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Phentermine/Topiramate extended release versus Lorcaserin for weight reduction in obese adult patients: design of a randomized, double-blind, multicentric clinical study

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Abstract:

Background and Aim: Obesity is a major health concern in the world. Pharmacological strategies are accepted as part of obesity treatment, but a standard intervention is yet to be established. Phentermine/Topiramate extended release (ER) and Lorcaserin have been approved for obesity treatment and a head-to-head comparison could help outline guidelines for standardized pharmacological therapy in this area. Therefore we aim to assess whether Phentermine/Topiramate ER is superior to Lorcaserin in body weight reduction after 54 weeks of follow up.

Design: Randomized, double blind, double-dummy, multicentric clinical trial.

Participants: Adults aged from 18 to 65 years, with body mass index (BMI)=30-40kg/m², or BMI=27-30kg/m² with at least one comorbidity.

Measurements and procedures: Participants will be randomized using a block design with randomly selected sizes, stratified by study center, and a 1:1 ratio, to receive either Phentermine/Topiramate ER 7.5mg/46mg qd (+placebo), or Lorcaserin 10mg bid (+placebo). Baseline laboratory characteristics will be documented at screening visit, and baseline clinical characteristics of eligible individuals, up to 2 weeks later. After a 2-week titration period, participants will be monthly assessed for 52 weeks.

Primary outcome: proportion of subjects with a minimum 5% weight reduction from baseline bodyweight after a 54-week follow up.

Secondary outcomes: mean weight change; proportion of subjects with a minimum 10% weight reduction; quality of life; blood pressure; waist circumference; lipoprotein lipids; fasting glucose; insulin; and glycated hemoglobin levels. Investigators and participants will be blinded to treatment.

Ethical aspects: This trial will follow the Declaration of Helsinki and the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, and only participants who sign informed consent form and fully understand every component of the study procedures will be eligible. A Data Monitoring Committee will be established to provide quality control and assure that study procedures are followed.

Key-Words: Obesity, Phentermine, Topiramate, Lorcaserin, Weight Loss, Obesity Treatment.

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INTRODUCTION

Obesity increasingly represents a major public health concern and economic problem in the Western world.

More than one third of the adult population in the United States of America (USA) is affected by this condition (Ogden, 2013), which is associated with long-

term comorbidities, in particular cardiovascular diseases, diabetes, and cancer (Ogden, 2013; Wannamethee, 2005; Calle, 2003). Billions of dollars are spent every year with the management of obesity and its associated diseases, in what amounts to more than 1.4 thousand times the expenses with non-obese patients (Ogden, 2013).

Several studies have indicated that modest weight reductions (5 to 10%) can reduce the risk and morbidity of several obese-associated diseases and decrease overall mortality (Ogden, 2013; Wannamethee, 2005; Wing, 2011). Hence the Endocrine Society and the Food and Drug Administration (FDA) have established that weight loss of at least 5% are indicators of efficacy for anti-obesity treatments (Ogden, 2013; Richard, 2002; Wannamethee, 2005; Calle, 2013; Jensen, 2014).

Non-pharmacological and pharmacological treatments are complimentary strategies to fight obesity. The non-pharmacological approach is the current cornerstone in the management of obese patients, and it is based on the combination between hypocaloric diets and physical activity (Ogden, 2013; Wannamethee, 2005; Calle, 2003). However, lifestyle modification strategies are difficult to sustain and maintenance of weight loss over time is unlikely (Ogden, 2013). Regarding pharmacological strategies, the Endocrine Society's guidelines suggest the use of approved medications to maintain long-term weight loss and improve comorbidities in the following situations: individuals with body mass index (BMI) of 30kg/m² or higher; individuals with BMI of 27kg/m² or higher in the presence of at least one associated comorbidity, including hypertension, dyslipidemia, diabetes mellitus, and obstructive sleep apnea (US Food and Drug Administration, 2013). Despite its overwhelming prevalence and association with increased morbidity and poor outcomes, obesity still does not have a standard pharmacologic treatment (US Food and Drug Administration, 2013; Ogden 2013). Phentermine/Topiramate and Lorcaserin emerge as viable alternatives.

