 56 (1-year studies; ITT-LOCF) in overweight and obese adults with and without weight-related comorbidities (EQUIP, CONQUER) and in adults with T2DM (DM-230) [88,92]. * $P < 0.0001$ vs. placebo. †Based on ITT-LOCF data from studies OB-302 and OB-303. ‡Based on ITT-LOCF data from study DM-230. ITT, intention to treat; LOCF, last observation carried forward; LS, least squares; PHEN/TPM-ER, phentermine and topiramate extended-release; T2DM, type 2 diabetes mellitus.

and 15/92 groups, respectively], which was significant vs. placebo (0.0 ± 10.2 b.p.m.) only in the PHEN/TPM-ER 15/92 group ($P < 0.0001$; Fig. 2) [88,89]. However, among patients with the highest heart rate at baseline (>90 b.p.m.), most showed reductions in heart rate at the 1-year endpoint (Fig. 3) [88].

Results were similar, although less pronounced in the 2-year cohort based on management to standard of care and medication changes; all PHEN/TPM-ER-treated patients showed reductions in SBP and DBP (see Table S1, Supplemental Digital Content, <http://links.lww.com/HJH/A339>) [87,92]. At 2 years, there was also a significant net reduction in concomitant antihypertensive medication use in patients treated with PHEN/TPM-ER, whereas placebo-treated patients experienced a net increase in antihypertensive medication use ($P = 0.0165$ for between-group differences; see Table S1, Supplemental Digital Content, <http://links.lww.com/HJH/A339>) [93]. The slight mean increases in heart rate vs. baseline with PHEN/TPM-ER treatment observed in the 1-year cohort were still evident after 2 years of treatment, but were not significant compared with placebo (see Table S1, Supplemental Digital Content, <http://links.lww.com/HJH/A339>) [92].

Changes in rate pressure product (1-year and 2-year cohorts, safety set)

Increased myocardial oxygen demand is the putative mechanism by which increased heart rate promotes cardiac ischaemia in patients with macrovascular or microvascular coronary disease [94]. The rate pressure product, defined as the product of heart rate and SBP divided by 1000, is related to myocardial oxygen demand, and was decreased in the placebo group and each of the PHEN/TPM-ER groups in the 1-year cohort (with greatest reductions seen in the PHEN/TPM-ER 7.5/46 dose; Fig. 2c) [88] and the 2-year cohort (see Table S1, Supplemental Digital Content,

<http://links.lww.com/HJH/A339>) [92]. These data suggest that the mild heart rate increase with PHEN/TPM-ER over 2 years may not increase myocardial oxygen demand.

Weight loss and changes in cardiovascular risk factors in patients with dyslipidaemia or hypertension

In patients with dyslipidaemia or hypertension at baseline participating in the 56-week CONQUER study, PHEN/TPM-ER induced significantly greater, dose-related mean percentage weight loss vs. placebo ($P < 0.0001$), with a greater proportion of PHEN/TPM-ER-treated patients achieving at least 5, 10, and 15% weight loss [85]. PHEN/TPM-ER treatment was associated with significant improvements in serum triglyceride, high-density lipoprotein cholesterol (HDL-C), and non-HDL-C levels vs. placebo ($P < 0.05$) in patients with dyslipidaemia at week 56, along with a net reduction in lipid-lowering medication use [85]. In patients with hypertension at baseline, PHEN/TPM-ER-treated patients showed significant improvements in BP at week 56 [SBP: -6.9 and -9.1 mmHg for PHEN/TPM-ER 7.5/46 and 15/92, respectively, vs. -4.9 mmHg for placebo ($P < 0.05$); DBP: -5.2 and -5.8 mmHg for PHEN/TPM-ER 7.5/46 and 15/92, respectively, vs. -3.9 mmHg for placebo ($P < 0.05$)], as well as a net decrease in antihypertensive medication use ($P < 0.0001$ for between-group differences) [85]. Similar to the overall CONQUER population, a slight increase in heart rate (0.1 to 1.3 b.p.m.) was observed in the dyslipidaemia and hypertension subgroups [85,86].

