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General Information

Key Personnel (in addition to PI):
 First Name: Hui
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Degree: MD, PhD
Primary Affiliation: Chengdu University of Traditional Chinese Medicine

Are external grants or funds being used to support this research?: External grants or funds are being used to support this research.
Project Funding Source: Science and Technology Department of Sichuan Province
How did you learn about the YODA Project?: PubMed

Conflict of Interest

https://yoda.yale.edu/system/files/coi_1.pdf

Certification

Certification: All information is complete; I (PI) am responsible for the research; data will not be used to support litigious/commercial aims.
Data Use Agreement Training: As the Principal Investigator of this study, I certify that I have completed the YODA Project Data Use Agreement Training

1. NCT00210535 - TOPMATMIG3006 - A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Topiramate for the Prophylaxis of Migraine in Pediatric Subjects 12 to 17 Years of Age
2. NCT00210860 - CAPSS-296 - An Open-label Study of the Safety and Efficacy of Topiramate for Migraine Prophylaxis: Extension Study to CAPSS-277
3. NCT00236509 - TOPMAT-MIGR-001 - A Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Dose-Response Study to Evaluate the Efficacy and Safety of Topiramate in the Prophylaxis of Migraine
4. NCT00231595 - TOPMAT-MIGR-002 - A Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Dose-Response Study to Evaluate the Efficacy and Safety of Topiramate in the Prophylaxis of Migraine
5. NCT00236561 - TOPMAT-MIGR-003 - A Randomized, Double-Blind, Parallel-Group, Dose-Response Study to Evaluate the Efficacy and Safety of Two Doses of Topiramate Compared to Placebo and Propranolol in the Prophylaxis of Migraine

What type of data are you looking for?: Individual Participant-Level Data, which includes Full CSR and all supporting documentation

Research Proposal

Project Title

Topiramate versus oral gepants in the treatment of patients with migraine: a matching adjusted indirect comparison

Narrative Summary:

Topiramate is used as a first-line treatment for migraine prophylaxis. Gepants, a new class of drugs for migraine prevention, are available as oral medications. Direct comparison between topiramate and gepants has not been conducted. Owing to the lack of comparative effectiveness between these two, patients and clinicians could not make appropriate clinical decisions based on evidence. We therefore aim to conduct a matching adjusted indirect comparison, adjusting for imbalance in baseline characteristics of the topiramate and gepants trials. The results will be helpful for patients with migraine, clinicians, and policy makers.

Scientific Abstract:

Background: Topiramate is the classical first-line treatment for migraine prophylaxis. Gepants are small molecules that block the CGRP docking station or CGRP receptor, which provide preventive effects for migraine attacks. Recently, oral gepants are approved by FDA for the preventive treatment of migraine or proved to be effective. However, the comparative effectiveness between topiramate and oral gepants is unknown.
Objective: To perform a systematic review of topiramate and oral gepants for the preventive treatment of migraine and to conduct a matching adjusted indirect comparison of topiramate versus oral oral gepants.
Study design: Matching adjusted indirect comparison
Participants: diagnosed with migraine.
Main outcome measure: Change in mean monthly migraine days
Statistical analysis: We will use a matching adjusted indirect comparison model, built based on the propensity score matching method, to compare the difference in the change of mean monthly migraine days between topiramate and oral gepants. We will calculate weights for the study population from topiramate trials, and use the weights to adjust for baseline imbalance among the treatment arms. Weighted t test will be used to compare the treatment effects of topiramate and oral gepants.

Brief Project Background and Statement of Project Significance:

Topiramate is the classical first-line treatment for migraine prophylaxis. Oral gepants, a new class of drugs approved for the treatment of migraine, show promising treatment effects for migraine prevention. Patients with migraine, clinicians, and policymakers will be interested in the comparative effectiveness between topiramate and

oral gepants which facilitates clinical decision making. Regarding the high prevalence of migraine, the general population will also be interested in this comparison.

Specific Aims of the Project:

Hypotheses to be evaluated:
1. Oral gepants reduce more monthly migraine days than topiramate.
2. Oral gepants cause fewer adverse events than topiramate in the treatment of migraine.

What is the purpose of the analysis being proposed? Please select all that apply.
New research question to examine treatment effectiveness on secondary endpoints and/or within subgroup populations
New research question to examine treatment safety
Participant-level data meta-analysis
Participant-level data meta-analysis using only data from YODA Project

Research Methods

Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:

Data source
1. A search for studies published in MEDLINE, EMBASE, CENTRAL, and Web of Science;
2. Participant-level data from YODA project will be acquired for the topiramate group;
3. Summary-level data will be acquired from the randomized controlled trials assessing the effect of oral gepants.
Inclusion/Exclusion Criteria
1. Diagnosed with migraine (with or without aura);
2. Received at least one-month treatment of topiramate or oral gepants.

Main Outcome Measure and how it will be categorized/defined for your study:

Change in monthly migraine days.
The number of migraine days is an outcome that was the most frequently used in trials studying migraine prevention. The assessment period of migraine days is normally one month. The primary outcome of our study will be the change from baseline in monthly migraine days.

Main Predictor/Independent Variable and how it will be categorized/defined for your study:

Main predictors.
1. Age (years). This variable will be used as a continuous outcome.
2. Proportion of females (%). The variable will be used as a number with 2 digits. For example, a trial recruiting 100 participants (70 female participants) will be recorded as 70/100=0.7.
3. Baseline migraine days (no. of days). The variable will be used as a continuous outcome, for example, 15 days/per month.
4. Previous treatments (no. of treatments). The variable will be a binary outcome (yes/no), and it will be transformed into a proportion number.

Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:

1. Duration of migraine. The variable will be a continuous outcome, preferably presented as months (eg, 12 months).
2. The body mass index(BMI). The BMI index will be used as a continuous outcome.

Statistical Analysis Plan:

1. Descriptive analysis. We will describe the distribution of the main outcome measure using mean, standard deviation, and 95%CI. We will also describe and compare the baseline characteristics of the two study populations: mean age, proportion of females, baseline migraine days, and the number of previous treatments.

2. Hypothesis testing. The hypothesis testing will have two steps, the first we will perform matching-adjusted indirect treatment comparison (MAIC), and the second we will perform multilevel network meta-regression models to incorporate data from both individual-level and summary-level datasets.

For the MAIC study, we will compare the inclusion criteria and baseline characteristics from topiramate trials and the oral gepant trials, and we will select one topiramate trial and one gepant trial in pairs. We will use the MAIC model, developed on the basis of the propensity score matching method, to calculate the propensity scores for each participant assigned to receive topiramate. We then use the propensity scores as weights and adjust baseline imbalance, and we will perform a weighted t-test to compare the effect of topiramate versus oral gepants.

For the multi-level multilevel network meta-regression (ML-NMR) models, we will include all trials (including summary-level data from gepants trial and individual-level data from topiramate trials). We will consider running a ML-NMR model adjusting for effect-modifying covariates (the 6 predictors). The analysis will be performed in the multinma package in the R environment (R 4.1.1).

Software Used:

RStudio

Project Timeline:

Anticipated project start date: 1 July 2022
Analysis completion date: 31 December 2022
Manuscript drafted date: 31 March 2022
First submitted for publication: 30 Apirl 2022
Date results reported back to the YODA project: 30 June 2022

Dissemination Plan:

The results will be submitted to a peer-reviewed journal, and if possible, be presented at a conference. Potentially suitable journals might be JAMA Neurology, Neurology, or European Journal of Neurology.

Bibliography:

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