Phentermine is a sympathomimetic amine that causes the release of hypothalamic catecholamines, which reduce caloric intake and appetite (Ogden 2013). Topiramate is a fructose monosaccharide derivative that has been approved as an epilepsy treatment and has an anorexic effect. (Ogden, 2013; Wannamethee, 2005; Calle, 2003). Since Phentermine and Topiramate work through different mechanisms, they have been used in combination for increased effect. Evidence exists showing a 9% weight loss after a 12-month use of Phentermine/Topiramate extended release (ER) in a dosage of 7.5mg/46 mg once a day (Ogden, 2013). Increases in dosage marginally increased weight loss,

with significant surge in adverse events (AEs), including paraesthesia, dizziness, dysgeusia, insomnia, constipation, and dry mouth (US Food and Drug Administration, 2013; Gadde, 2011).

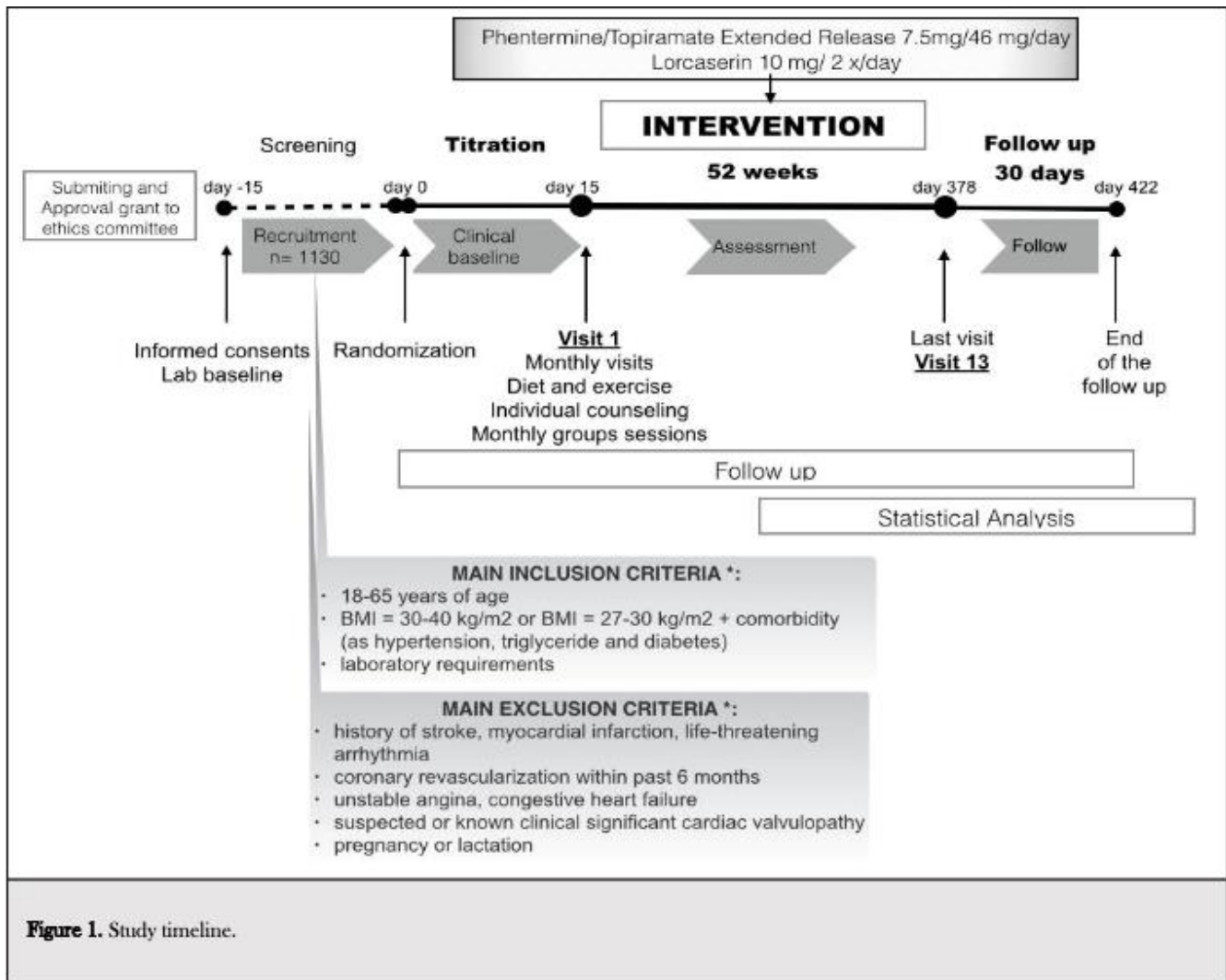
Lorcaserin is an agonist of central serotonin subtype 2c (5-HT_{2c}) receptors of hypothalamic pro-opiomelanocortin neurons (US Food and Drug Administration, 2013; Taylor 2013; Fidler, 2011). It apparently regulates eating behavior by reducing caloric intake and increasing satiety (Xu, 2008). The recommended dosage is 10mg twice a day and previous studies have found a 6% reduction in weight following a 12-month long treatment (US Food and Drug Administration, 2012; Smith, 2010). Lorcaserin was also associated with favorable changes in anthropometric measures, blood pressure and lipid control, and with a benign safety profile. Most common AEs were headaches, upper respiratory infections, nausea, dizziness, and fatigue (O'Neil, 2012; US Food and Drug Administration, 2012; Taylor, 2013; Smith, 2010).

