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Original Research Article

Real-world effect of a potential drug-drug interaction between topiramate and oral contraceptives on unintended pregnancy outcomes ☆,☆☆

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ABSTRACT

Objective: To evaluate the association of concomitant topiramate and oral hormonal contraceptive use with unintended pregnancies.
Study Design: We conducted a retrospective cohort design in MarketScan Research Databases (2005–2018) on women aged 12–48 who had migraines or chronic headaches and concomitantly used topiramate and oral contraceptives. We used a cohort of patients with oral contraceptives and concomitant use of other migraine prevention therapies (propranolol, metoprolol, amitriptyline, venlafaxine, or verapamil) as a comparator. We followed patients for up to 1 year from cohort entry to assess the occurrence of unintended pregnancy (i.e., contraception failure). Pregnancy events were measured via an algorithm harnessing medical encounters information with live births, terminations, or prenatal visits. Statistical models accounted for multiple cohort entries and adjusted for measured confounders via a propensity score weighting method.
Results: We identified 63,649 episodes of oral contraceptives+topiramateand 59,012 episodes of oral contraceptives+other maintenance therapies. The mean age was 29.2±9.0 and 29.0±9.3 years in the study cohorts. In the adjusted analysis, the contraception failure rate (95% confidence interval) was 1.3 (1.1, 1.6) per 100 person-years in the oral contraceptives+topiramate cohort and 1.3 (1.1, 1.6) in the oral contraceptives+other maintenance therapies cohort. The adjusted rate ratio and rate difference measures were 1.00 (0.80, 1.26) and 0.00 (-0.3, 0.3).
Conclusion: Concomitant use of low-dose topiramate and oral contraceptives among patients with migraines was not associated with a higher risk for unintended pregnancies.
Implications: Our real-world findings confirm clinical pharmacology trials, suggesting that low-dose (≤200 mg/d) topiramate may not influence oral contraceptive effectiveness.

1. Introduction

Hormonal contraceptives, particularly oral dosage forms, are commonly used for family planning worldwide [1,2]. Contraception failure, defined as an on-treatment unintended pregnancy, could have significant emotional and health consequences [3]. The real-world effectiveness of these agents depends on several factors, including obesity, smoking, adherence to treatment, and potential drug-drug interactions [4–6]. Hepatic metabolism via the CYP3A4 enzyme family is a significant clearance pathway for these products, allowing susceptibility to enzyme-inducing agents such as carbamazepine or rifampicin [7]. The speculated impact of such drug-drug interactions on contraceptive efficacy originates from pharmacokinetic studies evaluating changes in plasma levels of estrogen and progestin components when used concomitantly with

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perpetrator drugs [8]. Nevertheless, clinical evidence from large clinical trials or prospective cohort studies may hardly be available, given ethical and feasibility issues in this context.

Topiramate is a moderate CYP3A4 enzyme inducer indicated for epilepsy management and migraine prophylaxis with significant off-label use for neuropsychiatric conditions, including chronic pain and bipolar disorder [9,10]. Topiramate is also a teratogenic drug that requires preventing unintended pregnancy and possible congenital malformations [11]. Therefore, topiramate and hormonal contraceptives would likely be used concomitantly in clinical practice, and the potential drug-drug interaction between these products is critical.

Two clinical studies measured the impact of co-administration of topiramate with norethindrone (1 mg)/ethinyl estradiol (35 mcg) product, where the topiramate dose ranged from 50 to 200 mg and 200 to 800 mg. In doses ≤200 mg, the investigators reported minimal, insignificant change in the area under the curve (AUC), and in doses >200 mg, reduction in AUC was significant and dose-dependent [12,13]. Given the dose-dependent pattern of this interaction, there are conflicting clinical suggestions on whether to use or avoid concomitant use. The US drug labeling and some clinical guidelines state that topiramate doses ≤200 mg/d may not impact the effectiveness of oral hormonal contraceptives, while others recommend avoiding the combination [11,14]. Therefore, more clinical evidence on this potential interaction could inform clinical guidelines and treatment decisions.

We have previously established a pharmacoepidemiologic approach to evaluate the real-world impact of drug-drug interactions on the effectiveness of hormonal contraceptives [15]. We showed that the concomitant use of carbamazepine or oxcarbazepine (strong CYP3A4 inducers) with oral contraceptives significantly increased the contraception failure rate in the population [15]. In the present study, we aimed to evaluate the association of concomitant topiramate and oral contraceptive use with unintended pregnancy among patients with migraines or chronic headaches (typical use of topiramate dose ≤200 mg per day).

2. Methods

2.1. Study design and data source

We conducted a retrospective cohort study with an active comparator design to compare the unintended pregnancy rate for oral contraceptives when concomitantly used with topiramate or other maintenance therapies for migraine and chronic headaches. We used a national private health insurance database (IBM MarketScan Research Databases) that includes claims data from medical and pharmacy encounters (2005–2018). Insurance beneficiaries have unique encrypted identification numbers, and longitudinal follow-up for health outcomes is feasible. The University of Florida Institutional Review Board approved the study protocol as exempt from full-board review.

