Cardiovascular Safety of Phentermine and Topiramate in a United States Claims Database

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DISCLOSURE

MER, AH, SH, ST, MCA, KJR, EBA, and MSA are employees of RTI Health Solutions, which received funding from VIVUS, Inc. to conduct this study. The contract between RTI Health Solutions and the sponsor includes independent publication rights. RTI is a non-profit organization that conducts work for government, public, and private organizations, including pharmaceutical companies. LN and CP are employees and shareholders of VIVUS, Inc.

BACKGROUND

- Qsymia, an oral medication for weight management, is a fixed-dose combination of phentermine (PHEN) and topiramate (TPM).
- Increased heart rate was seen with the top dose of Qsymia (fixed-PHEN 15 mg/TPM 92 mg) in clinical trials. Beneficial effects on other risk markers (BP, lipids, glycemic parameters) were observed.
- The risk of cardiovascular (CV) outcomes (e.g., major adverse CV events [MACE]) with fixed-PHEN/TPM treatment are unknown.

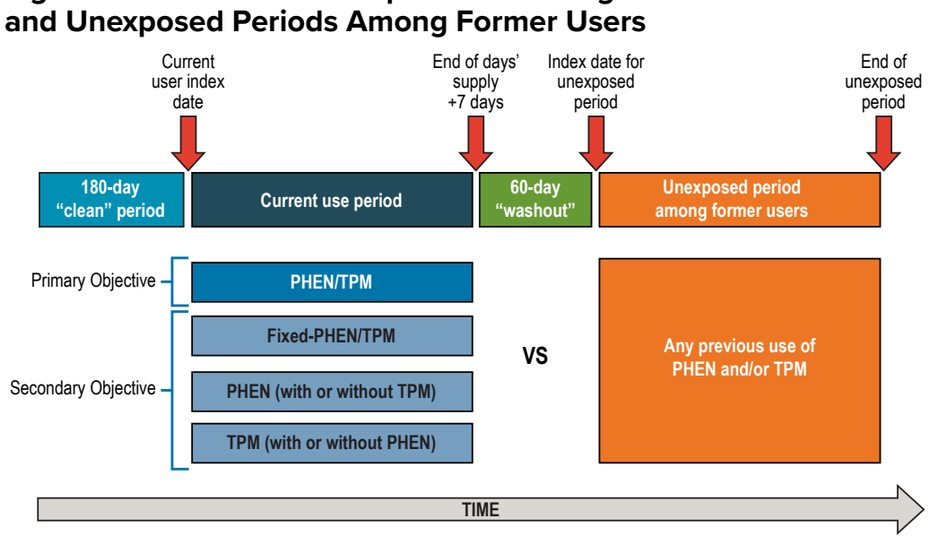
OBJECTIVES

- The primary objective was to determine the extent to which the occurrence of CV events is higher or lower among current users of PHEN and TPM than among patients not currently exposed to these medications.
- To accomplish this objective, we compared MACE incidence among current users of PHEN and TPM (including fixed dose) with former users of any of these medications. Former users were selected as the comparator due to the absence of consistent coding for obesity or overweight and because any drug effect on CV risk was assumed to end at drug discontinuation (e.g., transient increase in heart rate, no enduring effects anticipated).

METHODS

- A retrospective cohort study was conducted in MarketScan Commercial Claims and Medicare Supplemental data. This data source was chosen because it had the largest number of users of fixed-dose PHEN/TPM among databases evaluated during an earlier feasibility assessment.
- Patients were aged ≥ 18 years, with a required enrollment duration of ≥ 6 months before the index date.
- MACE was defined as hospitalization for acute myocardial infarction (AMI) or stroke and in-hospital CV-related death as determined via discharge status and ICD-9-CM diagnoses.
- Current-use periods began at the first prescription dispensing date after a ≥ 180-day clean period (initial entry) or after a gap of > 60 days (subsequent use) (Figure 1).