The FDA approved both drugs in 2012 for the treatment of obese adults, or overweight adults with weight-related comorbidities (US Food and Drug Administration, 2012; Garvey, 2012; Gadde, 2011; Fidler, 2011; O'Neil, 2012). Available data suggest that Phentermine/Topiramate ER might be more effective but also more toxic than Lorcaserin, although both drugs have profiles (Woloshin, 2014). From the perspective, it would be helpful to Phentermine/Topiramate performs better than Lorcaserin regarding both efficacy and safety in the treatment of obese adults. Such information would help in the development of guidelines and recommendations for obesity treatment. Therefore, our aim is to assess whether treatment with Phentermine/Topiramate ER is superior to Lorcaserin in producing a 5% reduction of body weight over a 54-week follow-up period of obese adults.

METHODS

Trial Design

This will be a randomized, double blind, double-dummy, multicenter trial. Patients will be randomly assigned in a 1:1 ratio to receive either Phentermine/Topiramate ER 7.5mg/46 mg/day orally plus placebo (simulating Lorcaserin), or Lorcaserin 10mg twice a day plus placebo (simulating Phentermine/Topiramate ER). After an initial 2-week titration period, participants will be followed for 52 weeks. Study data will be collected and managed using REDCap electronic data capture tools.



Population: Recruitment

Patients will be recruited in USA, where both Phentermine/Topiramate ER and Lorcaserin are commercially available. As the South and Midwest regions of the country have the highest prevalence of obesity (over 30%), recruitment will initially prioritize these regions (Ogden, 2014). Targeted enrollment strategies will be employed to recruit participants. The Endocrine Society, the American Association of Clinical Endocrinology, The Obesity Society and the American Association Family Physician will be approached to send electronic messages to endocrinologists and general practitioners containing details from the study, participating sites, and asking them for referrals. Additionally, public awareness campaigns will be promoted using patient directed advertisements in posters, banners, magazines, and waiting room televisions of hospitals and clinics.

