Effects of low-dose, controlled-release, phentermine plus topiramate combination on weight and associated comorbidities in overweight and obese adults (CONQUER): a randomised, placebo-controlled, phase 3 trial

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Summary

Background Obesity is associated with a reduction in life expectancy and an increase in mortality from cardiovascular diseases, cancer, and other causes. We therefore assessed the efficacy and safety of two doses of phentermine plus topiramate controlled-release combination as an adjunct to diet and lifestyle modification for weight loss and metabolic risk reduction in individuals who were overweight and obese, with two or more risk factors.

Methods In this 56-week phase 3 trial, we randomly assigned overweight or obese adults (aged 18–70 years), with a body-mass index of 27–45 kg/m² and two or more comorbidities (hypertension, dyslipidaemia, diabetes or prediabetes, or abdominal obesity) to placebo, once-daily phentermine 7·5 mg plus topiramate 46·0 mg, or once-daily phentermine 15·0 mg plus topiramate 92·0 mg in a 2:1:2 ratio in 93 centres in the USA. Drugs were administered orally. Patients were randomly assigned by use of a computer-generated algorithm that was implemented through an interactive voice response system, and were stratified by sex and diabetic status. Investigators, patients, and study sponsors were masked to treatment. Primary endpoints were the percentage change in bodyweight and the proportion of patients achieving at least 5% weight loss. Analysis was by intention to treat. This study is registered with Clinical Trials.gov, number NCT00553787.

Findings Of 2487 patients, 994 were assigned to placebo, 498 to phentermine 7·5 mg plus topiramate 46·0 mg, and 995 to phentermine 15·0 mg plus topiramate 92·0 mg; 979, 488, and 981 patients, respectively, were analysed. At 56 weeks, change in bodyweight was –1·4 kg (least-squares mean –1·2%, 95% CI –1·8 to –0·7), –8·1 kg (–7·8%, –8·5 to –7·1; p<0·0001), and –10·2 kg (–9·8%, –10·4 to –9·3; p<0·0001) in the patients assigned to placebo, phentermine 7·5 mg plus topiramate 46·0 mg, and phentermine 15·0 mg plus topiramate 92·0 mg, respectively. 204 (21%) patients achieved at least 5% weight loss with placebo, 303 (62%; odds ratio 6·3, 95% CI 4·9 to 8·0; p<0·0001) with phentermine 7·5 mg plus topiramate 46·0 mg, and 687 (70%; 9·0, 7·3 to 11·1; p<0·0001) with phentermine 15·0 mg plus topiramate 92·0 mg; for ≥10% weight loss, the corresponding numbers were 72 (7%), 182 (37%; 7·6, 5·6 to 10·2; p<0·0001), and 467 (48%; 11·7, 8·9 to 15·4; p<0·0001). The most common adverse events were dry mouth (24 [2%], 67 [13%], and 207 [21%] in the groups assigned to placebo, phentermine 7·5 mg plus topiramate 46·0 mg, and phentermine 15·0 mg plus topiramate 92·0 mg, respectively), paraesthesia (20 [2%], 68 [14%], and 204 [21%], respectively), constipation (59 [6%], 75 [15%], and 173 [17%], respectively), insomnia (47 [5%], 29 [6%], and 102 [10%], respectively), dizziness (31 [3%], 36 [7%], 99 [10%], respectively), and dysgeusia (11 [1%], 37 [7%], and 103 [10%], respectively). 38 (4%) patients assigned to placebo, 19 (4%) to phentermine 7·5 mg plus topiramate 46·0 mg, and 73 (7%) to phentermine 15·0 mg plus topiramate 92·0 mg had depression-related adverse events; and 28 (3%), 24 (5%), and 77 (8%), respectively, had anxiety-related adverse events.

Interpretation The combination of phentermine and topiramate, with office-based lifestyle interventions, might be a valuable treatment for obesity that can be provided by family doctors.

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Introduction

Obesity is associated with reduced life expectancy and increased mortality from cardiovascular disease, cancer, and other causes.[1–4] About 90% of cases of type 2 diabetes are attributable to excess weight, and there is a five-to-six times increase in hypertension among obese individuals compared with those with normal weight.[5–7]

In patients with diabetes, a weight reduction of 5–10% improves obesity-related risk factors and comorbidities,[8] with substantial improvements in glycaemia, blood pressure, and lipid concentrations.[9] Intensive lifestyle-modification programmes that produce significant weight loss, and concomitant benefits, in obese patients with prediabetes or diabetes have to be implemented by trained counsellors during frequent office visits, and are not readily incorporated into visits to the family doctor.[10,11] An effective pharmacological intervention that can produce 5–10% greater weight loss than does brief office-based

counselling alone could meet the need for improved medical management of the obese patient.

Phentermine, a central norepinephrine-releasing drug, approved in 1959 for short-term obesity treatment at 15·0–37·5 mg/day, remains the most widely prescribed antiobesity drug in the USA.[12] No long-term (≥1 year) randomised controlled trials of phentermine have been reported. At approved doses, phentermine has no serotonergic activity and has negligible effects on dopamine release.[13] Topiramate has several pharmacological mechanisms of action, and is marketed for the treatment of epilepsy and migraine prophylaxis. It was assessed alone for weight reduction in obese patients without and with type 2 diabetes and hypertension.[14–19] However, dose-dependent neuropsychiatric adverse events, mainly memory and mood events including depression, hindered its development as monotherapy for obesity.

See Online for webappendix

Since several neuronal and peripheral pathways are implicated in the regulation of food intake, satiety, and energy homoeostasis, combinations of drugs with additive or synergistic effects could overcome the biological compensatory mechanisms.[20] Furthermore, drug combinations might improve tolerability if doses could be carefully modulated. In the CONQUER study, we assessed efficacy and safety of two doses of a once-daily, controlled-release phentermine plus topiramate combination for weight reduction during 56 weeks in adults who were overweight or obese, and had weight-related comorbidities.

Methods

Patients and study design

CONQUER was a randomised, double-blind, placebo-controlled study undertaken in 93 centres in the USA. Patients (aged 18–70 years) were eligible if they were overweight or obese with a body-mass index (BMI) of 27–45 kg/m². No lower BMI limit was set for patients diagnosed with diabetes at baseline. Inclusion criteria were two or more of the following comorbidities at baseline: systolic blood pressure 140–160 mm Hg (130–160 mm Hg in patients with diabetes), diastolic blood pressure 90–100 mm Hg (85–100 mm Hg in patients with diabetes), or taking at least two antihypertensive drugs; concentration of triglycerides 2·26–4·52 mmol/L or using at least two lipid-lowering drugs; concentration of fasting blood glucose greater than 5·55 mmol/L, blood glucose greater than 7·77 mmol/L at 2 h after oral glucose load during oral glucose tolerance test, or diagnosed type 2 diabetes managed with lifestyle changes or metformin monotherapy; and waist circumference of at least 102 cm for men or at least 88 cm for women.

Exclusion criteria included blood pressure greater than 160/100 mm Hg, a concentration of fasting glucose greater than 13·32 mmol/L or triglycerides greater than 4·52 mmol/L at randomisation, type 1 diabetes, use of antidiabetic drugs other than metformin, history of nephrolithiasis, recurrent major depression, presence or history of suicidal behaviour or ideation with intent to act, and current substantial depressive symptoms (Patient Health Questionnaire [PHQ-9][21] total score ≥10). Antidepressant drugs (but not tricyclic antidepressant drugs and monoamine oxidase inhibitors) were allowed if the dose was stable for 3 months. Detailed exclusion criteria are provided in the webappendix p 1.

