# Real-World Evidence on Potential Drug-Drug Interaction Between Topiramate and Oral Hormonal Contraceptives Among Patients With Migraines

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## Background

- Topiramate is a weak/moderate CYP3A4 inducer agent. Studies have suggested low dose treatment (<200mg) has little impact on plasma levels of oral contraceptives. The clinical outcome of this potential interaction is unknown.
- Real-world data can provide an opportunity to evaluate the impact of this potential interaction on contraception failure.

## Objective

- To compare the rate of oral contraceptive failure (defined as unintended pregnancies) among women with migraines who use topiramate or alternative treatments

## Methods

- **Data Source & Study Design:**
  - MarketScan® Commercial Claims Databases (2005-2018)
  - Cohort design with active comparator
- **Patient selection:**
  - Inclusion criteria: Women of childbearing age (12-48 years old) with diagnosis for migraines
  - Exclusion criteria: diagnosis for infertility, ovary dysfunction, or hirsutism
- **Study Drugs:**
  - Cohort A: Topiramate
  - Cohort B: Alternative treatments (propranolol, metoprolol, amitriptyline, venlafaxine, verapamil)
- **Exposure Definition:**
  - Overlapping periods of combined or progestin-only contraceptives and study drug (pharmacy claims data)
  - Index date was the start date of concomitant use
  - Multiple observation periods if treatment lapse happened
- **Study Outcome:**
  Pregnancy was identified using an algorithm that uses information on medical encounters for pregnancy endpoints (live and non-live) and prenatal visits
- **Study follow up & Statistical Analysis:**
  - Patients were followed up to 1 year, pregnancy, or any of the censoring events
  - Rate ratio was estimated with a propensity-score weighted GEE model
  - Sensitivity analyses on exposure definition, outcome definition, and propensity score approach

## Results

- **Cohort A (Topiramate)**
  Mean age: 29.2±9.0 years
  Mean daily dose: 100 ±83 mg
  Total follow-up time: 11,882
  Number of Events: 158
  Pregnancy rate: 1.3 (1.1, 1.6) per 100 person-years
- **Cohort B (Alternative treatments)**
  Mean age: 29.0±9.3 years
  Total follow-up time: 11,038
  Number of Events: 144
  Pregnancy rate: 1.3 (1.1, 1.6) per 100 person-years
- All measured demographic and clinical variables were well-balanced between the two cohorts after propensity score weighting (i.e., minimal confounding)

**Figure 1 - Patient selection flow chart**

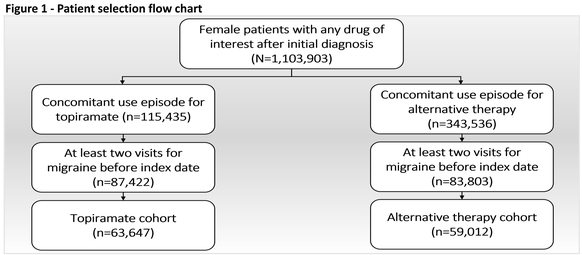
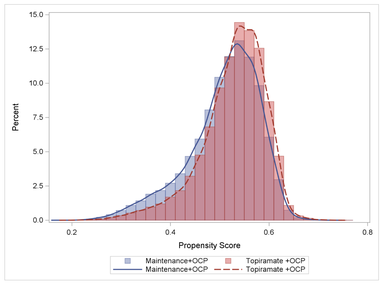
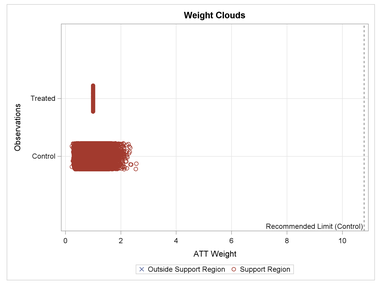