Population: Eligibility criteria

Adults aged 18 to 65 years with BMI of 30-40kg/m², or BMI of 27-30kg/m² with at least one comorbidity, will be considered for enrollment (US Food and Drug Administration, 2012; US Food and Drug Administration, 2013). Comorbidities of interest include: hypertension (defined as a previous clinical diagnosis of hypertension with the use of at least one antihypertensive drug); triglyceride concentration of 2.26-4.52mmol/L or using at least two lipid-lowering drugs; fasting blood glucose >5.55mmol/L, blood glucose >7.77mmol/L at 2 hours after oral glucose load during oral glucose tolerance test, or diagnosed type 2 diabetes. Exclusion criteria include history of stroke, myocardial infarction, life-threatening arrhythmia, coronary revascularization within past 6 months, unstable angina, congestive heart failure, and suspected or known clinically significant cardiac valve disease. See Appendix A for a full list of inclusion and exclusion criteria.

Measurements and procedures

The study primary outcome will be the proportion of subjects with a minimum 5% weight reduction at 54 weeks from baseline bodyweight. Secondary efficacy outcomes will include: mean weight change at 54 weeks from baseline bodyweight (grams) and proportion of subjects with a minimum 10% weight reduction at 54 weeks from baseline bodyweight. Besides investigating these outcomes at week 54, we will also evaluate the trajectory of these outcomes over time, based on measurement obtained at 14, 26, and 54 weeks after starting treatment. Additional efficacy and safety outcomes will be: blood pressure (mmHg), heart rate (beats per minute, bpm); waist circumference (centimeters); lipoprotein lipids; fasting glucose and insulin; glycated hemoglobin (in type 2 diabetics); quality of life as measured by the Short Form (36) Health Survey; incidence of AEs, including serious AEs; proportion of subjects that have the dosages of antidiabetic, lipid lowering or antihypertensive medications modified. These outcomes will be analyzed at 54 weeks and throughout the study.

Intervention and follow up

Informed consent will be obtained and baseline laboratory evaluation will be performed at screening visit (Figure 1). The randomization visit (V0) will take place up to 2 weeks later, when baseline clinical measurements will be assessed and eligible participants randomized to either arm of the study. Those randomized to receive Phentermine/Topiramate ER will initially receive the lowest dosage of the medication (3.75mg/23mg) for two weeks, which will be considered the titration period. Patients randomized to receive Lorcaserin will only receive placebo in this period.

Visit 1 (V1) will take place two weeks after V0, when participants will be reassessed and the final dose of Phentermine/Topiramate ER established and the Lorcaserin dose started. For the following twelve months, the medical team will evaluate participants every four weeks. A window of ±3 days will be accepted for the scheduling of these visits. In each visit, patients will be clinically examined, have biometric measures taken, have a detailed interview for AEs, and have adherence assessed through pill counting and diary. Quality of life questionnaires will be completed and blood samples will be drawn in V0, V5, V10 and V13. Monitoring for AEs will continue for 30 days after the end of follow-up in V13.

All participants will receive standardized manuals with educational content regarding lifestyle modification recommendations at enrollment. They will also be invited to participate in lifestyle modification counseling groups,

which will take place once a month and will be led by a dietitian and a physical educator.

Randomization

Patients will be randomized using a randomized block design with randomly selected size, stratifying by study center. The allocation sequence will be electronically generated by an open source web application and will contain a list of numerical sequences that will correspond to individual treatment packages. After a subject is allocated to one of these treatment codes, his/her study identity will remain linked to that code for the remainder of the study. Only the study pharmacist will have access to the allocation sequence key.

Blinding

All researchers and participating individuals will be blind to treatment allocation, except the study pharmacist, who will be responsible for centrally preparing, labeling and distributing the treatment packages. A company will be hired to manufacture placebos looking identical to the active medications. Study treatments will be identified with a numerical sequence specific to each subject that only the study pharmacist will have access.