The trial was approved by each centre's institutional review board, and overseen by an independent data safety review board. All patients provided written informed consent.

Randomisation and masking

Eligible patients were randomly assigned in a 2:1:2 ratio to once-daily treatment with placebo, once-daily, controlled-release combination of phentermine 7·5 mg plus topiramate 46·0 mg, and once-daily controlled-release combination of phentermine 15·0 mg plus topiramate 92·0 mg for 56 weeks with standardised counselling for diet and lifestyle modification. Medpace (coordinating centre) used a computer-generated algorithm that was implemented through an interactive voice response system to assign patients according to the random allocation sequence, with a block size of eight. Patients were stratified according to their sex and diabetic status (only diabetes, not prediabetes). Study drugs were administered as capsules that were identical in size and appearance. Investigators, patients, and study sponsors were masked to treatment assignment. Enrolment was skewed towards the higher dose of phentermine plus topiramate, and placebo to improve the capture of the benefit-risk profile and because the higher dose was believed to be the most effective. All patients had dose titration during the initial 4 weeks, starting at phentermine 3·75 mg plus topiramate 23·00 mg, or placebo, with weekly increases in phentermine (3·75 mg) plus topiramate (23·00 mg) until the achievement of the assigned doses, which were then maintained for 52 weeks. Masked dose reductions and interruptions were options, with discontinuation for patients who were unable to tolerate the drugs. Patients who discontinued the study drug were encouraged to remain in the study, continue lifestyle counselling, and complete study assessments. Comorbidities were managed according to national standards of care, and concomitant drugs could be adjusted to achieve these goals.

At baseline, each patient was provided with a LEARN manual,[22] advised to implement lifestyle changes as appropriate, and given instructions to reduce their caloric intake by 500 kcal/day. Progress was discussed with study staff during monthly visits.

Visits and assessments

Study visits were at screening, baseline, weeks 2 and 4 during drug titration, and every 4 weeks thereafter.

Assessments of patients included bodyweight, blood pressure, heart rate, waist circumference, clinical and laboratory variables, concomitant drugs, adverse events, and treatment compliance. The PHQ-9 was completed at each visit to assess depressive symptoms, with further assessment and referral to a mental health professional when clinically warranted. Trained clinicians administered the Columbia Suicide Severity Rating Scale (C-SSRS)[23] at each visit, and investigators further assessed patients with positive responses.

Study outcomes

The predefined coprimary outcomes were the mean percentage change in bodyweight and the proportion of patients achieving at least 5% weight loss.[24] Secondary outcomes were weight loss, proportion of patients achieving at least 10% weight loss, and change in waist circumference. Other efficacy variables included changes in BMI, blood pressure, lipids, glycaemic measurements (fasting glucose, glycated haemoglobin, fasting insulin), biomarkers, concomitant drugs for comorbidities, rate of progression to diabetes in patients without diabetes, and body composition assessed by use of dual-energy x-ray absorptiometry at selected study centres. Patients without diabetes were judged to have progressed to type 2 diabetes if two or more consecutive measurements showed fasting glucose concentrations of at least 6·99 mmol/L or the oral glucose tolerance test after 2 h was at least 11·1 mmol/L.[25] Safety outcomes included physical examination, vital signs, electrocardiogram (ECG), adverse events, PHQ-9, and C-SSRS.

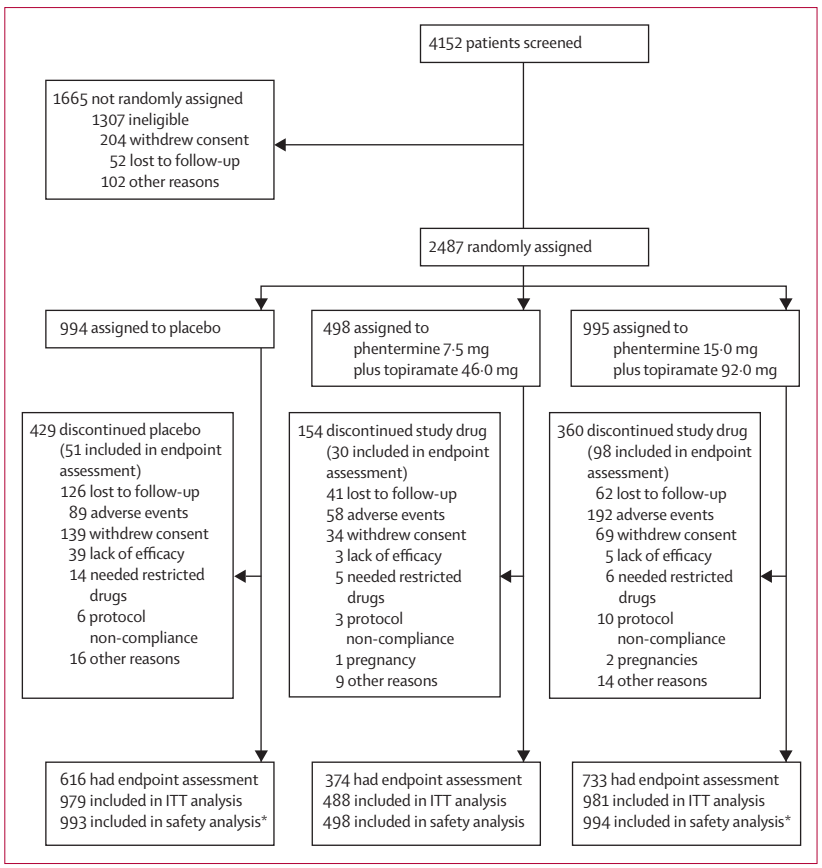

Figure 1: **Trial profile**
ITT=intention to treat. *One patient in the placebo group and one in the phentermine 15·0 mg plus topiramate 92·0 mg group discontinued without ever taking a dose of the study drug; these patients were not included in the safety analyses.

Statistical analysis

Power analysis based on data from a previous study[26] suggested that 250 patients in each group would provide greater than 95% power to detect a difference of 4·4% in weight loss between placebo and active treatments at a significance level of 0·05. To enhance the power for detecting differences in safety outcomes, we planned to enrol about 2500 patients.

The primary analyses were done on the intention-to-treat sample, consisting of all patients who were randomly assigned, took at least one dose of the study drug or placebo, and had one postbaseline bodyweight measurement. The primary efficacy endpoint of percentage weight loss was assessed at week 56 with last observation carried forward. ANCOVA was used to assess the percentage weight loss with treatment, sex, diabetic status, and baseline weight as covariates. This method was also used for analysis of all other continuous efficacy variables. Analyses of proportions of categorical endpoints were done by use of a logistic regression model with the covariates.

All randomised patients were included in the sensitivity analysis, which was done with multiple imputation for missing data (webappendix p 1). We also did an analysis of only the patients who completed the trial on study drug or placebo and for whom the final endpoint measurement was obtained within 7 days of the last dose of the study drug or placebo. The data were analysed with the ANCOVA model described above.

Safety analyses were based on incidence of adverse events, laboratory assessments, vital signs, ECG, physical examination, and rating scales to assess depression (PHQ-9) and suicidality (C-SSRS). Frequencies of adverse events were compared by use of Fisher's exact test with 2×2 contingency tables; the comparisons were phentermine 7·5 mg plus topiramate 46·0 mg with placebo, and phentermine 15·0 mg plus topiramate 92·0 mg with placebo.

