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# AN OBSERVATIONAL STUDY TO APPROACH THE SAFETY AND EFFICACY OF PHENTERMINE, TOPIRAMATE IN OBESE PATIENTS

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## ABSTRACT

*Obesity is a medical condition in which excess body fat has accumulated to the extent that it may have a negative effect on health.[1] People are generally considered obese when their body mass index (BMI), a measurement obtained by dividing a person's weight by the square of the person's height, is over 30 kg/m$^2$, with the range 25–30 kg/m$^2$ defined as overweight.[1] To evaluate safety and efficacy of phentermine 15 mg plus extended-release topiramate 92 mg for treatment for treating obesity. This single-center prospective, double-blind, placebo-controlled, parallel-group study randomized eligible subjects to receive placebo or phentermine 15 mg plus extended-release topiramate 92 mg once daily in the morning for 28 weeks (Figure 1). Subjects were randomized to study treatment via a computer-generated table that assigned subjects to treatments arms with equal probability. Both groups also received standardized lifestyle modification counseling (the LEARN program, a clinically proven behavioral weight loss and management program). The findings of this randomized controlled trial demonstrate significant improvements in OSA using phentermine 15 mg plus extended-release topiramate 92 mg combined with lifestyle interventions at 28 weeks. Phentermine 15 mg plus extended-release topiramate 92 mg resulted in significantly greater weight loss compared with lifestyle interventions alone. Furthermore, this study showed a correlation between improvements in AHI and weight loss and suggests that phentermine 15 mg plus extended-release topiramate 92 mg combined with lifestyle interventions may be useful as a primary treatment for OSA in patients who are unable to use PAP therapy. Future studies are needed to demonstrate the full potential of this therapy.S*

## KEY WORDS

*Obesity, Medical condition, Overweight, BMI*

## INTRODUCTION:

Obesity is a medical condition in which excess body fat has accumulated to the extent that it may have a negative effect on health.[1] People are generally considered obese when their body mass index (BMI), a measurement obtained by dividing a person's weight by the square of the person's height, is over 30 kg/m2, with the range 25–30 kg/m2 defined as overweight.[1]Some East Asian countries use lower values.[8] Obesity increases the likelihood of various diseases and conditions, particularly cardiovascular diseases, type 2 diabetes, obstructive sleep apnea, certain types of cancer, osteoarthritis and depression.[2][3].

Obesity is most commonly caused by a combination of excessive food intake, lack of physical activity, and genetic susceptibility.[1][4] A few cases are caused primarily by genes, endocrine disorders, medications, or mental disorder.[5] The view that obese people eat little yet gain weight due to a slow metabolism is not generally supported.[6] On average, obese people have a greater energy expenditure than their normal counterparts due to the energy required to maintain an increased body mass.[1][6]

Obesity is mostly preventable through a combination of social changes and personal choices.[1] Changes to diet and exercising are the main treatments.[7] Diet quality can be improved by reducing the consumption of energy-dense foods, such as those high in fat and sugars, and by increasing the intake of dietary fiber.[1] Medications can be used, along with a suitable diet, to reduce appetite or decrease fat absorption.[5] If diet, exercise, and medication are not effective, a gastric balloon or surgery may be performed to reduce stomach volume or length of the intestines, leading to feeling full earlier or a reduced ability to absorb nutrients from food.[8][9]

`Obesity is a leading preventable cause of death worldwide, with increasing rates in adults and children.[1][2] In 2015, 600 million adults (12%) and 100 million children were obese in 195 countries.[7] Obesity is more common in women than men.[1] Authorities view it as one of the most serious public health problems of the 21st century.[10] Obesity is stigmatized in much of the modern world (particularly in the Western world), though it was seen as a symbol of wealth and fertility at other times in history and still is in some parts of the world [11] In 2013, the American Medical Association classified obesity as a disease.

There are many ways in which a person's health in relation to their weight can be classified, but the most widely used method is body mass index (BMI). BMI is a measure of whether you're a healthy weight for your height. You can use the BMI healthy weight calculator to work out your score[12].