Figure 1. Overview of Comparisons Among Current-Use Periods and Unexposed Periods Among Former Users



- Unexposed periods among former users began after 60 days without exposure to any study medication.
- MACE incidence rates (IR) and IR ratios (IRR) with 95% confidence intervals (CIs) were estimated for PHEN, TPM, PHEN/TPM, and fixed-PHEN/TPM current-use periods versus unexposed periods in former users of any of the medications.
- Stratification by propensity score (PS), with exclusion of non-overlapping ranges, was used to control for confounding.
- A sensitivity analysis was performed assessing current exposure versus unexposed time in former users in mutually exclusive medication cohorts (e.g., current TPM vs. unexposed periods in former TPM users).

RESULTS

- Summaries of person-time, event counts, and crude IRs among current-use and unexposed time in former-users are presented in Table 1.
- As expected, AMI and stroke IR were higher than the IR of in-hospital CV death.
- PS trimming and stratification yielded balanced cohorts across covariates (Figures 2 and 3).
- MACE and its components were generally increased in patients who were older, male, and who had prior CV events (data not shown).
- MACE IRRs for current use of each medication group versus unexposed periods among former users are listed in Table 2.
- Results of the sensitivity analysis were quantitatively similar when limiting the comparison of current to former users within each specific medication cohort (e.g., current vs. former PHEN/TPM use), although the point estimates were closer to the null.

Table 1. Person-Time, Event Counts, and Crude Incidence Rates for Composite MACE Outcomes and Components

Outcome	Current Users				Former Users
	PHEN/TPM (n = 19,184)	Fixed-PHEN/TPM (n = 14,586)	PHEN (n = 124,334)	TPM (n = 316,388)	Unexposed (n = 386,136)
Person-years	3,244.9	2,587.2	24,106.6	64,606.5	310,664.9
MACE composite					
No. of events	3	1	22	218	622
IR (95% CI)	0.92 (0.19-2.70)	0.39 (0.01-2.15)	0.91 (0.57-1.38)	3.37 (2.94-3.85)	2.00 (1.85-2.17)
AMI					
No. of events	1	0	11	62	335
IR (95% CI)	0.31 (0.01-1.72)	0.00 (0.00-1.43)	0.46 (0.23-0.82)	0.96 (0.74-1.23)	1.08 (0.97-1.20)
Stroke					
No. of events	2	1	10	154	258
IR (95% CI)	0.62 (0.07-2.23)	0.39 (0.01-2.15)	0.41 (0.20-0.76)	2.38 (2.02-2.79)	0.83 (0.73-0.94)
CV death					
No. of events	0	0	1	2	29
IR (95% CI)	0.00 (0.00-1.14)	0.00 (0.00-1.43)	0.04 (0.00-0.23)	0.03 (0.00-0.11)	0.09 (0.06-0.13)

Fixed-PHEN/TPM = phentermine + topiramate extended-release formula.

Table 2. Crude and Adjusted Incidence Rate Ratios for Composite MACE Outcomes, Comparing Current Use and Unexposed Periods

Medication	Incidence Rate Ratios	
	Crude	Adjusted
PHEN/TPM	0.46 (0.09, 1.36)	0.57 (0.19, 1.78)
Fixed-PHEN/TPM	0.19 (0.00, 1.08)	0.24 (0.03, 1.70)
PHEN	0.46 (0.28, 0.70)	0.56 (0.34, 0.91)
TPM	1.69 (1.44, 1.97)	1.58 (1.33, 1.87)

Figure 2. Propensity Score Density Curves of Current Use and Unexposed Periods for Each Medication Cohort