This trial is registered with ClinicalTrials.gov, number NCT00553787.

Role of the funding source

The sponsor of the study collaborated with the investigators in protocol design, data analyses, interpretation, and preparation of the report. MLS had responsibility for the data and analyses. The authors had full freedom to express their views. The corresponding

	Placebo (n=994)	Phentermine 7·5 mg plus topiramate 46·0 mg (n=498)	Phentermine 15·0 mg plus topiramate 92·0 mg (n=995)
Age (years)	51·2 (10·25)	51·1 (10·43)	51·0 (10·65)
Women	695 (70%)	349 (70%)	693 (70%)
Ethnic origin			
White	861 (87%)	429 (86%)	850 (85%)
African	114 (11%)	56 (11%)	122 (12%)
Asian	6 (<1%)	5 (1%)	11 (1%)
Native American or Alaska Native	4 (<1%)	6 (1%)	8 (<1%)
Native Hawaiian or other Pacific Islander	2 (<1%)	2 (<1%)	3 (<1%)
Other	12 (1%)	5 (1%)	8 (<1%)
Weight (kg)	103·3 (18·1)	102·6 (18·2)	103·0 (17·6)
Body-mass index (kg/m²)	36·7 (4·6)	36·2 (4·4)	36·6 (4·5)
Waist circumference (cm)	113·4 (12·2)	112·6 (12·5)	113·2 (12·2)
Blood pressure (mm Hg)*			
Systolic	128·9 (13·5)	128·3 (13·8)	127·9 (13·4)
Diastolic	81·1 (9·2)	80·6 (8·8)	80·1 (9·1)
Heart rate (beats per min)*	72·1 (9·9)	72·1 (10·1)	72·6 (10·1)
Total cholesterol (mmol/L)†	5·3 (1·1)	5·2 (1·0)	5·3 (1·0)
LDL cholesterol (mmol/L)‡	3·2 (0·9)	3·1 (0·9)	3·2 (0·9)
HDL cholesterol (mmol/L)†	1·3 (0·4)	1·3 (0·3)	1·3 (0·4)
Triglycerides (mmol/L)†	1·8 (0·9)	1·8 (0·8)	1·8 (0·8)
Fasting glucose (mmol/L)§	5·9 (1·3)	5·9 (1·2)	5·9 (1·2)
Glycated haemoglobin (%)¶	5·9 (0·8)	5·8 (0·7)	5·9 (0·8)
Fasting insulin (pmol/L)‖	124·3 (95·1)	125·7 (88·9)	127·8 (120·1)
hsCRP (mg/L)**	6·4 (7·6)	6·9 (11·6)	6·7 (11·3)
Adiponectin (μg/mL)††	7·9 (4·6)	8·1 (4·5)	7·9 (4·6)
History of depression	179 (18%)	81 (16%)	165 (17%)
Antidepressant drugs	170 (17%)	83 (17%)	144 (14%)
Hypertension (systolic blood pressure 140–160 mm Hg or diastolic blood pressure 90–100 mm Hg, or controlled [<140/90 mm Hg] with two or more antihypertensive drugs)	524 (53%)	261 (52%)	520 (52%)
Hypertriglyceridaemia (fasting triglycerides between 2·26 mmol/L and 4·52 mmol/L, or taking two or more lipid-lowering drugs with fasting triglycerides <2·26 mmol/L)	354 (36%)	180 (36%)	363 (36%)
Type 2 diabetes or impaired glucose tolerance‡‡	675 (68%)	345 (69%)	664 (67%)
Abdominal obesity (waist circumference ≥102 cm for men, or ≥88 cm for women)	975 (98%)	490 (98%)	981 (99%)
Three or more comorbidities§§	514 (52%)	259 (52%)	500 (50%)

Data are mean (SD) or number (%). hsCRP=high-sensitivity C-reactive protein. *Values were missing for two patients—one in the placebo group and one in the group assigned to phentermine 15·0 mg plus topiramate 92·0 mg. †At baseline, values were missing for two patients—one in the placebo group and one in the group assigned to phentermine 15·0 mg plus topiramate 92·0 mg. ‡At baseline, values were missing for seven patients—four in the placebo group, and three in the group assigned to phentermine 15·0 mg plus topiramate 92·0 mg. §At baseline, values were missing for 11 patients—four in the placebo group, and seven in the group assigned to phentermine 15·0 mg plus topiramate 92·0 mg. ¶At baseline, values were missing for nine patients—five in the placebo group, and four in the group assigned to phentermine 15·0 mg plus topiramate 92·0 mg. ‖At baseline, values were missing for 20 patients—seven in the placebo group, three in the group assigned to phentermine 7·5 mg plus topiramate 46·0 mg, and ten in the group assigned to phentermine 15·0 mg plus topiramate 92·0 mg. **At baseline, values were missing for 14 patients—six in the placebo group, and eight in the group assigned to phentermine 15·0 mg plus topiramate 92·0 mg. ††At baseline, values were missing for 486 patients—251 in the placebo group, 77 in the group assigned to phentermine 7·5 mg plus topiramate 46·0 mg, 158 in the group assigned to phentermine 15·0 mg plus topiramate 92·0 mg. ‡‡An established diagnosis of type 2 diabetes, managed with lifestyle modifications or metformin; impaired glucose tolerance was defined as fasting glucose concentration greater than 5·55 mmol/L, or greater than 7·77 mmol/L at 2 h after a 75 g glucose load during an oral glucose tolerance test. §§Includes patients with abdominal obesity.

Table 1: **Demographic and baseline characteristics of patients**

author had full access to the study data and had final responsibility for the decision to submit for publication.

Results

The study was undertaken between Nov 1, 2007, and June 30, 2009. Figure 1 shows the trial profile. Patient characteristics at baseline were similar in the three groups (table 1). Most patients were women (n=1737 [70%]) and were white (n=2140 [86%]). Mean age for the whole group was 51·1 years (SD 10·4), bodyweight was 103·1 kg (17·9), and BMI was 36·6 kg/m² (4·5). According to protocol-specified definitions, 1305 (52%) patients had hypertension,

897 (36%) had hypertriglyceridaemia, 1684 (68%) had impaired glucose tolerance or impaired fasting glucose (including type 2 diabetes), and 393 (16%) had type 2 diabetes; 1273 (51%) had three or more protocol-specified comorbidities, and 2446 (98%) had abdominal obesity (large waist circumference; table 1). Among patients with diabetes, 14 had a BMI of less than 27 kg/m² at baseline. 425 (17%) patients had a history of depression, and 397 (16%) were taking antidepressant drugs at baseline.

In total, 943 (38%) patients discontinued the study drugs—43% in the placebo group, 31% in the group assigned to phentermine 7·5 mg plus topiramate 46·0 mg, and 36% in the group assigned to phentermine 15·0 mg plus topiramate 92·0 mg (figure 1). 1723 (69%) patients, irrespective of whether they were given the study drug throughout or completed all the visits, had endpoint (week 56) assessment.