In pooled data of hypertensive patients from the two 1-year studies (CONQUER and EQUIP), reductions in SBP and DBP were seen in all PHEN/TPM-ER groups, whereas heart rate was slightly increased in the 7.5/46 and 15/92 dose groups (Table 3) [92]. At endpoint in the 2-year cohort, patients with hypertension at baseline showed reductions

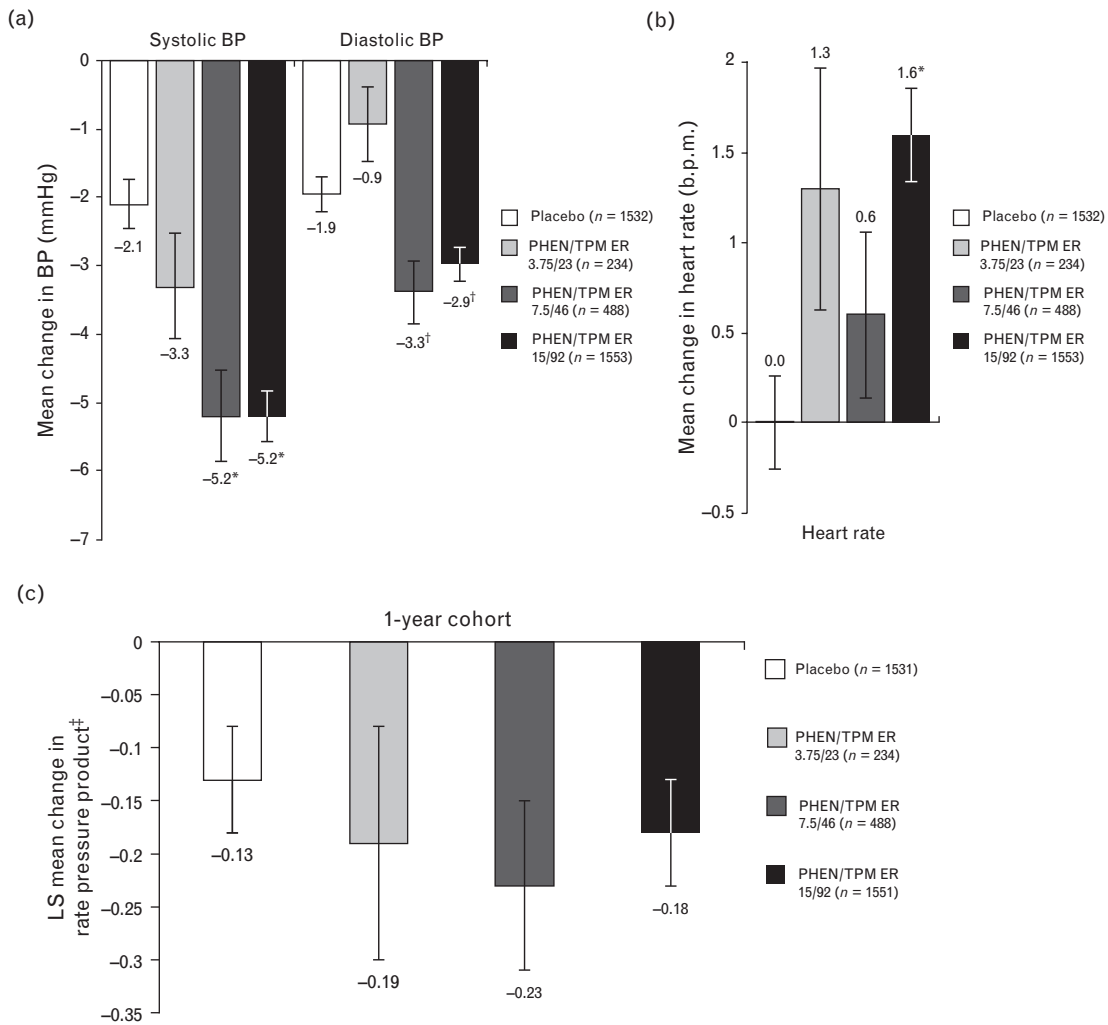


FIGURE 2 Changes in (a) blood pressure, (b) heart rate, and (c) rate pressure product from baseline to week 56 (1-year cohort; safety set) [88,89]. Rate pressure product was defined as the product of the heart rate and SBP, divided by 1000. * $P < 0.0001$ vs. placebo. [†] $P < 0.005$ vs. placebo. This cardiovascular effects analysis includes patients with baseline and endpoint measurements. BP, blood pressure; PHEN/TPM-ER, phentermine and topiramate extended-release.

in SBP and DBP. Concomitant antihypertensive medication use in PHEN/TPM-ER-treated patients was significantly reduced, compared to a net increase in antihypertensive medication use in the placebo group ($P = 0.0012$ for between-group differences; see Figure S1, Supplemental Digital Content, <http://links.lww.com/HJH/A339>) [93].