For most adults, a BMI of:

- 18.5 to 24.9 means you're a healthy weight
- 25 to 29.9 means you're overweight
- 30 to 39.9 means you're obese
- 40 or above means you're severely obese

BMI isn't used to definitively diagnose obesity, because people who are very muscular sometimes have a high BMI without excess fat. But for most people, BMI is a useful indication of whether they're a healthy weight, overweight or obese. A better measure of excess fat is waist circumference, which can be used as an additional measure in people who are overweight (with a BMI of 25 to 29.9) or moderately obese (with a BMI of 30 to 34.9). Generally, men with a waist circumference of 94cm (37in) or more and women with a waist circumference of 80cm (about 31.5in) or more are more likely to develop obesity-related health problems. Overweight and obesity are defined as abnormal or excessive fat accumulation that may impair health[13].

Body mass index (BMI) is a simple index of weight-for-height that is commonly used to classify overweight and obesity in adults. It is defined as a person's weight in kilograms divided by the square of his height in meters ($kg/m^2$). Adults For adults, WHO defines overweight and obesity as follows. overweight is a BMI greater than or equal to 25; and obesity is a BMI greater than or equal to 30. BMI provides the most useful population-level measure of overweight and obesity as it is the same for both sexes and for all ages of adults. However, it should be considered a rough guide because it may not correspond to the same degree of fatness in different individuals[14]. For children, age needs to be considered when defining overweight and obesity. Children under 5 years of age

For children under 5 years of age: overweight is weight-for-height greater than 2 standard deviations above WHO Child Growth Standards median; an obesity is weight-for-height greater than 3 standard deviations above the WHO Child Growth Standards median. Charts and tables: WHO child growth standards for children aged under 5 years

The worldwide prevalence of obesity nearly tripled between 1975 and 2016. In 2016, an estimated 41 million children under the age of 5 years were overweight or obese. Once considered a high-income country problem, overweight and obesity are now on the rise in low- and middle-income countries, particularly in urban settings. In Africa, the number of overweight children under 5 has increased by nearly 50 per cent since 2000. Nearly half of the children under 5 who were overweight or obese in 2016 lived in Asia[15].

Over 340 million children and adolescents aged 5-19 were overweight or obese in 2016. The prevalence of overweight and obesity among children and adolescents aged 5-19 has risen dramatically from just 4% in 1975 to just over 18% in 2016. The rise has occurred similarly among both boys and girls: in 2016 18% of girls and 19% of boys were overweight. While just under 1% of children and adolescents aged 5-19 were obese in 1975, more 124 million children and adolescents (6% of girls and 8% of boys) were obese in 2016.

Overweight and obesity are linked to more deaths worldwide than underweight. Globally there are more people who are obese than underweight – this occurs in

every region except parts of sub-Saharan Africa and Asia. Obesity means having too much body fat. It is different from being overweight, which means weighing too much. The weight may come from muscle, bone, fat, and/or body water. Both terms mean that a person's weight is greater than what's considered healthy for his or her height[10].

The aim of the study is to to evaluate safety and efficacy of phentermine 15 mg plus extended-release topiramate 92 mg for treatment for treating obesity. The objectives of this study were to evaluate the safety and efficacy of phentermine 15 mg plus extended-release topiramate 92 mg compared with placebo for the treatment of obese adults and to assess the relative contributions of weight loss at Week 28 to reductions.

**MATERIALS AND METHODS:**

**Study Design**

This single-center prospective, double-blind, placebo-controlled, parallel-group study randomized eligible subjects to receive placebo or phentermine 15 mg plus extended-release topiramate 92 mg once daily in the morning for 28 weeks (Figure 1). Subjects were randomized to study treatment via a computer-generated table that assigned subjects to treatments arms with equal probability. Both groups also received standardized lifestyle modification counseling (the LEARN program, a clinically proven behavioral weight loss and management program).42

Eligible subjects were 30-65 years of age with a body mass index (BMI) between 30 kg/m2 and 40 kg/m2, a diagnosis of moderate to severe OSA syndrome, and an apnea-hypopnea index (AHI) ≥ 15 at baseline (measured via overnight polysomnography [PSG]) and were unwilling or unable to comply with PAP treatment (defined as > 4 h/night, 70% of the time). Subjects were not eligible if they had a sleep disorder other than OSA syndrome, periodic limb movement arousal index > 10, uncontrolled or poorly controlled blood pressure (systolic > 160 mm Hg or diastolic > 100 mm Hg), or the presence or history of unstable angina, heart failure, cardiac valvulopathy, myocardial infarction, potentially life-threatening cardiac arrhythmia, or clinically significant abnormality on electrocardiogram.