Both doses of the phentermine plus topiramate combination showed greater efficacy than did placebo for each primary outcome measure (figure 2; webappendix p 4). The change in bodyweight was significantly greater in the groups assigned to phentermine 7·5 mg plus topiramate 46·0 mg (absolute change –8·1 kg, least-squares mean –7·8% [95% CI –8·5 to –7·1]; difference –6·6% [–7·4 to –5·8]; p<0·0001), and phentermine 15·0 mg plus topiramate 92·0 mg (–10·2 kg, –9·8% [–10·4 to –9·3]; –8·6% [–9·3 to –8·0]; p<0·0001) than in the placebo group (–1·4 kg; –1·2% [–1·8 to –0·7]) in the intention-to-treat analysis (figure 2A). Patients (1520 [61%]) who completed 1 year of treatment had an absolute bodyweight change of –9·9 kg (–9·6% [–10·4 to –8·7]; –8·0% [–9·0 to –7·0]; p<0·0001) with phentermine 7·5 mg plus topiramate 46·0 mg, and –12·9 kg (12·4% [–13·1 to –11·7]; –10·8% [–11·6 to –10·0]; p<0·0001) with phentermine 15·0 mg plus topiramate 92·0 mg compared with –1·8 kg (1·6% [–2·3 to –0·9]) in the placebo group.

In the intention-to-treat sample (figure 2B), 204 (21%) patients in the placebo group achieved a weight loss of at least 5% compared with 303 (62%) in the phentermine 7·5 mg plus topiramate 46·0 mg group (odds ratio 6·3 [95% CI 4·9 to 8·0]; p<0·0001), and 687 (70%) in the phentermine 15·0 mg plus topiramate 92·0 mg group (9·0 [7·3 to 11·1]; p<0·0001). A similar pattern was noted with the 10% or more threshold for weight loss: 72 (7%) patients in the placebo group achieved a weight loss of at least 10% compared with 182 (37%) in the phentermine 7·5 mg plus topiramate 46·0 mg group (7·6 [5·6 to 10·2]; p<0·0001), and 467 (48%) in the phentermine 15·0 mg plus topiramate 92·0 mg group (11·7 [8·9 to 15·4]; p<0·0001). The multiple imputation for continuous and categorical weight loss showed larger effects than those noted with the LOCF analysis with similar between-group differences (webappendix p 4).

In subgroup analyses of sex, age, race, baseline BMI, and comorbidities (webappendix p 4), phentermine plus topiramate resulted in greater weight loss than did placebo.

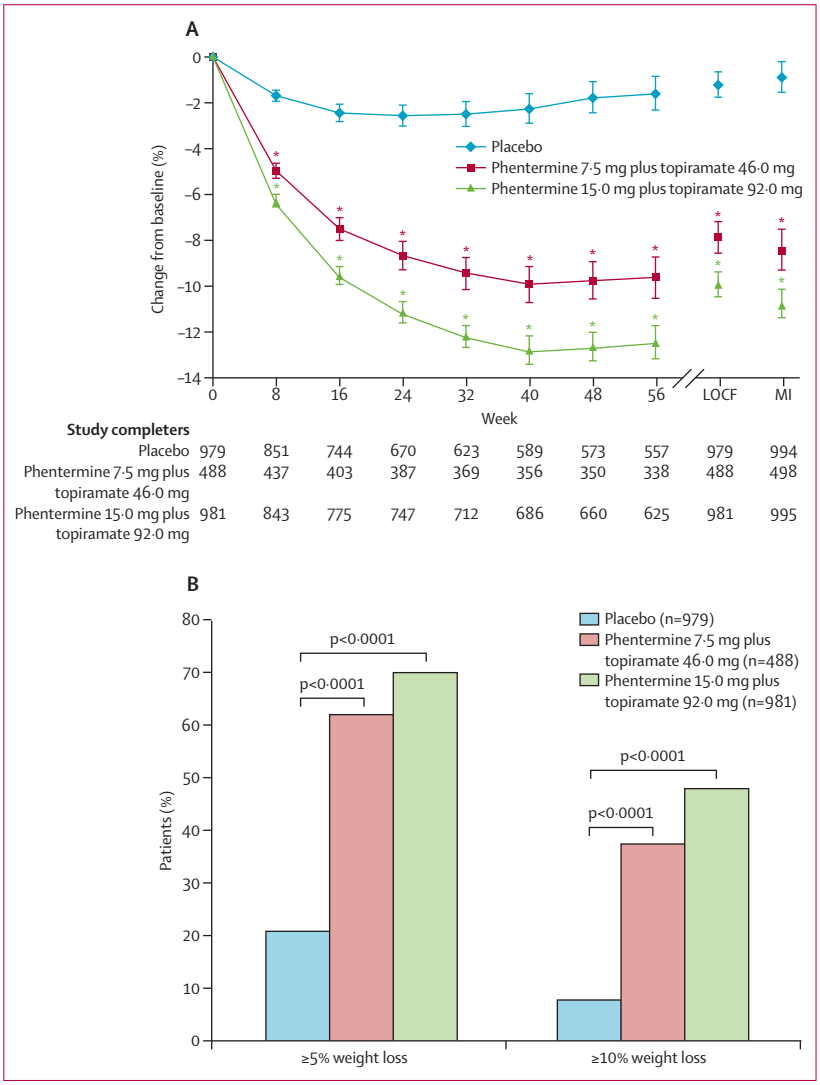

Figure 2: **Effects of phentermine plus topiramate on bodyweight**
(A) Least-squares mean change (95% CI) derived from three different statistical analyses. Weight change curves are plotted for completers by visit; shown to the right of the graph are data derived from the analyses of the intention-to-treat LOCF and MI. (B) Patients with at least 5% and at least 10% weight loss. LOCF=last observation carried forward. MI=multiple imputation.

Significant improvements were noted in blood pressure, waist circumference, concentrations of lipids, glycaemia, and inflammatory biomarkers (high-sensitivity C-reactive protein and adiponectin) with phentermine plus topiramate compared with placebo (table 2).

Improvements in risk factors were most pronounced in patients with pre-existing comorbid diseases, although comorbidities were generally well controlled at study entry (figure 3). In hypertensive patients, greater reductions in systolic blood pressure were noted with phentermine plus topiramate than with placebo (figure 3A), and more patients had their antihypertensive drugs withdrawn in the phentermine 7·5 mg plus topiramate 46·0 mg group (27 [11%] of 256) and phentermine 15·0 mg plus topiramate 92·0 mg group