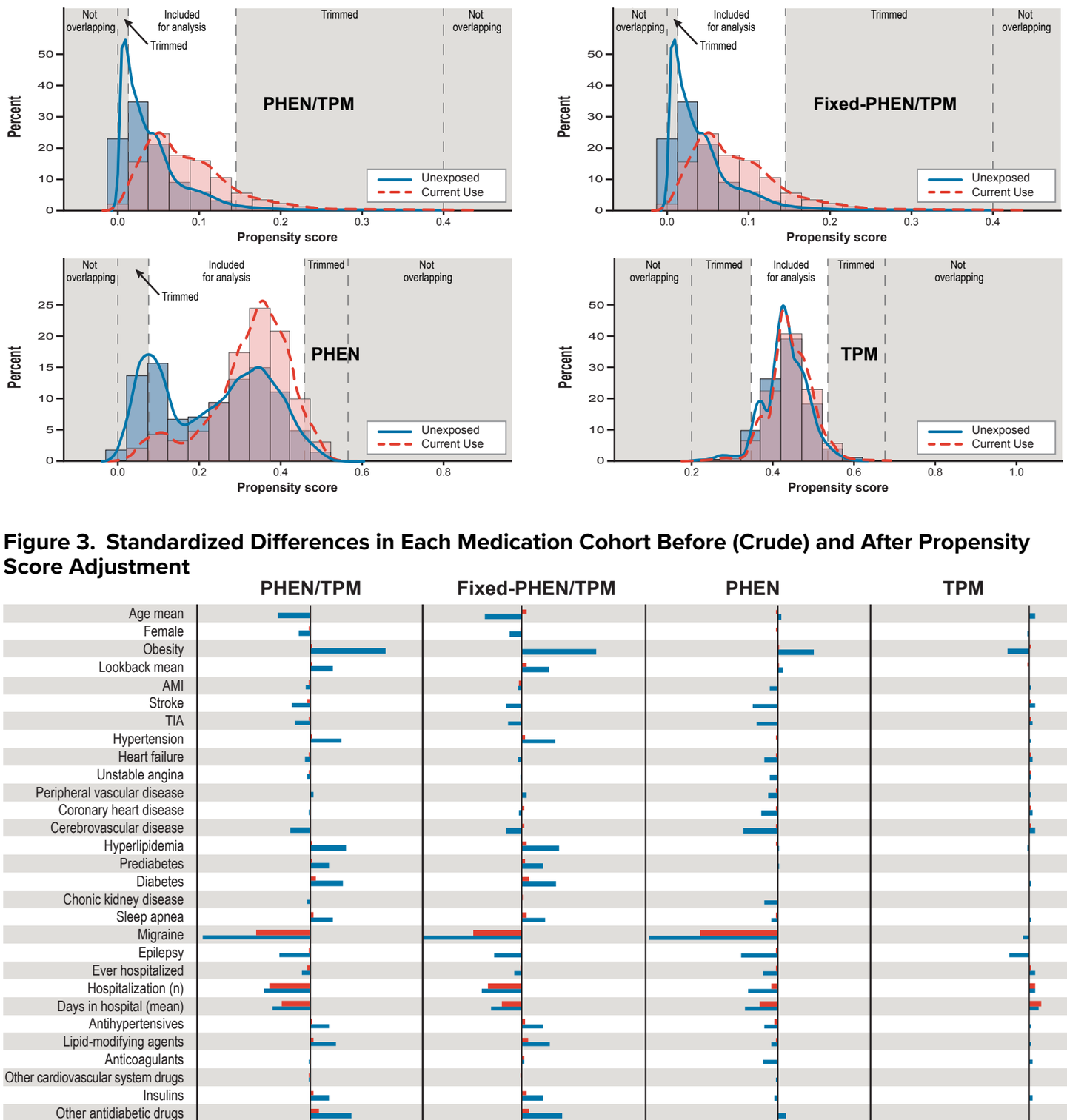


Figure 3. Standardized Differences in Each Medication Cohort Before (Crude) and After Propensity Score Adjustment

TIA = transient ischemic attack.

CONCLUSIONS

- MACE risk was lower with current PHEN use and higher with current TPM use compared with the unexposed cohort.
- MACE risk trended lower with current PHEN/TPM use (including fixed PHEN/TPM) compared with the unexposed cohort.
- However, the small number of events produced considerable statistical uncertainty in the PHEN/TPM analysis, and the results are consistent with a range of effects from a strong negative association to a modest positive association.

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