Subjects were screened at Visit 1, and eligible participants were scheduled for baseline overnight PSG (Visit 2). Immediately following the overnight PSG at Visit 2, which provided the baseline AHI value, qualified subjects were randomized 1:1 to receive oral phentermine 15 mg plus extended-release topiramate 92 mg or placebo, both of which were titrated over the first 4 weeks of treatment in increments of phentermine 3.75 mg plus topiramate 23 mg as tolerated, with each step in the titration lasting 1 week until maximum dosage was reached. Subjects then received an additional 24 weeks of treatment for a total treatment period of 28 weeks. Study visits were conducted at Weeks 4, 8, 12, 16, 20, 24, and 28. Overnight assessments of OSA, including PSG, laboratory testing, and quality-of-life surveys, were performed at baseline, Week 8, and Week 28 (or upon early withdrawal).

Prior to randomization, subjects were counseled on reducing their caloric intake by 500 kcal/day and on the importance of light daily exercise. Subjects completed a 24-h dietary recall at their randomization visit, and this information was used for discussions related to recommended dietary modification. Subjects were advised to initiate lifestyle interventions using the LEARN Program.41Each subject was provided with a LEARN manual and advised to read and implement the material as appropriate to their individual situation. Subjects were also given pedometers and counseled to increase their step count as a form of their light daily exercise. Site personnel were encouraged to discuss these materials with subjects at their regularly scheduled visits; however, no data were collected to document the level of compliance with the program's dietary, lifestyle, and/or exercise recommendations. This study was conducted between August 2008 and September 2009 and was approved by an institutional review board. All subjects provided written informed consent for participation in the study. This trial is registered with ClinicalTrials.gov, number PHEC00745251.

**Study Assessments**

The primary efficacy endpoint was the change in AHI between baseline, Week 8, and Week 28 or early withdrawal. An AHI score of 5-14 is considered mild, 15-29 is considered moderate, and ' 30 is considered severe. Secondary endpoints included changes in additional OSA parameters, such as respiratory disturbance index (RDI), apnea index, hypopnea index, desaturation index, mean overnight oxygen saturation, overnight minimum oxygen saturation, and arousal index (sleep quality defined as the number of arousals from REM and NREM sleep per hour). Subject-reported outcomes were also assessed, including the Pittsburgh

Sleep Quality Index (PSQI), Epworth Daytime Sleepiness Scale (ESS), and 36-item Short-Form Health Survey (SF-36) scores. The PSQI is a subjective, self-administered questionnaire used to assess the quality and patterns of sleep in older adults.43 The ESS is a subjective, self-administered, 8-question tool to assess excessive daytime sleepiness and is also used to differentiate between average and significant issues with sleepiness that require intervention.44,45 The SF-36 questionnaire is a 36-item, self-administered health-related quality-of-life questionnaire designed to evaluate functional health and well-being.46

Additional secondary endpoints included changes in cardiometabolic risk factors: blood pressure, heart rate, lipid profile (total cholesterol, low-density lipoprotein [LDL] cholesterol, high-density lipoprotein [HDL] cholesterol, and triglycerides), and glycemic variables (fasting insulin, fasting glucose, and insulin resistance based on homeostasis model of assessment-insulin resistance [HOMA-IR]). Percent weight loss and the percentage of subjects achieving ≥ 5% and 10% weight loss were also assessed as secondary endpoints.

Safety endpoints included laboratory parameters, electrocardiogram, physical examination, and reports of adverse events. Adverse events were assessed throughout the study and were coded using the Medical Dictionary for Regulatory Activities, version 10.1. Treatment-emergent adverse events (TEAE) were defined as adverse events that started on or after the first dose and up to 28 days after the last dose of study drug.

**Statistical Methods**

The sample size was based on the expected effect on AHI. With 21 subjects per arm, this study had 80% power to detect a mean difference of a 10-point reduction in AHI from baseline (Visit 2) between the 2 treatment groups by a 2-tailed t-test at 5% type I error and an assumed standard deviation of 11.

The randomized set included all subjects randomized to treatment and was used to summarize demographic and baseline variables. The safety set included all randomized subjects who received at least 1 dose of study medication. All safety analyses were conducted based on the safety set. The intent-to-treat (ITT) set included all randomized subjects who received ≥ 1 dose of study medication, had a baseline efficacy measurement, and ≥ 1 post-baseline efficacy assessment. The ITT set was used for the primary and secondary efficacy analysis.