	Placebo	Phentermine 7·5 mg plus topiramate 46·0 mg	p value	Phentermine 15·0 mg plus topiramate 92·0 mg	p value
Waist circumference (cm)	−2·4 (−3·0 to −1·8); n=979	−7·6 (−8·4 to −6·9); n=488	<0·0001	−9·2 (−9·8 to −8·6); n=981	<0·0001
Systolic blood pressure (mm Hg)	−2·4 (−3·3 to −1·5); n=979	−4·7 (−5·9 to −3·5); n=488	0·0008	−5·6 (−6·5 to −4·6); n=980	<0·0001
Diastolic blood pressure (mm Hg)	−2·7 (−3·3 to −2·1); n=979	−3·4 (−4·2 to −2·6); n=488	0·1281	−3·8 (−4·4 to −3·2); n=980	0·0031
Total cholesterol (%)	−3·3 (−4·4 to −2·3); n=941	−4·9 (−6·3 to −3·6); n=475	0·0345	−6·3 (−7·4 to −5·3); n=964	<0·0001
LDL cholesterol (%)	−4·1 (−5·8 to −2·4); n=936	−3·7 (−6·0 to −1·5); n=475	0·7391	−6·9 (−8·6 to −5·2); n=961	0·0069
HDL cholesterol (%)	1·2 (−0·1 to 2·5); n=941	5·2 (3·5 to 6·9); n=475	<0·0001	6·8 (5·5 to 8·1); n=964	<0·0001
Triglycerides (%)	4·7 (1·4 to 8·0); n=941	−8·6 (−12·9 to −4·2); n=475	<0·0001	−10·6 (−13·9 to −7·3); n=964	<0·0001
Fasting glucose (mmol/L)	0·13 (0·06 to 0·19); n=938	−0·01 (−0·09 to 0·08); n=473	0·0047	−0·07 (−0·14 to −0·01); n=954	<0·0001
Glycated haemoglobin (%)	0·1 (0 to 0·1); n=805	0 (−0·1 to 0); n=449	<0·0001	−0·1 (−0·1 to 0); n=895	<0·0001
Fasting insulin (pmol/L)	5·1 (−6·0 to 16·3); n=925	−24·0 (−38·6 to −9·3); n=464	0·0004	−27·6 (−38·7 to −16·6); n=937	<0·0001
HOMA-IR	0·46 (−0·09 to 1·02); n=925	−0·93 (−1·67 to −0·20); n=464	0·0007	−1·07 (−1·62 to −0·52); n=937	<0·0001
hsCRP (mg/L)	−0·79 (−1·32 to −0·26); n=779	−2·49 (−3·17 to −1·81); n=440	<0·0001	−2·49 (−3·00 to −1·97); n=880	<0·0001
Adiponectin (µg/mL)	0·33 (0·11 to 0·56); n=737	1·40 (1·12 to 1·68); n=419	<0·0001	2·08 (1·87 to 2·29); n=836	<0·0001

Data are least-squares means (95% CI) derived from the intention-to-treat analysis with last observation carried forward, unless otherwise indicated. hsCRP=high-sensitivity C-reactive protein. HOMA-IR=homoeostasis model assessment–insulin resistance, calculated as (fasting glucose in mmol/L × fasting insulin in µIU/mL)/ 22·5. p values are for comparison of phentermine plus topiramate with placebo.

***Table 2*: Changes from baseline to week 56 in secondary endpoints**

(76 [15%] of 514) than in the placebo group (24 [5%] of 516). For the entire sample, reduction in diastolic blood pressure was only significant with phentermine 15·0 mg plus topiramate 92·0 mg (table 2); however, both doses were associated with a reduction in diastolic blood pressure in hypertensive patients (figure 3A). Similarly, for patients with hypertriglyceridaemia, phentermine plus topiramate led to greater improvements in concentrations of triglycerides and HDL cholesterol than did placebo, with more pronounced changes than in the overall sample (figure 3B).

Patients with diabetes (n=388), in addition to significant weight loss (least squares mean −1·9% [95% CI −3·1 to −0·8] with placebo; −6·8% [−8·6 to −5·1] with phentermine 7·5 mg plus topiramate 46·0 mg; difference −4·9 [−7·0 to −2·9; p<0·0001; and −8·8% [−9·9 to −7·7] with phentermine 15·0 mg plus topiramate 92·0 mg; difference −6·9% [−8·4 to −5·3]; p<0·0001), had greater reductions in glycated haemoglobin with both doses of phentermine plus topiramate than with placebo, showing more pronounced changes (figure 3C) than in the overall sample (table 2). Patients with prediabetes had greater reductions in fasting blood glucose and insulin with both doses of phentermine plus topiramate than with placebo (figure 3D). Fewer patients progressed to type 2 diabetes (webappendix p 5); the relative risk (*vs* placebo) was 0·78 (0·40–1·50) with phentermine 7·5 mg plus topiramate 46·0 mg, and 0·47 (0·25–0·88) with phentermine 15·0 mg plus topiramate 92·0 mg. More patients in the placebo group (23 [15%] of 157) needed an increase in the number of antidiabetic drugs than did those treated with phentermine 7·5 mg plus topiramate 46·0 mg (three [4%] of 67), and phentermine 15·0 mg plus topiramate 92·0 mg (seven [4%] of 164; webappendix p 5).

Quality of life, as assessed by use of Impact of Weight on Quality of Life-Lite Questionnaire[27] and Short Form 36[28] scales, showed greater improvements on most measurements in both active treatment groups than with placebo (data not shown).

Dose-related trends were noted for rates of dry mouth, constipation, dysgeusia, paraesthesia, insomnia, dizziness, anxiety, irritability, and disturbance in attention (table 3). Rates of serious adverse events were similar across treatment groups: 40 (4%) with placebo, 15 (3%) with phentermine 7·5 mg plus topiramate 46·0 mg, and 50 (5%) with phentermine 15·0 mg plus topiramate 92·0 mg. Dose-related increases in discontinuations due to adverse events were noted with phentermine 7·5 mg plus topiramate 46·0 mg (58 [12%]), and phentermine 15·0 mg plus topiramate 92·0 mg (191 [19%]) compared with placebo (88 [9%]; table 4). One placebo-treated patient died as a result of a cardiopulmonary arrest. A small increase in the mean heart rate was noted with phentermine 15·0 mg plus topiramate 92·0 mg (1·7 beats per min [95% CI 0·9 to 2·4], p<0·0001; phentermine 7·5 mg plus topiramate 46·0 mg, 0·1 beats per min [−1·0 to 1·1], p=0·92; placebo, −0·1 beats per min [−0·9 to 0·8], p=0·90; webappendix p 3). A greater proportion of patients in the phentermine plus topiramate groups than in the placebo group had increases of more than 10 beats per min at two consecutive visits (webappendix p 6).

Consistent with topiramate's inhibition of carbonic anhydrase, changes were noted in some laboratory tests of metabolism. Mean change in the concentration of serum bicarbonate was mild with phentermine 15·0 mg plus topiramate 92·0 mg (−1·0 [95% CI −1·2 to −0·8]; phentermine 7·5 mg plus topiramate 46·0 mg, −0·3 [−0·6 to 0]; and placebo, 0·5 [0·3 to 0·7]); substantial reductions (<17·0 mmol/L at two consecutive visits or at