Unblinding prior to study completion is forbidden, except in the occurrence of a serious adverse event for which the identity of the study medication is required to provide adequate treatment. In such occasions, only the principal investigator or attending subinvestigator will be authorized to perform the unblinding procedures. The participant will no longer receive any medication, but will be asked to complete the follow-up as initially planned.

Adherence

We have planned to perform numerous adherence-enhancing strategies. These will include: providing detailed information for the participants regarding each step of the study; inviting family members and friends to act as sponsors (with authorization from participants); sending monthly summary reports showing the participants' progress, along with lifestyle modification tips; instructing on how to make the best use of smartphone apps to monitor diet and exercise; and promoting social networking between participants. Participants will also be reminded of their visits on the day before their appointment, and will be required to bring their treatment packages for pill count. Adherence will be monitored based on pill count and assessment of participant's diary.

Modification and discontinuation

Dosage modifications will not be performed after the initial titration period. Discontinuation from study treatment will take place in the following circumstances (US Food and Drug Administration, 2012; US Food and Drug Administration, 2013): serious adverse event potentially caused the study medications; cardiovascular events (e.g. myocardial infarction, stroke, heart failure); heart rate decrease to <50bpm in two separate measures on two different days; heart rate increase from baseline in ≥ 20 bpm in two separate measures on two different days; uncontrolled hypertension (systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg) in two separate measures on two different days.

These circumstances may result in temporary or definitive discontinuation from study medications at the discretion of the investigator. Regardless of interruption of study treatment, participants will be encouraged to proceed with the scheduled follow-up appointments.

See Appendix A for a full list of discontinuation criteria.

Adverse events

Adverse events will be classified for severity (mild, moderate, severe) and relationship with investigational products (probable, possible, unlikely, or not related).

All AEs will be detailed, documented and monthly reported to a data safety monitoring board. Serious adverse events will be reported within 24 hours of notification and include events that result in death, are life-threatening, require inpatient hospitalization or cause prolongation of existing hospitalization, result in persistent or significant disability/incapacity, are congenital anomaly/birth defect, or require intervention to prevent permanent impairment or damage (ICH, 1994; Edwards, 1994).

Statistical considerations

Through descriptive statistics, we will evaluate the presence of outliers and assumptions for all statistical tests, and, if necessary, variables may be transformed, for instance using a logarithm transformation. Treatment groups will be compared at baseline through summary statistics. Baseline laboratory variables will be defined as those values obtained at the screening visit, and baseline clinical variables as those obtained at V0.

The primary study population will be based on the intention-to-treat (ITT) group and will include all randomized subjects with or without information available at 54 weeks post-randomization (V13). Secondary analysis will be based on the intention-to-treat

population and on the per-protocol population, defined as participants who attend at least 80% of visits and for V13, and who do not discontinue study medication for more than 15 consecutive days or 30 non-consecutive days.

The main study outcome is binary presence (vs. absence) of 5% weight reduction between baseline and V13. Primary analysis of this outcome and other categorical outcomes will be based on Pearson's Chi-square or Fisher Exact tests, when appropriate. Primary analysis of continuous outcomes will be based on independent sample t-tests or Wilcoxon rank sum tests, as appropriate. Additionally, we will consider adjusting all analyses by gender and study site through linear regression for continuous variables and logistic regression for categorical variables. The trajectory of weight loss over the 54-week period will be studied through multivariate linear models with random effects to account for correlation within subjects over time.

When analyzing safety outcomes, we will compare treatment groups with regards to incidence of adverse events, laboratory and clinical assessments, vital signs, and ECG. Although conclusions will be mainly based on summary statistics, statistical significance of these comparisons between groups will be assessed, mostly through non-parametric tests.

Subgroup analyses will be performed according to gender, BMI, presence of hypertension and presence of prediabetes or diabetes. Strata specific effects will be reported and interaction terms between these variables and treatment groups will be tested and considered statistically significant if the p-value is less or equal to 0.10.