Analysis of the primary efficacy variable, the change in AHI between baseline (Visit 2) and Week 8 (Visit 5) and between baseline and Week 28 or early withdrawal (Visit 10) with last observation carried forward (LOCF), was accomplished using an analysis of covariance (ANCOVA) model, with treatment groups as the main effect and baseline body weight as the covariate. The least-squares (LS) means and corresponding standard errors were presented for the within-group AHI change for each treatment group. For the between-treatment group comparison, the difference in LS means, corresponding standard error, 95% confidence interval, and 1-sided P value were also derived from this ANCOVA model and presented. The normality assumption of the efficacy data was examined prior to fitting the ANCOVA models to ensure that normality was observed. The same statistical methodology described above for the analysis of the primary efficacy variable was performed for secondary variables. Analyses of percentage of categorical weight loss were conducted using a logistic regression model with treatment as the fixed effect and baseline body weight as a covariate. For the between-treatment group comparison, the estimated odds ratio, standard error, 2-sided 95% confidence interval, and 2-sided P value for treatment comparison were to be presented.

To assess the effect of dropout on the robustness of the conclusions from the prespecified LOCF results, several sensitivity analyses were performed including baseline observation carried forward (BOCF), completers only, and multiple imputation. For BOCF, for subject who did not complete 28 weeks of treatment, the baseline value was carried forward and imputed as the Week 28 result. The completers analysis was performed on subjects who completed the entire 28 weeks of treatment. In addition, the multiple imputation approach used all observed data and treatment assignment to impute missing observations for subjects who discontinued prior to Week 28. For all 3 analyses, the ANCOVA model described above was applied to the imputed datasets (Supplemental Table S1).

## RESULTS AND DISCUSSION:

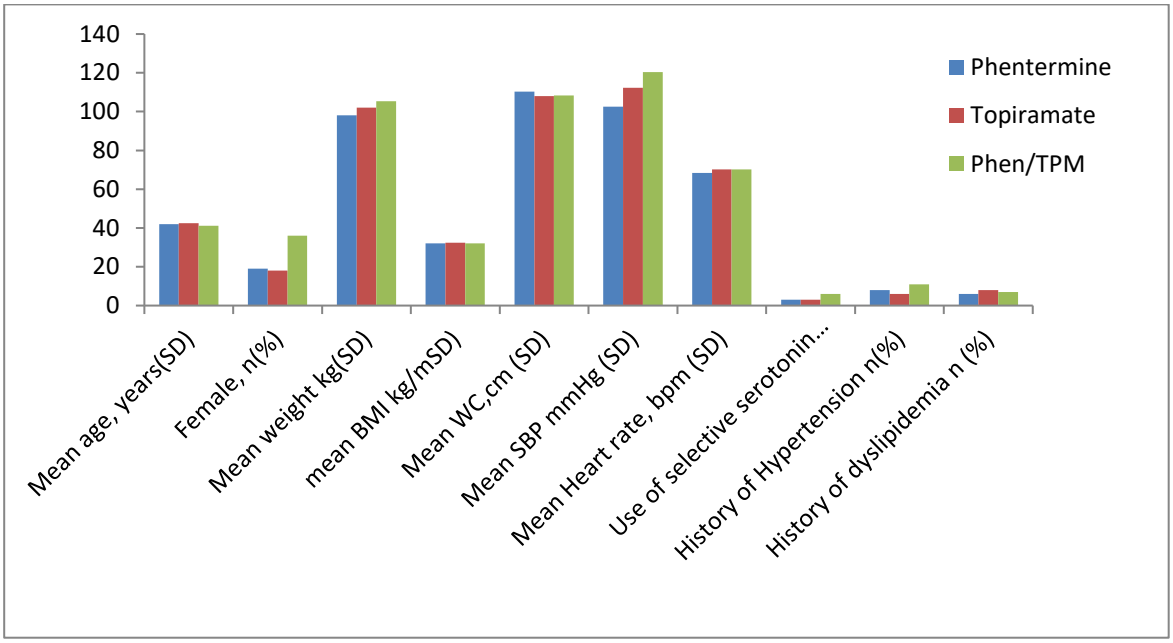
In total, 150 subjects were randomized to one of the seven treatment arms (Figure 1). The majority of subjects were female (79.2%) with a mean age of

41.2±11.7years. At baseline, subjects had a mean weight of 105.3±10.12 kg, BMI of 32.0±4.10 kg/m$^2$, waist circumference of 111.1 ± 11.1 cm, SBP of 120.32±10.23 mm Hg, and heart rate of 70.12±8.6 beats per minute (Table 1). Of the 150 subjects, 100 (66.6%) completed all study visits on study drug, whereas 50 (33.3%) discontinued study drug, with rates similar between treatment groups (Figure 1). The most common reasons for discontinuation were adverse events (12.4%), loss to follow-up (8.7%), and withdrawal of consent (5.6%).