Safety in all exposed patients

Common adverse events in PHEN/TPM-ER clinical trials were paraesthesia, dizziness, dysgeusia, insomnia, constipation, and dry mouth. Adverse events were generally dose-related and mild to moderate in severity, occurring mostly during the titration period [26,84,86–88].

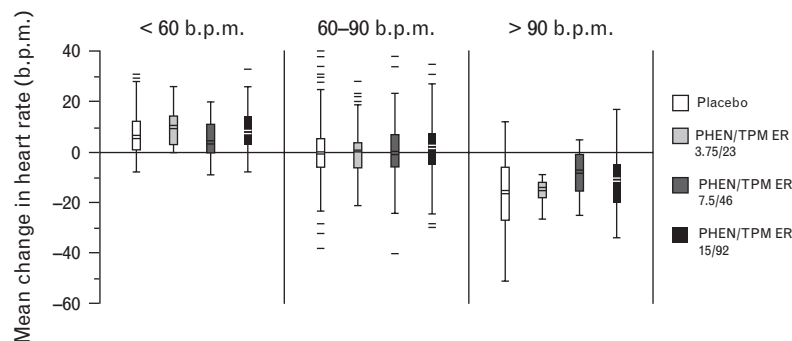


FIGURE 3 Effects on heart rate at week 56 based on baseline heart rate (1-year cohort; safety set) [88]. b.p.m., beats per minute; PHEN/TPM-ER, phentermine and topiramate extended-release.

TABLE 3. Change in blood pressure, heart rate, and rate pressure product in patients with hypertension at baseline (1-year cohort; safety set) [92]

Mean change at week 56	Placebo (n = 627)	PHEN/TPM-ER 3.75/23 (n = 33)	PHEN/TPM-ER 7.5/46 (n = 261)	PHEN/TPM-ER 15/92 (n = 642)
SBP (mmHg) (SE)	-5.5 (0.6)	-5.8 (3.0)	-7.0 (1.0)	-8.5 (0.6)
DBP (mmHg) (SE)	-3.9 (0.4)	-2.3 (1.7)	-5.0 (0.6)	-5.3 (0.4)
Heart rate (b.p.m.) (SE)	0.1 (0.4)	-0.7 (1.8)	1.0 (0.6)	1.1 (0.4)
Rate pressure product ^a (SE)	-0.4 (0.1)	-0.5 (0.3)	-0.4 (0.1)	-0.5 (0.1)

b.p.m., Beats per minute; PHEN/TPM-ER, phentermine and topiramate extended-release; SE, standard error.

P > 0.05 for both doses of PHEN/TPM-ER vs. placebo, all comparisons.

^aRate pressure product, heart rate (b.p.m.) × SBP (mmHg)/1000.

PHEN/TPM-ER contraindications are similar to those of phentermine and topiramate monotherapy (Table 2) [18–20,26,65,66].

Cardiac arrhythmia-related adverse events reported by patients (as defined by mapping to the Medical Dictionary for Regulatory Activities Cardiac Disorders System Organ Class) were palpitations, increased heart rate, and tachycardia, and occurred in between 0.1 and 2.4% of patients (palpitations: 0.8, 0.8, 2.4, and 1.7% for placebo and PHEN/TPM-ER 3.75/23, 7.5/46, and 15/92, respectively; heart rate increased: 0.1, 0.0, 0.4, and 0.8%, respectively; tachycardia: 0.1, 0.4, 0.4, and 0.7%, respectively) [92]. There were low rates of serious adverse events classified as cardiac disorders [92].