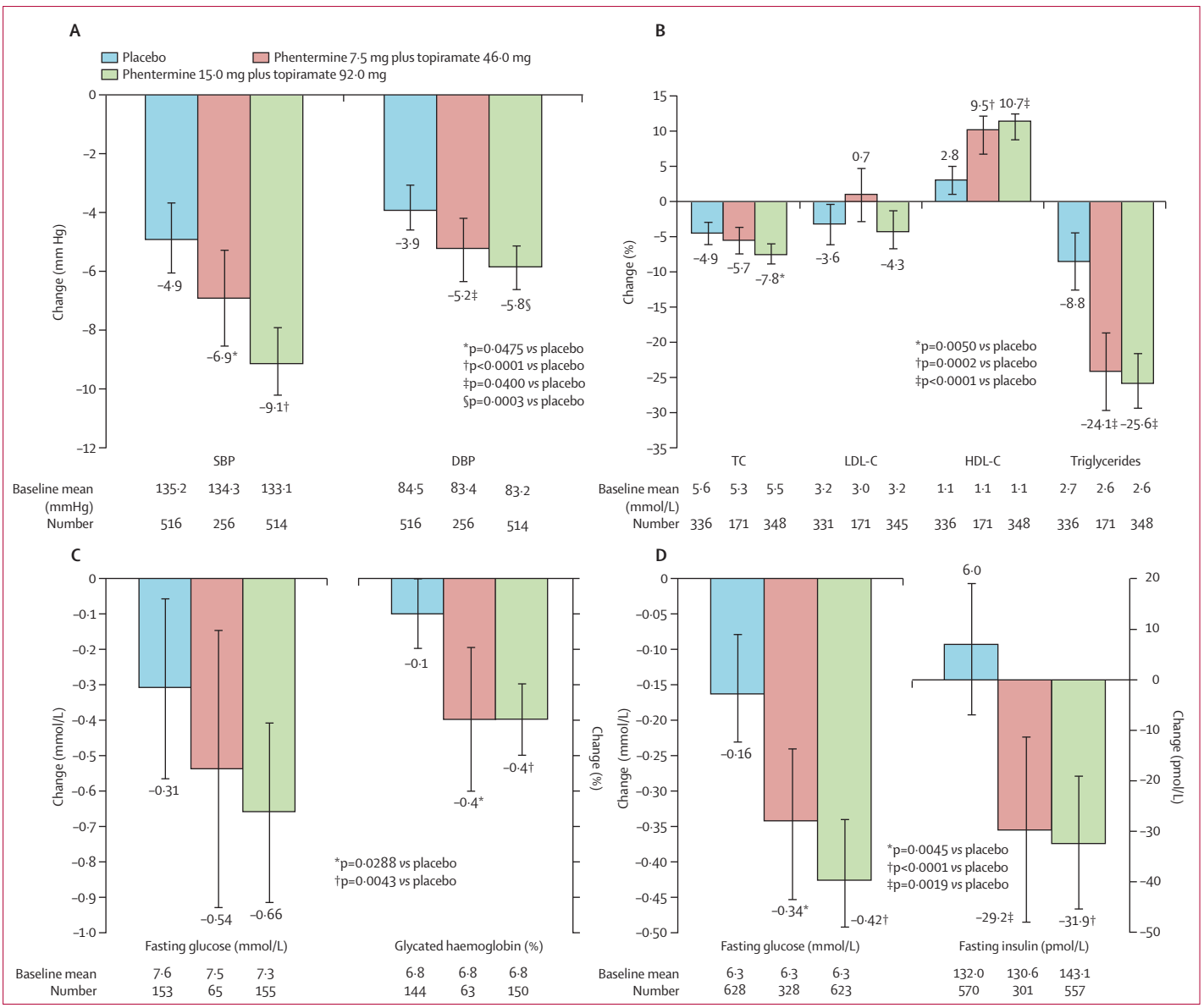

Figure 3: **Effects of phentermine plus topiramate on cardiometabolic variables in high-risk patients**
(A) Changes in blood pressure in patients with hypertension. (B) Changes in lipids in patients with hypertriglyceridaemia. (C) Changes in fasting glucose and glycated haemoglobin in patients with diabetes. (D) Changes in fasting glucose and fasting insulin in patients with prediabetes. Data are least-squares means (95% CI). Sample sizes for metabolic variables vary because the intention-to-treat sample consisted of all randomly assigned patients who took at least one study drug dose and had at least one postbaseline bodyweight measurement, and because some blood samples were missed. SBP=systolic blood pressure. DBP=diastolic blood pressure. TC=total cholesterol. LDL-C=LDL-cholesterol. HDL-C=HDL-cholesterol.

study exit) were noted in one patient (<1%) each with placebo and phentermine 7·5 mg plus topiramate 46·0 mg, and seven (<1%) with phentermine 15·0 mg plus topiramate 92·0 mg. Risk of nephrolithiasis, including three serious adverse events, was increased with phentermine 15·0 mg plus topiramate 92·0 mg, but not with the lower dose (table 4). Hypokalaemia showed a small dose-dependent increase in the rate with phentermine 7·5 mg plus topiramate 46·0 mg (seven [1%]), and phentermine 15·0 mg plus topiramate 92·0 mg (30 [3%]) compared with placebo (three [<1%]), and none of the cases was rated as severe. Persistence of potassium concentrations that were less than the lower limits of normal (<3·5 mmol/L at two consecutive visits or at study exit) was noted in 11 patients (1%) with placebo, 18 (4%) with phentermine 7·5 mg plus topiramate 46·0 mg, and 53 (5%) with phentermine 15·0 mg plus topiramate 92·0 mg. 40 (4%), 20 (4%), and 54 (5%) patients, respectively, had potassium supplementation at any point during the course of the study.

Based on the reported adverse events or the C-SSRS questionnaire, the incidence of suicidality was not

	Placebo (n=993)	Phentermine 7·5 mg plus topiramate 46·0 mg (n=498)	p value	Phentermine 15·0 mg plus topiramate 92·0 mg (n=994)	p value
Dry mouth	24 (2%)	67 (13%)	<0·0001	207 (21%)	<0·0001
Paraesthesia	20 (2%)	68 (14%)	<0·0001	204 (21%)	<0·0001
Constipation	59 (6%)	75 (15%)	<0·0001	173 (17%)	<0·0001
Upper respiratory tract infection	128 (13%)	61 (12%)	0·7422	133 (13%)	0·7906
Nasopharyngitis	86 (9%)	53 (11%)	0·2204	98 (10%)	0·3947
Dysgeusia	11 (1%)	37 (7%)	<0·0001	103 (10%)	<0·0001
Insomnia	47 (5%)	29 (6%)	0·3832	102 (10%)	<0·0001
Headache	90 (9%)	35 (7%)	0·1983	101 (10%)	0.4467
Dizziness	31 (3%)	36 (7%)	0·0005	99 (10%)	<0·0001
Sinusitis	67 (7%)	34 (7%)	1·0000	85 (9%)	0·1511
Back pain	49 (5%)	28 (6%)	0·6199	72 (7%)	0·0386
Nausea	42 (4%)	18 (4%)	0·6754	68 (7%)	0·0139
Fatigue	50 (5%)	22 (4%)	0·7010	67 (7%)	0·1270
Diarrhoea	48 (5%)	32 (6%)	0·2229	58 (6%)	0·3690
Blurred vision	36 (4%)	20 (4%)	0·7729	60 (6%)	0·0157
Urinary tract infection	37 (4%)	26 (5%)	0·1753	54 (5%)	0·0855
Arthralgia	54 (5%)	23 (5%)	0·5373	44 (4%)	0·3025
Bronchitis	43 (4%)	22 (4%)	1·0000	52 (5%)	0·4004
Psychiatric adverse events†					
Depression	29 (3%)	14 (3%)	0·9054	39 (4%)	0·2188
Anxiety	21 (2%)	9 (2%)	0·6899	41 (4%)	0·0100
Irritability‡	8 (<1%)	13 (3%)	0·0053	34 (3%)	<0·0001
Time to onset (days; median, IQR)	92 (26–164)	36 (8–138)	0·0988	29 (17–118)	0·0049
Duration (days; median, IQR)	44 (17–121)	35 (11–81)	0·2989	29 (12–63)	0·0252
Resolution among patients discontinuing drug	4/5 (80%)	10/10 (100%)	0·3333	33/37 (89%)	0·4876
Cognitive adverse events§					
Disturbance in attention	7 (<1%)	10 (2%)	0·0362	35 (4%)	<0·0001
Time to onset (days; median, IQR)	22 (8–119)	23 (10–100)	0·8958	25 (11–51)	0·8223
Duration (days; median, IQR)	39 (13–76)	51 (8–149)	0·4452	36 (18–81)	0·7353
Resolution among subjects discontinuing drug	3/3 (100%)	2/2 (100%)	NA	21/21 (100%)	NA

Data are number (%) or n/N (%), unless otherwise indicated. p values are for comparisons of phentermine plus topiramate with placebo. NA=not applicable. *Psychiatric and cognitive adverse events arising at a frequency of 2% or more, and other adverse events arising at a frequency of 5% or more with any treatment are shown. †Including the preferred terms in the psychiatric class, except sleep-related adverse events, from the Medical Dictionary for Regulatory Activities (MedDRA). ‡Included in the psychiatric adverse event category although it is classified as a general disorder in MedDRA. §Including the preferred terms from MedDRA: disturbance in attention, memory impairment, amnesia, confusional state, cognitive disorder, bradyphrenia, disorientation, mental impairment, aphasia, and dysarthria.

