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Is phentermine/topiramate ER with lifestyle modifications effective in achieving weight loss in obese patients with comorbidities?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

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ABSTRACT

Objective: The objective of this selective EBM review is to determine whether or not "Is phentermine/topiramate ER with lifestyle modifications effective in achieving weight loss in obese patients with comorbidities?"

Study Design: A systematic review of three placebo-controlled randomized controlled trials (RCTs) published in English in 2012 or after.

Data Sources: All three studies were found by searching PubMed and were published in peer-reviewed journals. The articles were selected based on ability to answer the proposed question.

Outcome Measured: Percent weight loss was the outcome measured in all three studies. This was measured based on mean percent weight loss from baseline at various weekly intervals.

Results: Aronne, et al, conducted a double-blind RCT that showed phentermine/topiramate (PHEN/TPM ER) 15/92 mg produced greater percent weight loss at every 4 weeks than the placebo group ($p < 0.05$) with LS mean percent weight loss of -11.63 compared to placebo at -2.28 for mITT analysis.[8] The ITT-LOCF analysis showed LS mean percent weight loss of -1.71 for the placebo and -9.21 for PHEN/TPM ER ($p < 0.05$).[8] The Winslow, et al double-blind RCT found a LS mean percent weight loss from baseline of -10.3% (standard error 1.17) for PHEN/TPM ER and -4.2% (standard error 1.15) for placebo ($p = 0.0006$).[9] Garvey, et al's double-blind RCT showed that PHEN/TPM ER produced a LS mean percent weight loss of 12.1% and the placebo group only achieved 2.5% (ITT-MI; $p = 0.0001$).[10]

Conclusion: The three studies in this review found PHEN/TPM ER to produce greater weight loss that was statistically significant when compared to placebo. This demonstrates the utility of PHEN/TPM ER in helping patients achieve weight loss and subsequently reduce the prevalence or risk of obesity-related comorbidities. Further research should be conducted to assess the role lifestyle modifications play in the success of PHEN/TPM ER and to determine its effectiveness in adolescents.

Key Words: phentermine, topiramate, extended release, obesity

INTRODUCTION

Obesity is diagnosed based on having a BMI (body mass index) of 30.0 or higher. This can be further subdivided into Class I Obesity – BMI of 30.0-34.9, Class II Obesity – BMI of 35.0-39.9, and Class III Obesity – BMI ≥ 40.0.[1] Both genetics and environmental factors contribute to the development of obesity.[1] Obesity increases an individual's risk for developing other comorbidities like heart disease, diabetes, hyperlipidemia, OSA, etc. The National Health and Nutrition Survey's (NHANES) data has shown a steady rise in obesity within the US regardless of age, gender, race, or ethnicity since the 1970s.[2] About 30% of the world, more than 2.1 billion people, in 2014 were overweight or obese.[3] The prevalence of obese adults in the US was 42.4% in 2017-2018.[4] The economic impact of obesity globally in 2014 was estimated at $2.0 trillion.[3] Data from 2014 determined that annual medical spending nationwide for obesity was $149.4 billion.[5] 11 million office visits for obesity among adults 20 years and older in the US were made in 2012.[6]

It is known that obesity can be caused by a multitude of things including lifestyle, genetics, and other medical conditions. There are many avenues to achieve weight loss, but there is no known treatment that is 100% effective in all people. No one size fits all regimen exists and often achieving and maintaining weight loss takes many months and even years. The mainstay treatment regimen for obesity is diet modification, including being in a calorie deficit, following a low fat/low carb diet, etc., and exercise of an average of 30 minutes a day, 5 days a week. Other pharmacological treatment options include liraglutide, semaglutide, and orlistat to name a few. Usually as a last resort surgery can be considered such as gastric bypass (Roux-en-Y procedure), gastric banding, or sleeve gastrectomy.