2.2. Patient population

We identified female patients aged 12–48 years with migraines or chronic headache diagnoses. Given the existing labeling and clinical guidelines for topiramate use in migraines, the study sample would predominantly include patients with a topiramate daily dose of ≤200 mg (i.e., low-dose topiramate). We required patients to have continuous insurance eligibility for at least 6 months before the cohort entry date (described below) and excluded patients diagnosed with infertility, ovary dysfunctions, or hirsutism to rule out other potential indications for oral contraceptives. Figure 1 provides a conceptual framework for operationalizing contraception failure in real-world data.

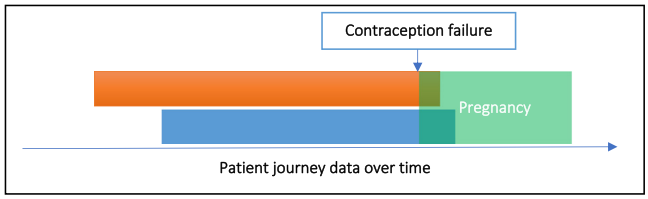

Fig. 1. . Conceptual Framework for Operationalizing Contraception Failure in the Presence of Drug-Drug Interaction using Real-World Data
Duration of *Contraceptive* and *Perpetrator* (e.g., CYP 3A4 inducer) drug use is operationalized using 'days of supply' information on prescription dispensing claims or other proxy measures based on medical care claims. *Pregnancy* events are identified based on observed medical care claims for prenatal care, birth, or termination visits. The gestation duration and pregnancy conception date are estimated based on gestational age codes (ICD-10 era) or other proxy information (ICD-9 era). The intersection of these 3 periods (*Contraceptive, Perpetrator, and Pregnancy*) resolves "real-world" contraception failure.

2.3. Measurement of concomitant drug use and medical history

We used prescription dispensing data and the "days of supply" information to determine drug use periods for each study drug. A concomitant use episode was defined as periods with overlapping days of supply for oral contraceptives and maintenance drugs. Patients entered the cohort on the first day of concomitancy if they had at least 14 days of concomitant use, and we allowed for multiple cohort entries if more than 1 concomitant use episode per patient (time gap between episodes > 14 days). The comparator group consisted of propranolol, metoprolol, amitriptyline, venlafaxine, and verapamil users.

We measured demographic characteristics on the cohort entry date. Patients were required to have at least 2 medical claims with migraine or chronic headache diagnosis before cohort entry in the 6-month look-back period. All other medical history and drug use variables were measured by observing at least 1 encounter for the attribute of interest during the look-back period. (eAppendix-1)

2.4. Study outcome

The study outcome was contraception failure operationalized as pregnancy conception occurring during concomitancy episodes. We estimated the pregnancy conception via a pregnancy identification algorithm previously developed by our team [16]. Our database does not explicitly record the pregnancy start date. The algorithm harnesses medical encounters for pregnancy end points (e.g., live birth, stillbirth, terminations) and prenatal visits to identify pregnancy episodes to estimate conception dates based on validated algorithms for gestational age. The majority of pregnancy episodes (~65%) have live birth outcomes with high accuracy in gestational age estimation (>90%) and modest performance for other types of pregnancy end points [17,18].

2.5. Statistical analysis

Patients were followed from the cohort entry date up to 1 year, end of concomitancy, study outcome, teratogenic drug use, hormonal dysfunction diagnosis, or lack of insurance eligibility in the following 3 months (required for outcome ascertainment). We estimated the contraception failure rates using a generalized linear model (Poisson distribution and offset of follow-up time) with a generalized estimating equation approach to account for multiple cohort entries. Using a propensity score weighting method, we adjusted for potential confounders, including clinical and demographic factors. We conducted several sensitivity analyses to assess the robustness of our findings: (1) Allowed episodes with only 1 diagnosis code for migraine/chronic headaches, (2) Reduced

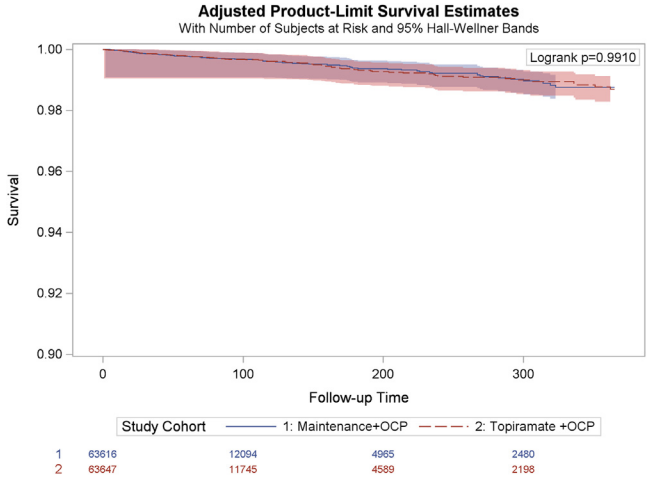

Fig. 2. . Adjusted survival estimates during follow up of oral hormonal contraceptive users with concomitant episodes of topiramate or other migraine prevention therapies (MarketScan 2005–2018).
Maintenance drugs (i.e., comparators) included propranolol, metoprolol, amitriptyline, venlafaxine, or verapamil. The term survival means no contraception failure or unintended pregnancy event during follow-up. Abbreviations: OCP - Oral Contraceptive Pill

the concomitancy gap to 1 day, (3) Varied the estimated conception date by +/-14 days, (4) Applied a high-dimensional propensity score approach for confoudning control, (5) Restricted to episodes with topiramate dose ≤200 mg daily, and (6) Restricted episodes with concomitancy duration of at least 56 days [19].