Cardiac events in all exposed patients

Within the 1-year safety cohort, 752 (19.8%) patients were considered to have low cardiovascular risk, 2498 (65.6%) had moderate cardiovascular risk, and 14.6% were in a high cardiovascular risk category [modified Adult Treatment Panel (ATP) III criteria] [92]. In the 1 and 2-year safety cohorts, the different outcome definitions of major adverse cardiac events (MACEs) each had a hazard ratio (PHEN/TPM-ER vs. placebo) below 1.0, ranging from 0.49 [95% confidence interval (CI) 0.19, 1.25] for US FDA MACE to 0.84 (95% CI 0.26, 2.64) for the traditional MACE composite endpoint (cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke; Table 4) [92]. The traditional MACE composite endpoint (cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke) was incident in 12 of the 4323 patients (5/1742 in

the placebo group and 7/2581 in the PHEN/TPM-ER group; Table 4); the wide CI found in the analysis of the traditional MACE composite endpoint indicates that a larger sample is required to sufficiently address this issue [92]. The hazard ratio for the broadest MACE criteria (cardiovascular/neurovascular serious adverse events), which had a total of 43 events (20/1742 in the placebo group and 23/2581 in the PHEN/TPM-ER group), had a 95% CI with an upper bound of 0.98, representing a statistically significant reduction in cardiovascular risk (Table 4) [92]. At this time, there are too few events from clinical trial data to draw firm conclusions about decreases or increases in MACE in patients treated with PHEN/TPM-ER; however, available data do not indicate any increased cardiovascular risk associated with PHEN/TPM-ER. A cardiovascular outcomes trial is planned by the drug's manufacturer, in accordance with one of the US FDA's post-marketing study requirements [95]. The EMA's CHMP has indicated that a long-term cardiovascular outcomes trial would be necessary to support PHEN/TPM-ER centralized approval in Europe [96]. In addition to the planned long-term cardiovascular outcomes trial, future research might beneficially be directed at exploring the effects of PHEN/TPM-ER on surrogate physiologic measures of cardiovascular health, such as endothelial function, and in obese individuals with resistant hypertension.

CLINICAL PERSPECTIVE

There is a current unmet need for an effective weight-loss pharmacotherapy that can be used for long term for the

TABLE 4. Incidence rates for cardiovascular event outcomes (MACE endpoints; all exposed patients) [92]

Cardiovascular event parameter	Placebo (n = 1742)	PHEN/TPM-ER 3.75/23 (n = 240)	PHEN/TPM-ER 7.5/46 (n = 604)	PHEN/TPM-ER 15/92 (n = 1737)	PHEN/TPM-ER total (n = 2581)	Hazard ratio ^b (95% CI)
MACE endpoint ^a						
Cardiovascular death, MI, stroke	0.3	0.5	0.3	0.2	0.3	0.84 (0.26, 2.64)
Jupiter MACE	0.6	0.5	0.3	0.3	0.3	0.55 (0.21, 1.42)
US FDA MACE	0.6	0.5	0.3	0.3	0.3	0.49 (0.19, 1.25)
Modified US FDA MACE	0.8	0.5	0.6	0.5	0.5	0.62 (0.29, 1.33)
Cardiac disorders SOC SAEs	0.6	0.5	0.6	0.3	0.4	0.68 (0.28, 1.68)
Cardiovascular/neurovascular SAEs	1.5	1.0	0.9	0.7	0.8	0.54 (0.29, 0.98)

CI, confidence interval; MACE, major adverse cardiovascular event; MedDRA, Medical Dictionary for Regulatory Activities; MI, myocardial infarction; PHEN/TPM-ER, phentermine and topiramate extended-release; SAE, serious adverse event; SOC, system organ class; US FDA, US Food and Drug Administration.

^aComposite endpoint definitions: Jupiter MACE – cardiovascular death, myocardial infarction, stroke, coronary revascularization, and unstable angina; US FDA MACE – cardiovascular death, stroke, coronary revascularization, unstable angina, and congestive heart failure; modified US FDA MACE – cardiovascular death, acute coronary syndrome (nonfatal transient ischaemic attack), coronary revascularization, hospitalization for heart failure, stent thrombosis, hospitalization for other cardiovascular causes, carotid artery revascularization, peripheral vascular revascularization, lower extremity amputation, hospitalization for cardiac arrhythmia; cardiac disorders SOC SAEs – all SAE-preferred terms mapping to MedDRA; cardiovascular and neurovascular SAEs – all SAE-preferred terms mapping to the MedDRA Cardiac Disorders SOC, and SAEs with preferred terms of deep vein thrombosis, hypertension, hypotension, brain stem infarction, cerebral infarction, cerebrovascular accident, haemorrhage intracranial, transient ischaemic attack, chest pain, non-cardiac chest pain, and pulmonary embolism.