**Table 1 - Comparative risk estimates for contraception failure outcome**

| Analysis | Rate Ratio | Confidence Interval (95%) |
|---|---|---|
| Main analysis (Crude) | 1.02 | 0.81, 1.28 |
| Main analysis (Adjusted) | 1.00 | 0.80, 1.26 |
| Sensitivity analysis 1: Dx visits (1 visit) | 0.92 | 0.78, 1.07 |
| Sensitivity analysis 2: Concomitancy gap (1 day) | 0.92 | 0.73, 1.15 |
| Sensitivity analysis 3: Conception date + 14 days | 1.15 | 0.88, 1.49 |
| Sensitivity analysis 4: Conception date – 14 days | 1.05 | 0.85, 1.30 |
| Sensitivity analysis 5: High-dimensional PS | 1.03 | 0.81, 1.31 |

**Figure 2-4: Distribution of propensity scores, treatment weights (ATT), and covariate balance before/after adjustment**



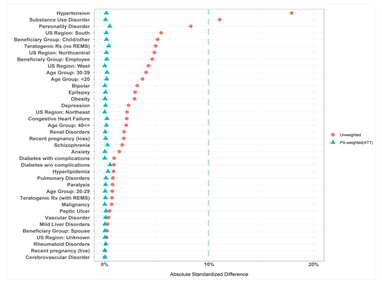
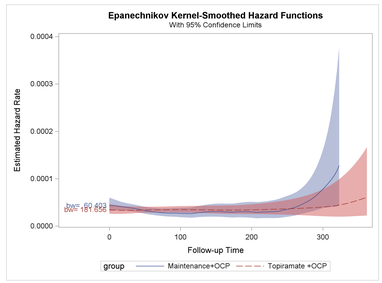
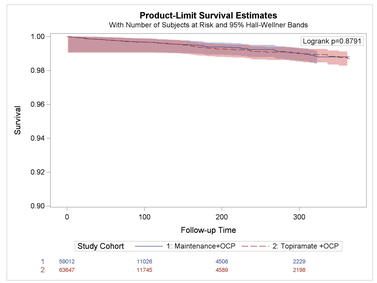
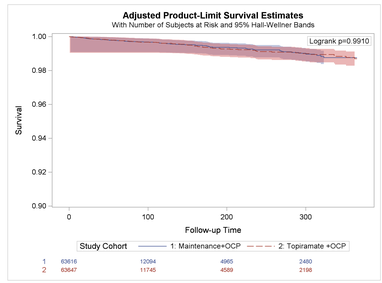




**Figure 5-7: Hazard functions, unadjusted, and adjusted survival plots**




## Discussion

- This is the first study to use real-world data to evaluate the impact of potential interaction between topiramate and oral contraceptives.
- Doose et al (2003) conducted a randomized study with two 28-day cycles of combined oral contraceptives and topiramate. They reported that the mean area under the curve (AUC) of ethinyl estradiol changed by -12%, +5%, -11% with topiramate doses of 50, 100, and 200 mg (all p values > 0.05). A similar change pattern was observed for norethindrone (-8.8%, +7.9%, -11.8%; all p > 0.05). However, no clinical outcome was evaluated.

### Limitations

- Pharmacy dispensing data may not translate to actual drug use. However, this approach could be more reliable than self-report by patients.
- Smoking status, non-hormonal contraception, and sexual activity were unmeasured in our study. High-dimensional propensity score did not change the risk estimates.
- Pregnancy start date in claims data is estimated and not explicitly recorded. Varying the estimated conception date had little impact on risk estimates.

## Conclusions

- Concomitant use of topiramate (<200 mg) and oral contraceptives was not associated with higher contraception failure among patients with migraines.
- Our findings were consistent with clinical pharmacology evidence and can inform clinical decision making where concomitant use is needed.
- Integration of RWE in drug research & development appears to be a promising approach.

## References

1. Sarayani et al., A Pharmacoepidemiologic Approach to Evaluate Real-world Effectiveness of Hormonal Contraceptives in the Presence of Drug-Drug Interactions. Epidemiology (2021)
2. Sarayani et al. Impact of the Transition from ICD-9-CM to ICD-10-CM on the Identification of Pregnancy Episodes in US Health Insurance Claims Data. Clinical Epidemiology (2020)

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