**Table 1: Baseline demographics and clinical characteristics (randomized population)**

| Parameter | Phentermine (25) | Topiramate (25) | Phen/TPM (50) |
|---|---|---|---|
| Mean age, years (SD) | 42.0±11.57 | 42.4±12.62 | 41.2±11.7 |
| Female, n (%) | 19(76.4) | 18(72.5) | 36(72.3) |
| Mean weight kg (SD) | 98.16±11.96 | 102±13.2 | 105.3±10.12 |
| mean BMI kg/mSD) | 32.01±3.61 | 32.4±4.32 | 32.0±4.10 |
| Mean WC,cm (SD) | 110.31±9.63 | 108±10.48 | 108.3±11.98 |
| Mean SBP mmHg (SD) | 102.6±11.92 | 112.2±10.2 | 120.32±10.23 |
| Mean Heart rate, bpm (SD) | 68.3±8.96 | 70.12±8.32 | 70.12±8.6 |
| Use of selective serotonin reuptake inhibitors | 3(11.9) | 3(13.1) | 6(12.3) |
| History of Hypertension n (%) | 8(32.1) | 6(22.1) | 11(21.6) |
| History of dyslipidemia n (%) | 6(25.3) | 8(30.1) | 7(14.2) |

**Graph 1: Baseline demographics and clinical characteristics (randomized population)**




After 28 weeks of treatment, mean percent WL with PHEN/TPM 7.5/46 was significantly greater than with either placebo ($P < 0.0001$) or the combination's individual components at all time points ($P < 0.05$; mITT and ITT-LOCF; Figure 2). The PHEN/TPM 7.5/46 group also achieved statistically greater WL versus phentermine 15 or topiramate ER 92 at week 28 in the ITT-LOCF population ($P < 0.05$; Figure 2; Supporting Information Figure S1). PHEN/TPM 15/92 also induced greater WL than either placebo ($P < 0.05$) or the combination's individual components at all-time points in both the mITT and ITT-LOCF analyses ($P < 0.05$; Figure 2; Supporting Information Figure S1). This percent WL translated to an absolute WL of 8.3 kg for the PHEN/TPM 7.5/46 group and 9.0 kg for the PHEN/TPM 15/92 group, compared with 1.5 kg for placebo, 5.3 kg for phentermine 7.5, 4.7 kg for topiramate ER 46, 6.0 kg for phentermine 15, and 6.4 kg for topiramate ER 92.

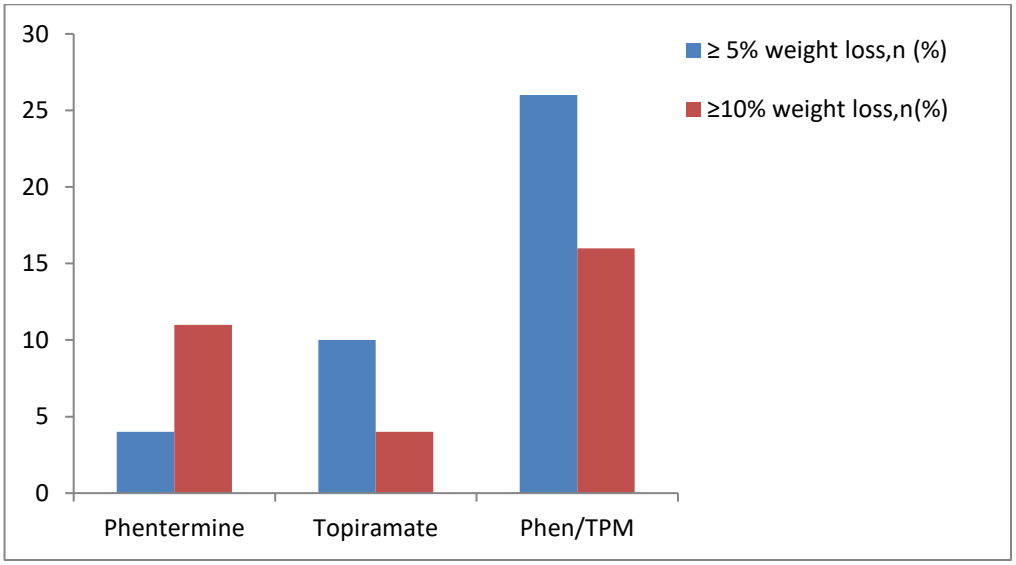
More subjects receiving PHEN/TPM 7.5/46 achieved ≥5% and ≥10% WL than with placebo ($P < 0.0001$; Table 2) or with its individual components, phentermine