Phentermine alone can be used for weight loss, but only for a short term. It is a sympathomimetic amine anorectic and therefore causes the release of norepinephrine and epinephrine.[7] It essentially helps decrease appetite. Topiramate is used as an anticonvulsant and prophylaxis for migraines, but also curbs appetite and increases feelings of fullness.[7] The combination of these two medications along with lifestyle modifications can enable and sustain weight loss. This combination medication, phentermine/topiramate ER (PHEN/TPM ER), goes by the brand name Qsymia and is a once daily dosing that can be taken indefinitely. It is available in 3.75/23mg, 7.5/46mg, 11.25/69mg, 15/92mg capsules.[7] This combination medication has been shown to result in increased weight loss compared to either medication as monotherapy. This review discusses three randomized controlled trials that analyze the effectiveness of PHEN/TPM ER for weight loss in obese adults (≥ 18 years old) who have various comorbidities including metabolic syndrome, prediabetes, and obstructive sleep apnea.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not "Is phentermine/topiramate ER with lifestyle modifications effective in achieving weight loss in obese patients with comorbidities?"

METHODS

The three articles discussed in this paper were chosen based on their ability to answer the proposed clinical question as stated in the objective. The studies were all double blind and were selected based on the criteria of being randomized control trials published in or after 2010, in English, and in peer-reviewed journals. PubMed was searched to find the selected articles using the key words "phentermine", "topiramate", "extended release", and "obesity". All the articles

utilized the same basic population of obese adults, determined to be at least 18 years old with a of BMI 27-45 kg/m^2, with various comorbidities. The three chosen articles also all used the intervention of PHEN/TPM ER 15/92 mg with lifestyle modifications, the comparison of placebo with lifestyle modifications, and measured the patient-oriented outcome (POEM) of percent weight loss from baseline. The lifestyle intervention utilized in all three studies was based on the LEARN program (Lifestyle, Exercise, Attitude, Relationships, Nutrition). Studies that used only PHEN/TPM CR or did not include lifestyle modifications along with pharmacological treatment were excluded from consideration. The statistics reported in the selected articles were LS means and p values. Reference Table 1 below for demographics and characteristics of the three selected studies.

Table 1. Demographics & Characteristics of Included Studies

Study	Type	# Patients	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Aronne, et al[8] (2013)	RCT	756	18-70	18-70 yrs old, BMI ≥ 30 and ≤ 45 kg/m^2	Within the last 3 months, use of phentermine or topiramate, weight gain or loss of > 5kg, very low calorie diet, use of pharmacotherapy for weight loss, or participation in weight loss program	261	PHEN/TPM ER 15/92 mg + lifestyle counseling vs. placebo + lifestyle counseling; for 28 weeks
Winslow, et al[9] (2012)	RCT	45	30-65	30-65 yrs old with BMI 30-40kg/m^2, severe OSA syndrome, AHI ≥ 15 at baseline and can't/won't comply with PAP treatment (compliance: > 4 hrs/night, 70% of the time)	Sleep disorder other than OSA, periodic limb movement arousal index > 10, poorly/uncontrolled BP (sys > 160 or dia > 100), or history/diagnosed with unstable angina, heart failure, cardiac valvulopathy, MI, life-threatening arrhythmia, or significant abnormality on EKG	5	PHEN/TPM ER 15/92 mg + lifestyle counseling vs. placebo + lifestyle counseling; for 28 weeks
Garvey, et al[10] (2014)	RCT	475	18-70	18-70 yrs old, BMI 27-45	Subjects from the original study	77	PHEN/TPM ER 15/92 mg +

				kg/m^2, prediabetes and/or metabolic syndrome	diagnosed with Type II DM were excluded from the extension study		lifestyle counseling vs. placebo + lifestyle counseling; for 108 weeks

OUTCOMES MEASURED

Weight loss is the patient-oriented outcome assessed in this evidence based medicine review. In the three selected studies this was measured based on mean percent weight loss from baseline at various weekly intervals. The study conducted by Aronne, et al[8] (2013) and Winslow, et al[9] (2012) conducted their last weigh-in of participants at the end of 28 weeks, and the Garvey, et al[10] (2014) study which was an extension of a previous study conducted their last weigh-in at 108 weeks.