Table 3*: Adverse events in the safety population (n=2485)

For the **Medical Dictionary for Regulatory Activities** see http://www.meddramsso.com/

increased and there were no suicide attempts (webappendix p 6). Psychiatric adverse events (depression, anxiety, and irritability) and cognitive adverse events (disturbance in attention) occurred mainly during the early phase of treatment, generally resolved on drug discontinuation, and occurred at a higher frequency with phentermine plus topiramate in a dose-dependent manner (table 3). 38 (4%) patients assigned to placebo, 19 (4%) to phentermine 7·5 mg plus topiramate 46·0 mg, and 73 (7%) to phentermine 15·0 mg plus topiramate 92·0 mg had depression-related adverse events (excluding sleep disorders); and 28 (3%), 24 (5%), and 77 (8%), respectively, had anxiety-related adverse events (including irritability). Whereas depression incidence was higher with phentermine 15·0 mg plus topiramate 92·0 mg than with placebo (table 3), various analyses of PHQ-9 scores showed no differences (webappendix p 6). Use of new antidepressant drugs did not increase among patients treated with phentermine plus topiramate.

Discussion

The results of this study show robust efficacy of the phentermine plus topiramate combination for weight loss (as assessed with change in bodyweight and proportion of patients who achieved a weight loss of at least 5%) that was shown in a preliminary trial.[26] A major strength of our study was that we were able to assess the effects of weight loss on weight-related comorbidities—half the patients had at least three comorbidities, and a

	Placebo (n=993)	Phentermine 7·5 mg plus topiramate 46·0 mg (n=498)	p value	Phentermine 15·0 mg plus topiramate 92·0 mg (n=994)	p value
Nervous system disorders					
Paraesthesia	0	5 (1%)	0·0041	15 (2%)	<0·0001
Dizziness	2 (<1%)	6 (1%)	0·0196	9 (<1%)	0·0647
Headache	8 (<1%)	1 (<1%)	0·2865	6 (<1%)	0·6058
Dysgeusia	0	2 (<1%)	0·1114	8 (<1%)	0·0077
Disturbance in attention	1 (<1%)	0	1·0000	7 (<1%)	0·0698
Memory impairment	1 (<1%)	0	1·0000	5 (<1%)	0·2180
Lethargy	0	0	NA	5 (<1%)	0·0622
Psychiatric disorders					
Insomnia	6 (<1%)	2 (<1%)	0·7259	16 (2%)	0·0512
Depression	1 (<1%)	4 (<1%)	0·0453	14 (1%)	0·0009
Anxiety	3 (<1%)	1 (<1%)	1·0000	9 (<1%)	0·1448
Irritability	1 (<1%)	4 (<1%)	0·0453	9 (<1%)	0·0212
Gastrointestinal disorders					
Nausea	3 (<1%)	3 (<1%)	0·4075	5 (<1%)	0·7260
Constipation	2 (<1%)	1 (<1%)	1·0000	6 (<1%)	0·2881
Dry mouth	0	2 (<1%)	0·1114	7 (<1%)	0·0155
Other disorders					
Fatigue	4 (<1%)	0	0·3077	9 (<1%)	0·2653
Blurred vision	6 (<1%)	4 (<1%)	0·7394	8 (<1%)	0·7898
Hypertension	5 (<1%)	2 (<1%)	1·0000	3 (<1%)	0·5068
Nephrolithiasis	2 (<1%)	1 (<1%)	1·0000	11 (1%)	0·0220

Data are number (%). Only adverse events leading to discontinuation of 0·5% or more patients in any treatment group are reported. p values are for comparisons of phentermine plus topiramate with placebo. NA=not applicable.

Table 4: **Treatment-emergent adverse events leading to discontinuation of study drug in the safety population (n=2485)**

substantial proportion was receiving several concomitant treatments. Another notable strength was the inclusion of susceptible patients—ie, those with mild depressive symptoms, stable on most widely used antidepressant drugs, and patients with a history of no more than one major depressive episode. Furthermore, patients with a history of suicidality were not excluded as long as there was no intent to act.

A limitation of the study was that endpoint assessments were not available for 31% of the sample, which is consistent with what has been generally noted in 1-year large weight loss trials of pharmaceutical interventions, and lower than the roughly 50% dropout rates in phase 3 trials of lorcaserin and naltrexone plus bupropion, two new investigational drugs.[29,30] To address this potential concern, we analysed the data by use of three different methods, all of which provided similar results. Other limitations were restriction of the upper limit of BMI to 45 kg/m², lack of ethnic diversity (86% white), and few men (30%), and thus affected the generilisability of the findings. Lifestyle intervention alone (placebo) resulted in a small weight loss of 1·2%, indicating that it was ineffective; hence, how much additional weight loss this drug combination could achieve when added to a robust lifestyle intervention programme is not known. Furthermore, with the trial lacking an active comparator group, comparisons with other available and emerging interventions are speculative.

Both doses of the controlled formulation of phentermine plus topiramate, with a slight lifestyle intervention, resulted in robust weight loss and comorbid risk reduction. Only 7% of placebo-treated patients achieved 10% weight loss, whereas almost half those treated with the higher dose of phentermine plus topiramate, and 37% of those treated with the lower dose achieved this benchmark. Most importantly, weight loss achieved with phentermine plus topiramate was sustained during 56 weeks (figure 2A) with improvements in blood pressure, lipids, glycaemia, and inflammatory markers. Reduction in concomitant use of drugs with phentermine plus topiramate suggests that an effective weight loss treatment could reduce the need for treatment of each disease by addressing the underlying pathophysiological changes of obesity-related disease.

Phentermine plus topiramate was effective for patients with different BMIs, and those with hypertension, type 2 diabetes, impaired glucose tolerance (prediabetes), and hypertriglyceridaemia. Obese patients with diabetes, not receiving insulin, and treated only with diet and exercise or metformin, achieved clinically significant weight loss and glycaemic improvement with phentermine plus topiramate, with fewer patients needing additional

	Duration (years)	Sample size	Dropouts	Weight loss with drug	Weight loss with placebo
Orlistat					
Meta-analysis[32] of 13 randomised controlled trials	1–4	6196	~30%	−2·9%*	NA
Lorcaserin					
BLOOM†[29]	1	3182	50%	−5·8%	−2·2
BLOSSOM‡[29]	1	3206	45%	−5·8%	−2·8
Naltrexone plus bupropion					
NB-301[30]	1	1164	50%	−6·1	−1·3
NB-302§[30]	1	793	42%	−9·3	−5·1
NB-303¶[30]	1	1496	46%	−6·5	−1·9
NB-304‖[30]	1	505	45%	−5·0	−1·8

In most cases, results were based on a modified intention-to-treat analysis of data for patients who took one dose of the study drug and had at least one follow-up assessment. In some studies, overweight patients were included in addition to those who were obese. There were many differences between studies in terms of the eligibility criteria. For lorcaserin and naltrexone plus bupropion, data are shown for the most effective dose when more than one dose was tested. NA=not applicable. *Relative to placebo. †First-year data only. ‡Data are for the highest dose (10 mg twice a day). §Ancillary intensive lifestyle intervention was administered to all patients. ¶Patients showing inadequate response were rerandomised at 6 months to a higher dose. ‖Overweight or obese patients with diabetes.

