A Randomized, Double-Blind, Placebo-Controlled Study of an Oral, Extended-Release Formulation of Phentermine/Topiramate for the treatment of Obstructive Sleep Apnea in Obese Adults

BACKGROUND

- Obstructive Sleep Apnea (OSA) is a condition in which individuals experience multiple nighttime episodes of apnea or hypopnea, during which blood oxygen saturation levels fall and normal sleep architecture is disrupted.
- Phentermine 37.5 mg is approved by the FDA for short-term treatment of obesity.
- Topiramate is FDA approved for the treatment of epilepsy. However, it has shown to promote weight loss in obese patients.

OBJECTIVE

- The objective of the study was to evaluate the safety and efficacy of phentermine 15 plus extended-release topiramate 92 mg compared with placebo for treatment of OSA in obese adults with moderate to severe OSA and to assess the relative contributions of weight loss at Week 28 to reductions in OSA symptoms.

METHODS

- **Design:** Single site, randomized, double-blind, controlled study with a parallel group study design
- **Inclusion Criteria:** 30-75 years of age, BMI: 30 kg/m2 – 40 kg/m2, diagnosis of moderate to severe OSA syndrome, apnea-hypopnea index (AHI) ≥ 15 at baseline , unwilling or unable to comply with PAP treatment.
- **Exclusion Criteria:** sleep disorder other than OSA syndrome, periodic limb movement arousal index > 10, uncontrolled or poorly controlled blood pressure, presence or history of unstable angina, heart failure, cardiac vavulopathy, myocardial infarction, potentially life-threatening cardiac arrhythmia, or clinically significant abnormality on electro cardiogram.
- 45 patients
    - Treatment Group (22 patients) → received phentermine 15 mg plus extended-release topiramate 92 mg once daily in the morning for 28 weeks.
    - Control Group (23 patients) → received placebo daily for 28 weeks.
    - Both groups were titrated over the first 4 weeks in increments of phentermine 3.75 mg plus topiramate 23 mg as tolerated.
    - Both groups also received standardized lifestyle modification counseling.
- **Primary Outcome Measures:** Change in AHI between baseline, Week 8, and Week 28 or early withdrawal.
- **Secondary Outcome Measures:** Changes in additional OSA parameters such as: percent weight loss, respiratory disturbance index (RDI), apnea index, hypopnea index, desaturation index, mean overnight oxygen saturation, overnight minimum oxygen saturation, arousal index and cardiometabolic risk factors: blood pressure, heart rate, lipid profile, and glycemic variables.
- **Data handling**
    - Data handling method was intent-to-treat with LOCF, BOCF, or MI.

RESULTS

- **Primary Outcome Measure:** The change from baseline in AHI, significantly favored phentermine 15 mg plus extended-release topiramate 92 mg treatment group (Week 8: P = 0.0009 & Week 28: P = 0.0084).
- **Secondary Outcome Measure:** At week 8, the LS mean percent change in weight from baseline was -5.6% in the treatment group and -2.3% in the placebo group. At week 28, the LS mean percent change in weight from baseline was -10.3% in the treatment group and -4.2% in the placebo group. From baseline to week 28, a positive correlation was found between the percent change in weight and the change in AHI score (n=43, r = 0.5218, P=0.003).
- **Authors Conclusion:** Phentermine 15 mg plus extended-release topiramate 92 mg combined with lifestyle interventions demonstrated significant improvements in OSA.

STRENTGHS

- Experimental, randomized, controlled, double-blind study design
- Appropriate doses of the drugs were administered in both study groups
- Researchers accurately explained their limitations or weakness in the discussion section

LIMITATIONS

- Baseline characteristics' of the treatment groups varied
- Study should have been conducted for a longer time period to analyze if weight loss was maintained in patients
- Titration period during discontinuation of therapy should have been included in the study design
- Unblinding is a concern in the study and could have influenced the results
- Study adverse events dependent upon patient reporting
- No data provided on compliance to dietary, exercise, or LEARN program

CONCLUSION

- Results showed that the addition of phentermine 15 mg and topiramate 92 mg once daily clinically improves weight loss which in turn helps improve the Apnea/hypopnea Index in OSA.
- Future Research:
    - An experimental design study for a longer time frame needs to be conducted along with monitoring lifestyle interventions (diet and exercise) to determine true efficacy and safety phentermine 15 and extended release topiramate 92 mg for treatment of OSA.

Reference: Winslow et al. A randomized, Double-Blind, Placebo-Controlled Study of an Oral, Extended-Release Formulation of phentermine/Topiramate for the Treatment of Obstructive Sleep Apnea in Obese Adults. SLEEP. 2012;35(11):1529-1539.

Shannon Bilyeu, PharmD Candidate