RESULTS

A double blind RCT was conducted by Aronne, et al to determine the effectiveness of PHEN/TPM ER 15/92 mg for weight loss in obese adults determined by a BMI between 30 and 45 kg/m^2. [8] The study ran from December 2007 to September 2008. Inclusion and exclusion criteria for participants are described in detail in Table 1. Subjects were randomized to treatment groups and blinding was achieved by masking group assignment to both staff and participants. In addition, the drug capsules were masked to all look identical. [8] 109 participants were randomized to the placebo group and 108 into the PHEN/TPM ER 15/92 mg group. [8] Participants in the treatment group were started at a dose of 3.75/23 mg daily and the dose was increased weekly over a 4-week period to reach the desired treatment dose. [8] The placebo group underwent the same “titration”. All participants also received lifestyle intervention based on the LEARN

manual and discussed their progress at brief monthly visits.[8] Participants were weighed every 4 weeks until the study was completed at the end of 28 weeks.

Out of the total 756 enrolled participants, 261 (34.5%) discontinued the study and the dropout percentages were comparable across treatment groups.[8] Reasons for discontinuation included loss to follow-up, withdrawal of consent, or adverse events.[8] No serious adverse events were found to be the result of PHEN/TPM ER.[8] Last observation carried forward (LOCF) was used to fill in these participants' missing data for intention to treat (ITT) analysis, and a separate modified ITT analysis was also conducted.[8] In both the mITT and ITT-LOCF analyses, PHEN/TPM ER 15/92 mg was found to result in a statistically significant greater percent weight loss at every 4 weeks than placebo ($p < 0.05$).[8] At 28 weeks the LS mean percent weight loss (mITT) for the placebo group was -2.28 and for PHEN/TPM ER 15/92 mg was -11.63.[8] The ITT-LOCF analysis at 28 weeks respectively showed LS mean percent weight loss of -1.71 for the placebo and -9.21 for PHEN/TPM ER 15/92 mg ($p < 0.05$).[8]

Table 2. LS Mean Percent Weight Loss at Week 28

	mITT	**ITT-LOCF**
Placebo	-2.28	-1.71
PHEN/TPM ER 15/92mg	-11.63	-9.21
P-value	< 0.05	< 0.05

Winslow, et al also conducted a double blind RCT to investigate the effectiveness of PHEN/TPM ER 15/92 mg for weight loss in obese adults, but their participants also had moderate to severe obstructive sleep apnea (OSA).[9] This study ran from August 2008 to September 2009 and encompassed 45 participants with BMIs between 30-40 kg/m^2.[9] Table 1 outlines the specific inclusion and exclusion criteria for participants that was used. All participants received lifestyle modification counseling with the LEARN program.[9] Subjects were randomized to either PHEN/TPM ER 15/92 mg or placebo group with 22 and 23

participants in each respectively. [9] Just like the study conducted by Aronne, et al, there was a 4-week titration period of the medication where the dose was increased weekly by 3.75mg of phentermine and 23mg of topiramate until the desired dose. [9] Once the desired dose was achieved subjects were followed for an additional 24 weeks. Follow up visits with participants occurred every 4 weeks. [9]

Of the 45 participants who were randomized into groups, only 5 did not complete the study due to adverse events or withdraw of consent. [9] Those who did not complete the study accounted for 11% of the enrolled participants. There were 2 participants who discontinued the study from the placebo group and 3 from the PHEN/TPM ER group. [9] Analysis using LOCF for mean percent weight loss in the two groups was done using the data collected at weeks 8 and 28. LS mean percent weight loss at week 8 was -5.6% (standard error 0.59) for the PHEN/TPM ER group and -2.3% (standard error 0.59) for placebo group ($p = 0.0003$). [9] By the completion of the study at week 28, LS mean percent weight loss from baseline was -10.3% (standard error 1.17) for PHEN/TPM ER and -4.2% (standard error 1.15) for placebo ($p = 0.0006$). [9] A placebo-adjusted LS mean percent weight loss was also conducted and found to be -3.3 at week 8 (95% CI: -5.0, -1.6; $p = 0.0003$) and -6.1 at week 28 (LOCF; 95% CI: -9.4, -2.7; $p = 0.0006$). [9]

Table 3. LS Mean Percent Weight Loss at Weeks 8 and 28

	Placebo	**PHEN/TPM ER 15/92mg**	**P-value**
Week 8	-2.3% (standard error 0.59)	-5.6% (0.59)	0.0003
Week 28	-4.2% (1.15)	-10.3% (1.17)	0.0006