^bHazard ratio is from a univariate Cox proportional hazards regression analysis comparing PHEN/TPM-ER total to placebo.

many patients unable to attain or to maintain weight loss through dietary interventions and exercise. Given the increased cardiovascular and metabolic risk in this patient population, obesity pharmacotherapies must present minimal unwanted or adverse cardiovascular risks, which if present, should be outweighed by their other cardiovascular-related benefits. The rationale of combining low doses of PHEN/TPM-ER is to minimize side effects while maintaining weight loss efficacy. However, the treatment is not without side effects. For example, the topiramate extended-release component can induce paraesthesia and taste change, likely through carbonic anhydrase inhibition. Topiramate cannot be used by pregnant women due to teratogenic risks. The phentermine component can produce adrenergic symptoms, such as dry mouth. However, it is clinically reassuring that weight loss induced by PHEN/TPM-ER was associated with improved BP through 1 and 2 years of treatment. Although small, usually transient, increases in heart rate were observed in some patients, there were concurrent reductions in BP and rate pressure product, suggesting that, when used in conjunction with lifestyle modifications, PHEN/TPM-ER may represent a safe and effective therapy for the management of obesity in the patient populations studied (those with low-to-intermediate cardiovascular risk). The influences of PHEN/TPM-ER treatment on cardiovascular outcomes are currently being tested in a large multinational trial.

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Conflicts of interest

J.J. has participated in advisory boards for Boehringer-Ingelheim, Sanofi-Aventis, and Novartis, has been a consultant for Sanofi-Aventis and Novartis, and has received research support from Novartis, Sanofi-Aventis, CVRx, Inc., and Boehringer-Ingelheim. A.A. has been a consultant for Arena Pharmaceuticals, Basic Research, Gelesis, Inc., Doyen Medical Inc., Novo Nordisk, Orexigen Therapeutics Inc., Rhythm Pharmaceuticals, S-Biotek, Twinlab, and VIVUS, Inc. S.E. has received research support for clinical trials from Novartis. K.N. has participated in advisory boards for Medtronic and Boehringer-Ingelheim, has been a consultant for Medtronic, and has received research support for clinical trials for Abbott and Daiichi Sankyo. K.N. has also received honoraria for speakers/chairmanship at meetings for Abbott, Adamed, Astra Zeneca, Bayer, Berlin-Chemie, Boehringer-Ingelheim, Daiichi-Sankyo, Krka, Menarini, Novartis, Pfizer, Polpharma, Sanofi-Aventis, and Servier. W.W.D. is an employee of VIVUS, Inc. N.F. has been a consultant to VIVUS, Inc., and has participated in advisory board(s) for Novo Nordisk, Abbott, and Sanofi-Aventis, is a stockholder of Counterweight plc, and is an employee of UCLH NHS Trust.

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Reviewers' Summary Evaluations

Reviewer 1

This review showed that combining low doses of phentermine and topiramate for the treatment of obesity minimized side effects while maintained weight loss efficacy. The side effects were paraesthesia, taste changes and dry mouth.

Weight loss induced by the combination was associated with improved BP through one and two years of treatment. A small, usually transient increase in heart rate was observed. However, reductions in BP and rate pressure product were seen suggesting that when used in conjunction with lifestyle modifications, the combination may represent a safe and effective therapy for the management of obesity. A large multinational trial concerning cardiovascular outcomes is ongoing.

Reviewer 2

Combination drug treatment based on phentermine and topiramate has been recently approved by the FDA for the treatment of overweight and obesity. The paper by Jordan et al. provides an updated review on the cardiovascular effects of this new therapeutic approach which, along with its significant and sustained weight loss effects, improves triglycerides and HDL cholesterol and significantly decreases blood pressure values throughout the body weight reduction.

The information available so far on the impact the drug has on cardiovascular events (limited at present at the one year follow-up) confirms the favourable effects the drug has on cardiovascular risk.