All other analysis will be considered statistically significant if the p-value is less or equal to 0.048, after adjusting a significance level of 0.05 for one interim analysis.

Statistical analyses will be performed using Stata 13.1 (Stata Corp, College Station, TX).

Interim analysis

Periodic A Data Monitoring Committee (DMC) will be established to assess study conduct, data quality and safety. Before starting the study the DMC will approve the protocol and monitoring chart and afterwards, monitor the study in periodic meetings during the trial. After half of the target sample has completed the trial, an interim analysis will be performed for futility and efficacy. Based on O'Brien Fleming Spending function, the trial may be stopped early if analysis meets a significance level of 0.00516.

Missing data

We will examine the pattern of missing data and unless otherwise suggested by the data, we will assume it is missing at random and perform multiple imputation for weight at week 54 in the ITT analyses. As sensitivity analysis, we will also repeat the tests using complete case analysis and simulating weight regain.

Power and sample size calculations

A total of 1130 patients (565 patients/group) will be enrolled in this study to analyze a minimum of 790 patients (395 patients/group), assuming a 30% dropout rate. With this sample size, our study will attain 80% power to detect differences between the two treatment groups of at least 7% to 10% in a two-sided, 0.048 alpha-level Pearson chi-square test, assuming that 10 to 50% of Lorcaserin treated patients achieve 5% or more of weight loss at week 54 (Figure 2 in Appendix A). Therefore, our study shall have enough power to test hypothesis for the primary outcome in likely scenarios. For instance, previous studies have estimated that 48% of patients treated with Lorcaserin reduced their weight by 5% or more during the 54 weeks post-treatment (Fidler, 2011). Under this scenario, our study will attain 80% power to detect a difference in proportion between the two groups as low as the 10%, i.e., a proportion of 58% Phentermine/Topiramate-patients achieving the target weight reduction of 5%.

Ethical aspects

This trial will be registered under the name "Phentermine/Topiramate Extended release versus Lorcaserin for Weight Reduction in Obese Adult Patients: a Randomized, Double Blinded, Multicentric Clinical Study. The PERL trial" in ClinicalTrials.gov. As it is an investigator-initiated study, we plan to seek sponsorship with privately owned pharmaceutical companies.

It will follow the Declaration of Helsinki and the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, and only participants who sign the informed consent and fully understand every component of the study protocol will be eligible to participate. Finally, all patient identifiable information will be stored in locked cabinets and/or secure electronic servers. Any samples or participant data collected during the study will be de-identified and have only an encoded identification number to ensure participant confidentiality. The key file relating the patient identity with the patient identification number will be stored in a separate, password protected, to whom only the principal investigator and a designated person will have access.

DISCUSSION

The main limitations of this trial may include the high dropout rate, which is common in phase 3 trials evaluating obesity treatment (Gadde, 2011; Garvey, 2012). We considered a 30% discontinuation rate as there will be no placebo arm and, thus, patients are expected to be more motivated to proceed in the trial. Every effort will be done to collect information about main outcomes at week 54 and patients will be offered a home visit to be clinically evaluated and have blood samples drawn.

The double-dummy design is an important feature of this trial, as Phentermine/Topiramate ER is a capsule and Lorcaserin a tablet. Hence, such design helps to maintain the blinding, reducing the possibility of bias.

CONCLUSION

There were no other RCTs comparing both Phentermine/Topiramate ER and Lorcaserin on a search performed in ClinicalTrials.gov. Therefore, the PERL trial aims to contribute with more knowledge regarding the pharmacological treatment of obesity, providing data to support future treatment algorithms in this challenging disease.

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Conflict of interest and financial disclosure

The authors followed the International Committee or Journal of Medical Journals Editors (ICMJE) form for disclosure of potential conflicts of interest. All listed authors concur with the submission of the manuscript, the final version has been approved by all authors. The authors have no financial or personal conflicts of interest.

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