Like the previously discussed studies, Garvey, et al also conducted a double blind, placebo-controlled RCT investigating the effects of PHEN/TPM ER 15/92 mg in obese adults (BMI 27-45 kg/m^2). [10] This study, called SEQUEL, lasted 52 weeks and was an extension of the phase 3 CONQUER study that assessed weight loss using PHEN/TPM ER in obese adults with 2

or more obesity-related comorbidities over 56 weeks. [10] SEQUEL's specific participant population also had prediabetes, as defined by the American Diabetes Association, and/or metabolic syndrome. [10] The entirety of this study, including both CONQUER and SEQUEL, ran from December 2008 to June 2010, a total of 108 weeks. [10] 475 participants were enrolled into SEQUEL based on criteria detailed in Table 1, and they remained in their same randomly assigned treatment groups from the CONQUER study. [10] 451 participants were diagnosed with metabolic syndrome, 316 with prediabetes, and 292 had both conditions. [10] The placebo group had 159 participants and PHEN/TPM ER group had 201.[10] Baseline demographics and clinical features were comparable across treatment groups. [10] All participants received lifestyle modification counseling using the LEARN program just like the previously discussed studies. Participants had follow-up visits every 4 weeks for a total of 108 weeks where their weight was measured and lifestyle modifications were discussed. [10]

Only 398 participants, 84% of original participants, completed the study and had data at week 108. [10] Withdraw from the study due to treatment emergent adverse events occurred in 3.1% of the placebo and 5.5% of the PHEN/TPM ER group. [10] Both multiple imputation (MI), using a two-step imputation process, and LOCF were utilized separately to fill in missing data for analysis purposes. [10] Analysis was conducted using ANCOVA on the ITT population for the entirety of the 108 weeks. [10] The difference in weight loss between the two groups was found to be statistically significant, with PHEN/TPM ER producing a greater deficit at every time point assessed in analysis. [10] The PHEN/TPM ER group was found to have a LS mean percent weight loss of 12.1% and the placebo group only had 2.5% (ITT-MI; $p = 0.0001$). [10] Analysis using ITT-LOCF showed similar results to ITT-MI. [10]

Table 4. LS Mean Percent Weight Loss at Week 108

	Placebo	PHEN/TPM ER 15/92mg	P-value
Week 108	2.5%	12.1%	0.0001

DISCUSSION

PHEN/TPM is a schedule IV medication due to the fact that phentermine is similar to amphetamines which are often abused for their stimulant properties.[11] A Risk Evaluation and Mitigation Strategy (REMS) was enacted by the FDA for PHEN/TPM to ensure safe use of the medication, and therefore has limited availability as only certified pharmacies can distribute it.[11] Currently this medication is only available for use in adults with a BMI $\geq$ 27 kg/m^2 and at least one weight-related comorbidity.[11] A similar titration strategy to the one utilized in the three studies discussed for PHEN/TPM is recommended for initiating therapy. A starting dose of 3.75/23mg is taken for 14 days and then titrated up to the desired dose, not to exceed 15/92mg.[11] The medication is best tolerated if taken in the morning as opposed to bedtime to avoid insomnia.[11] Dose restrictions exist for patients with renal and hepatic impairments. If CrCl $\geq$ 30 mL/min, a daily dosage of PHEN/TPM 7.5/46 mg should not be exceeded.[11] Those with severe hepatic impairment should not use this medication.[11]

Abrupt discontinuation of PHEN/TPM can result in seizures and thus it needs to be gradually tapered.[11] Besides insomnia, other common side effects include dizziness, constipation, dry mouth, paresthesia, and altered taste.[11] Absolute contraindications to taking this medication include pregnancy (due to risk of fetal harm and birth defects), use of an MAOI within the last 14 days, glaucoma, hyperthyroidism, or known hypersensitivity to sympathomimetic amines.[11] Prescribers also need to monitor patients for changes in behavior such as suicidal thoughts and depression as suicidality can occur while taking this medication.[11]