7.5 and topiramate ER 46. Subjects in the PHEN/TPM 7.5/46 group also achieved ≥5 and ≥10% WL at higher percentages than did those assigned to phentermine 15 or topiramate ER 92 ($P < 0.05$ for all comparisons except ≥5% WL for PHEN/TPM 7.5/46 vs. topiramate ER 92). In addition, the PHEN/TPM 15/92 group had greater numbers of subjects with ≥5% WL versus placebo, phentermine 15, or topiramate ER 92 treatment groups ($P < 0.05$, all comparisons; Table 2).

**Table 2. Percentage of subjects achieving ≥5 or ≥10% weight loss from baseline to week 28**

| Variables | Phentermine | Topiramate | Phen/TPM |
|---|---|---|---|
| ≥ 5% weight loss,n (%) | 4(14.6) | 10(41.36) | 26(52.3) |
| ≥10% weight loss,n(%) | 11(11.4) | 4(16.4) | 16(32.45) |

**Group 2. Percentage of subjects achieving ≥5 or ≥10% weight loss from baseline to week 28**




**Cardiometabolic parameters**

Greater improvements in SBP were observed among subjects receiving PHEN/TPM compared with placebo ($P < 0.05$ vs. placebo; Figure 3). Improvements in DBP were not significant versus placebo or versus the individual phentermine and topiramate ER components (Figure 3). Significantly greater improvements with the combination doses versus placebo or some of the individual components were observed in waist circumference, $HbA_{1c}$, and adiponectin, but improvements were not significant with fasting glucose and hsCRP (Table 3).

**Adverse events**

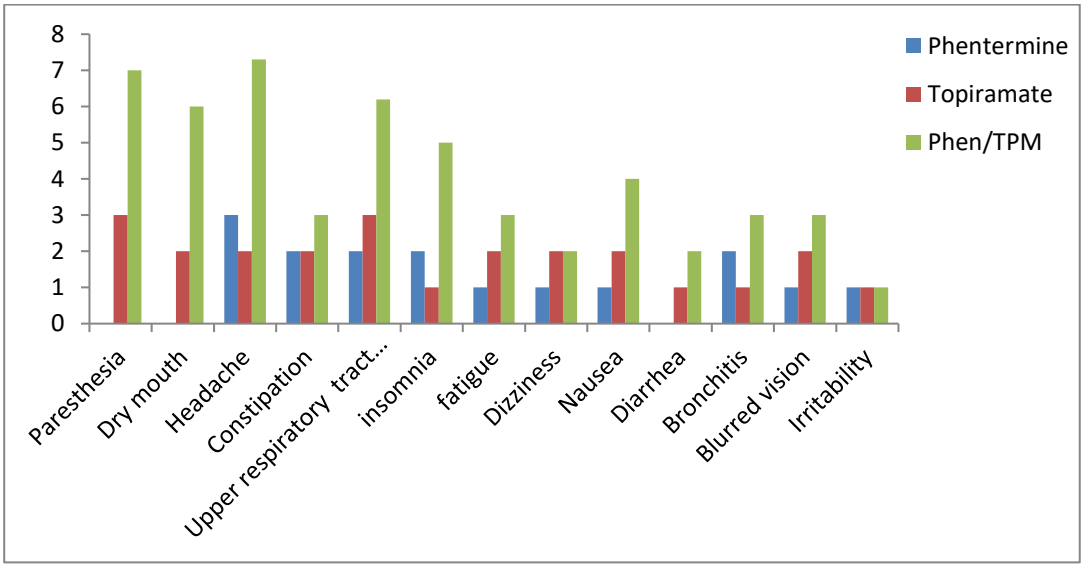
Most treatment-emergent adverse events (Table 4) were mild to moderate in severity. There were no deaths during the study. In total, seven (0.9%) subjects had a serious adverse events: two (1.8%) subjects in the phentermine 7.5 mg group (pelvic mass, hypotension, jaundice cholestatic, and malignant neoplasm of ampulla of vater), one (0.9%) in the PHEN/TPM 7.5/46 group (appendicitis), one (0.9%) in the phentermine 15 mg group (chest pain), one (0.9%) in the topiramate ER 92 group (arrhythmia), and two (1.9%) with PHEN/TPM 15/92 (blurred vision and humerus fracture). None of the serious adverse events was considered by the investigators to be related to study drug. A total of 94 (12.5%) subjects discontinued study drug owing to any adverse event, with more subjects discontinuing study drug from the PHEN/TPM 7.5/46 (15.1%) and PHEN/TPM 15/92 (21.3%) groups than from the placebo group (7.3%). Seventy-two (9.6%) subjects discontinued study drug owing to a drug-related treatment-emergent adverse event (based on investigator attribution), and one subject from the 15/92 group discontinued treatment owing to a serious adverse event (humerus fracture). One subject in the topiramate 92 group experienced a serious adverse event (arrhythmia), which resolved with sequelae; the remaining serious adverse events resolved without sequelae. An increase in heart rate was observed in the phentermine