Table 5: **Current and emerging antiobesity drugs**

Panel: Research in context

Systematic review

We searched PubMed for papers with the terms "weight reduction", "weight loss", "obesity", "appetite suppressants", and "weight loss drugs". We reviewed randomised clinical trials and meta-analyses. For drugs that were being reviewed by the US Food and Drug Administration, we reviewed briefing documents that were posted in the context of advisory committee meetings.

Interpretation

After subtraction of the weight loss with placebo, 1-year weight loss with phentermine plus topiramate (−6·6% to −8·6%, some diabetic patients) compared favourably with orlistat (−2·9% after 1–4 years, some diabetic patients),[32] the only drug approved for long-term treatment of obesity, and emerging drugs with reported phase 3 trial data—lorcaserin (−3·3% for non-diabetic patients),[29] and naltrexone plus bupropion (−4·2% with some diabetic patients, −4·5% for non-diabetic patients).[30]

antidiabetic drugs. Further studies in diabetic patients with advanced disease might be worth consideration. Although intensive lifestyle interventions can produce meaningful weight loss,[9–11] such efforts are labour-intensive and not easily available to primary-care physicians. A combination of a more intensive lifestyle intervention with phentermine plus topiramate for patients with type 2 diabetes to achieve maximum cardiometabolic improvement merits investigation. Lower rates of incident diabetes with phentermine plus topiramate in individuals who were not diabetic at baseline suggest the magnitude of weight loss associated with this treatment might be meaningful for long-term diabetes prevention, consistent with the results of other studies.[25,31]

The safety of obesity drugs is paramount because they should be taken long-term to achieve meaningful benefits. Topiramate plus phentermine are widely prescribed drugs and much is known about their safety and tolerability. Adverse events with this combination treatment were as expected and consistent with those of the constituent drugs and low doses used in these formulations. Treatment with phentermine plus topiramate was generally well tolerated, with dry mouth, constipation, and paraesthesia being the most common adverse events. Inhibition of carbonic anhydrase by topiramate presumably accounts for the paraesthesia and taste alteration, decreased concentrations of serum bicarbonate and potassium, and risk of nephrolithiasis. A dose-related increase in the incidence of psychiatric and cognitive adverse events was noted. Discontinuation rates attributable to adverse events roughly doubled with the higher dose versus placebo, with a smaller increase at the lower dose. Although too soon to draw conclusions about the safety from one study, the lower dose of phentermine plus topiramate showed better tolerability; the magnitude of weight loss and cardiometabolic risk reduction was slightly lower than with the higher dose.

Phentermine plus topiramate combination was efficacious at both doses in reducing weight and improving cardiometabolic variables in a patient population—obese individuals with two or more comorbidities—that is commonly encountered in the offices of family doctors. This treatment showed significant metabolic benefits with side-effects that are tolerable (paraesthesias and taste disturbance) or manageable by stopping the drug (nephrolithiasis, metabolic acidosis, and cognitive and psychiatric adverse events).

Like all treatments for obesity, pharmacological treatment should be adapted to each individual. Patients with clinically significant depression were excluded from this study, and a cautious approach is warranted when considering administration of this treatment to patients with mood disorders. Depression and anxiety occurred at a higher incidence with phentermine 15·0 mg plus topiramate 92·0 mg than with placebo. This pattern was not the case with the lower dose; however, fewer patients were assigned to this dose. Not all patients treated with this experimental combination of the two drugs achieved significant weight loss; hence, continued treatment should be restricted to those who show the desired clinical response. Some side-effects, such as nephrolithiasis, metabolic acidosis, and neuropsychiatric problems, might need drug discontinuation, but patients with paraesthesias and taste disturbance could perhaps be reassured to continue the treatment.

After market withdrawal of sibutramine in 2010 due to cardiovascular safety concerns, clinicians are left with only one prescription drug, orlistat, for the long-term treatment of obesity. Orlistat, available since 1998, is a gastric and

pancreatic lipase inhibitor that reduces dietary fat absorption in the gut by about a third.[32] Two investigational drug treatments, other than phentermine plus topiramate, have been investigated in phase 3 trials, and are being reviewed by the US Food and Drug Administration. Lorcaserin is a new drug that is thought to reduce food intake through the activation of serotonin 5-HT2C receptors.[33] Bupropion, mainly a norepinephrine uptake inhibitor, marketed as a treatment for depression and as a smoking cessation aid, has shown moderate efficacy in terms of weight loss in three trials.[34] Naltrexone, an opioid receptor antagonist, is marketed for the treatment of alcoholism and opioid addiction. The combination of bupropion and naltrexone has been assessed for treatment of obesity based on the pharmacodynamic synergy shown in animal models.[35] The robust efficacy of phentermine plus topiramate shown in this trial compares favourably with the efficacy shown by existing and other emerging drugs (table 5).

Therefore, topiramate plus phentermine with office-based lifestyle interventions, such as those used in this study, could be a valuable addition to the small arsenal of effective obesity treatments that are available to family doctors (panel).

Contributors

KMG was the principal investigator for the study. KMG, DBA, CAP, MLS, and WWD planned the statistical analyses. MLS, employed by Medpace, a contract research organisation, was the primary statistician. All authors participated in data analysis or interpretation. KMG drafted the first and subsequent versions of the report with input and critical revisions by all authors, who reviewed and approved the final report as submitted.

Conflicts of Interest

In the past 3 years, KMG received research support from Bristol Myers Squibb, Forest Labs, National Institute of Diabetes and Digestive and Kidney Diseases, Pfizer, and Vivus. Before November, 2008, he served on the scientific advisory boards of Arena and Merck, and as a consultant for Vivus. He owns stocks in Orexigen, and has been awarded several patents for inventions related to obesity and weight loss interventions that are unrelated to the interventions tested in the current investigation. DBA has received grants, honoraria, donations, and consulting fees from the following with related interests—Vivus, GlaxoSmithKline, Merck, Merck (SciMed), Merck (Gray Consulting), Pfizer, Eli Lilly, Abbott Laboratories, SlimFast Foods, Ipsos Health, Calorie Control Council, Dunn Group, Duke University, Datamonitor, Ideo, Medifast, Wolters Kluwer Pharma Solutions, Paul Weiss Rifkind Wharton and Garrison (Weight Watchers), National Institutes of Health, and Arena Pharmaceuticals. DHR has not accepted compensation from industrial ties since January, 2008, and, before that, she received consulting fees from Arena, NutriSystem, Merck, Sanofi Aventis, Abbott, and Shionogi. WWD, BT, and CAP are employees of Vivus. MLS was an employee of Medpace.

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