In all three of the discussed studies, PHEN/TPM ER was found to cause a significant percent weight loss when compared to placebo. All three studies demonstrated results that were statistically significant with p-values < 0.05 and large effect sizes. Weight loss was achieved in all three studies even though they had participant populations with varying comorbidities. These findings indicate a wide-ranging effectiveness of PHEN/TPM and support its continued use and prevalence in obese participants across the board. Winslow, et al[9] and Garvey, et al[10] conducted a couple different analyses to account for participants that dropped out of the study and all were found to be statistically significant demonstrating the effectiveness of PHEN/TPM ER. It is important to note that all the studies enacted the LEARN lifestyle modification program for all participants in order to control for any differences and standardize the educational information participants received on this topic. PHEN/TPM ER is intended to be taken in combination with lifestyle modifications and therefore by implementing the LEARN program, the studies intended the results to reflect this.

These studies were not without their limitations. Even though the LEARN program was used across all three studies and all treatment groups, it is not clear in any of the studies the extent to which participants incorporated these lifestyle modifications into their daily routines. Compliance with the LEARN program should have been better monitored and evaluated as this could have impacted results. A major limitation throughout all three studies was that worst case analysis for participants who did not complete the study was not performed. Aronne, et al[8] had the largest dropout rate with 34.5% of their original participants not completing the study. Sample size was also an issue in the Winslow, et al[9] study with only 45 enrolled participants. Both the Aronne, et al[8] and Winslow, et al[9] studies lasted only 28 weeks, which was an

acceptable amount of time, but could have been extended to demonstrate the long-term effectiveness of PHEN/TPM ER since it is designed for chronic weight management.

Since the Garvey, et al[10] study was an extension study, it came with a unique set of limitations. For example, only treatment centers that had high-enrollment and participant retention were utilized to recruit for the SEQUEL study. [10] These treatment centers achieved slightly higher weight loss in the CONQUER study compared to other centers. [10] These participant selection factors introduced an element of bias that likely influenced the resulting data. Also of note, a higher percentage of participants in the PHEN/TPM ER treatment arm elected to participate in the SEQUEL study and therefore the original 2:1:2 randomization ratio was not maintained from the original CONQUER study.[10] These reasons could all contribute to some bias in the overall study and subsequent results that were found.

CONCLUSION

The findings of these three studies all clearly answer the question that indeed PHEN/TPM ER plus lifestyle modifications is effective in achieving weight loss in obese adults. Despite participants all having various obesity-related comorbidities, Aronne, et al[8], Winslow, et al[9], and Garvey, et al[10] all found statistically significant weight loss with PHEN/TPM ER compared to placebo with p-values < 0.05. For future research on this topic it would be beneficial to assess the role lifestyle modifications play in the success of PHEN/TPM ER in achieving weight loss. Future studies can control the lifestyle modifications participants utilize by having scheduled workouts and meal preparation services in addition to educational information about healthy diet and exercise. At the very least the lifestyle modifications should be monitored to track subjects' participation and see if this was consistent across treatment groups as this could greatly impact results.

It would also be informative to pursue additional studies investigating the effectiveness of PHEN/TPM in other comorbidities where obesity is a common symptom and weight loss is notoriously challenging, such as hypothyroidism and polycystic ovarian syndrome. If PHEN/TPM is proven effective in these populations, it could have profound effects on not only their disease course, but also their overall physical and mental health state. Although the study by Garvey, et al[10] ran for 108 days which was significantly longer than the other two studies, future studies of even longer duration, such as a longitudinal study, would be beneficial to see if PHEN/TPM ER can help obese adults maintain and/or continue achieving weight loss over the years. As the popularity of weight loss medications continues to rise, future studies should look into comparing these medications to each other to see not only which medication achieves weight loss, but which sustains it over time.

The majority of weight loss medications are only approved for use in adults. Currently however there are clinical trials in progress assessing the use of PHEN/TPM ER in adolescents. At the University of Minnesota there are two ongoing trials with one investigating PHEN/TPM for achieving weight loss in severely obese children ages 12-20[12], and the other looking at PHEN/TPM's use in obese adolescents (ages 12-18) with Type 2 diabetes.[13] This research would greatly impact the ongoing prevalence of childhood obesity by hopefully providing evidence for the use of these weight loss medications in the adolescent patient population.

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