monotherapy groups, whereas the placebo, topiramate ER monotherapy, and PHEN/TPM combination groups all experienced a decrease in heart rate (Table 5).

**Table 3: Treatment-emergent adverse events (≥5% of subjects in any treatment group) by preferred term**

| Preferred term, n (%) | Phentermine | Topiramate | Phen/TPM |
|---|---|---|---|
| Paresthesia | 0(3.2) | 3(10.2) | 7(14.2) |
| Dry mouth | 0(0) | 2(6.4) | 6(12.4) |
| Headache | 3(10.32) | 2(6.2) | 7.3(14.6) |
| Constipation | 2(7.6) | 2(6.1) | 3(6.4) |
| Upper respiratory tract infection | 2(8.1) | 3(10.3) | 6.2(12.4) |
| insomnia | 2(6.2) | 1(3.2) | 5(10.6) |
| fatigue | 1(2.1) | 2(6.5) | 3(5.2) |
| Dizziness | 1(4.2) | 2(6.2) | 2(3.6) |
| Nausea | 1(4.2) | 2(7.2) | 4(7.2) |
| Diarrhea | 0(0.6) | 1(2.1) | 2(3.6) |
| Bronchitis | 2(1.6) | 1(1.6) | 3(5.2) |
| Blurred vision | 1(5.2) | 2(7.2) | 3(6.4) |
| Irritability | 1(5.2) | 1(2.4) | 1(1.8) |

**Graph 3: Treatment-emergent adverse events (≥5% of subjects in any treatment group) by preferred term**




The RBANS assessment of cognitive function demonstrated a dose-related decrement in total index score among subjects treated with both doses of PHEN/TPM relative to placebo at week 4 with placebo-compared effect sizes of 0.30 and 0.42 for PHEN/TPM 7.5/46 and PHEN/TPM 15/50, respectively (Supporting Information Table S1). This cognitive deficit was mainly due to changes in the attention (placebo-compared effect size of 0.58 and 0.66 for PHEN/TPM 7.5/50 and PHEN/TPM 15/50 at week 4, respectively) and delayed memory index scores (placebo-compared effect size of 0.25 and 0.30 for PHEN/TPM 7.5/50 and PHEN/TPM 15/50, respectively). Although effects on total index score were attenuated at week 28 (placebo-compared effect size of 0.14 and 0.32 for PHEN/TPM 7.5/50 and PHEN/TPM 15/50, respectively), impairments in the attention domain (placebo-compared effect size of 0.39 and 0.70 for PHEN/TPM 7.5/50 and PHEN/TPM 15/50, respectively) remained constant throughout study treatment. Effects on cognitive domains were

comparable to the effects observed with topiramate ER monotherapy (Supporting Information Table S1). Attention was the only domain that exceeded the clinically relevant effect size threshold of 0.5 with PHEN/TPM (i.e., effect sizes of 0.2-0.49 were considered small, 0.5-0.79 were considered moderate, and >0.8 were considered large) [14].

**DISCUSSION:**

This 28-week study found that combining phentermine with an ER formulation of topiramate produced significantly greater WL than either component as a monotherapy. Importantly, the PHEN/TPM 7.5/46 dose produced greater WL than did higher doses of monotherapy. This suggests that the combination of PHEN/TPM is more effective in increasing WL than is increasing the dose of monotherapies and also satisfies FDA guidance for fixed-dose combination drug treatments for obesity [15, 16].

The combination formulation of PHEN/TPM was designed to allow once-daily dosing, with phentermine released in the morning and topiramate ER released in the evening. When taken in the morning, the IR of phentermine allows for peak exposure in the morning, whereas the delayed release of topiramate ER lowers the maximum observed plasma drug concentration by 29% and delays the time to maximum plasma concentration by 7 h, allowing for peak topiramate ER exposure to occur in the late afternoon and evening. The apparent half-life of phentermine and topiramate was shown to be 20 and 65 h, respectively. This pharmacokinetic profile may be responsible for the improved efficacy and tolerability of the combination doses versus their monotherapy counterparts [17].

The American Diabetes Association, the American Heart Association, and the National Heart, Lung, and Blood Institute recommend WL of 5-10% for obese and overweight subjects with or without weight-related comorbidities [18-20]. The combinations of PHEN/TPM 7.5/46 and PHEN/TPM 15/50 helped more subjects achieve these goals, with significantly more subjects achieving WL of ≥5 and ≥10% compared with all monotherapy arms except for topiramate ER 50. The efficacy of PHEN/TPM 15/50 further exceeded that of each individual agent and placebo. This suggests that the doses used in this combined formulation allow for a decreased dosing level without loss of efficacy.

The improvements in SBP in this study induced by PHEN/TPM 7.5/50 and PHEN/TPM 15/50 were greater than those achieved with phentermine monotherapy. The PHEN/TPM 7.5/50 dose produced reductions in SBP that also were greater than those observed with phentermine 25 or topiramate ER 25 monotherapy. As with previous studies of an IR topiramate for WL [3, 4, 7], SBP was improved with topiramate ER in this study. Because of the significant influence of the topiramate ER component, the PHEN/TPM combination group did not always show improvements in SBP that were significantly greater versus the topiramate ER monotherapy arms. $HbA_{1c}$ was also improved with the PHEN/TPM 7.5/50 dose versus its individual components, but the improvement with PHEN/TPM 15/50 was not statistically significant versus topiramate ER. This is in line with a previous RCT of topiramate controlled release, in which the mean change from baseline for $HbA_{1c}$ was significantly improved with topiramate controlled release (−0.9%) versus placebo (−0.4%) after 16 weeks in obese and overweight subjects with type 2 diabetes ($P < 0.001$). The combination PHEN/TPM led to greater improvements in waist circumference compared with the individual component arms. Taken together, this suggests that the combination of PHEN/TPM may provide greater WL and related metabolic improvements than either agent as a monotherapy.

The risk of increased heart rate with phentermine appeared to be mitigated by the addition of topiramate ER. This may have occurred because of the additional WL achieved with topiramate ER, which would tend to reduce or minimize an increase in heart rate [21, 22]. Further, psychomotor slowing, accompanied by difficulty with memory, concentration/attention, and confusion are well-documented adverse effects of topiramate [2]. In this study, cognitive deficits at weeks 4 and 28 were driven primarily by changes in the attention index score of the RBANS tests of cognitive function. At week 28, no clinically important treatment differences in immediate memory, visuospatial/constructional, language, and delayed memory scores were noted. Small decrements were observed with the PHEN/TPM combination arms and topiramate ER monotherapy, suggesting that topiramate ER, when given alone or in combination with phentermine, may lead to some impairment in cognition, with attention being the most affected.

The EQUATE study had several limitations. The study duration was only 28 weeks, which may have been too short to observe maximum changes in weight and cardiometabolic parameters, including blood pressure, and in lipid and glycemic parameters. In this trial, for topiramate monotherapy, an ER formulation was used, thus making comparisons to the FDA-approved topiramate IR challenging. In addition, a low-intensity program of behavior modification was used; larger WLs may have been achieved with a higher intensity program of lifestyle modification [23].

## CONCLUSIONS:

The findings of this randomized controlled trial demonstrate significant improvements in OSA using phentermine 15 mg plus extended-release topiramate 92 mg combined with lifestyle interventions at 28 weeks. Phentermine 15 mg plus extended-release topiramate 92 mg resulted in significantly greater weight loss compared with lifestyle interventions alone. Furthermore, this study showed a correlation between improvements in AHI and weight loss and suggests that phentermine 15 mg plus extended-release topiramate 92 mg combined with lifestyle interventions may be useful as a primary treatment for OSA in patients who are unable to use PAP therapy. Future studies are needed to demonstrate the full potential of this therapy.

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