3. Results

We identified 63,649 episodes of oral contraceptives+topiramate, of whom 95% had ≤200 mg topiramate daily, and 59,012 episodes of oral contraceptives+other maintenance therapies. A patient selection flowchart is available in eAppendix 1 (eFigs. 1). The mean age was 29.2±9.0 years in the oral contraceptives+topiramate cohort and 29.0±9.3 years in the oral contraceptives+other maintenance therapies cohort. The total follow-up time in the study cohorts was 11,882 and 11,038 person-years, respectively, and the mean follow-up time in both cohorts was 68 days.

Before propensity score weighting, the 2 cohorts had similar demographics and comorbidities. (Table 1) Hypertension was more prevalent in the oral contraceptives+other maintenance therapies cohort (10.9%) than the oral contraceptives+topiramate cohort (5.9%). All study variables were well-balanced after the propensity score weighting, implying that confounding by these attributes should be minimal (eFigs. 2).

We identified 158 pregnancies in the oral contraceptives+topiramate cohort and 144 events in the oral contraceptives+other maintenance therapies cohort. Most pregnancy events were identified via medical claims for birth (~55%), followed by abortions (~20%). Table 2 provides the breakdown of pregnancy events. In the unadjusted analysis, the contraception failure rate was 1.3 (1.1, 1.6) per 100 person-years in the oral contraceptives+topiramate cohort and 1.3 (1.1, 1.5) per 100 person-years in the oral contraceptives+other maintenance therapies cohort. The rate ratio was 1.02 (0.81, 1.28), and the rate difference was 0.02 (-0.27, 0.32).

In the adjusted analysis, the contraception failure rates were 1.3 (1.1, 1.6) and 1.3 (1.1, 1.6) per 100 person-years, respectively, and the adjusted rate ratio and rate difference were 1.00 (0.80, 1.26) and 0.00 (-0.3, 0.3). Figure 2 illustrates the adjusted survival curves for each study cohort. In the sensitivity analyses, the estimated

Table 1
Demographic and clinical characteristics of oral hormonal contraceptive users with concomitant episodes of topiramate or other migraine prevention therapies (MarketScan 2005–2018)

Conditions	Topiramate (%, *N*=63,647)	Comparators[a] (%, *N*=59,012)	ASD[b] (%)
Age			
<20	17.6	19.0	4
20–29	35.4	35.0	1
30–39	30.8	29.0	4
40<=	16.2	17.0	2
Comorbidities			
Hypertension	5.9	10.9	18
Hyperlipidemia	6.6	6.9	1
Obesity	1.8	2.2	3
Epilepsy	2.1	1.7	3
Bipolar	3.6	3.9	3
Schizophrenia	0.5	0.7	2
Depression	18.3	21.6	2
Personality disorder	0.8	1.0	8
Anxiety	18.1	22.5	1
Substance use disorder	1.1	1.4	11
Myocardial infection	0.0	0.1	2
Congestive heart failure	0.1	0.2	2
Vascular disorder	0.5	0.5	0
Cerebrovascular disorder	1.9	1.9	0
Pulmonary disorders	9.4	9.2	1
Paralysis	0.3	0.4	1
Diabetes w/o complications	1.8	2.0	1
Diabetes with complications	0.2	0.2	1
Renal disorders	0.3	0.4	2
Mild liver disorders	1.0	1.0	0
Peptic ulcer	0.3	0.4	0
Rheumatoid disorders	1.4	1.4	0
AIDS	0.0	0.0	0
Malignancy	0.8	0.7	1
Recent pregnancy (live birth)	0.2	0.2	0
Recent pregnancy (termination)	0.8	1.0	2
Potentially teratogenic medication	33.9	36.2	5
Teratogenic medication with REMS[c]	0.5	0.5	1
Concomitancy type			
New contraception initiated	16.1	17.1	3
New migraine therapy initiated	71.5	68.9	6
Both contraception and migraine therapy initiated	12.4	14.1	5
Beneficiary status			
Employee	49.9	47.7	5
Spouse	18.8	18.7	0
Child/other	31.3	33.7	5
Residence region			
Northeast	16.8	16.0	2
Northcentral	22.4	24.5	5
South	45.6	42.9	5
West	13.8	15.3	4
Unknown	1.3	1.3	0
Health plan type[d]			
Comprehensive	1.7	1.5	2
HMO	13.8	13.9	0
PPO	59.4	59.6	0

(*continued on next page*)

Table 1 (*continued*)

Conditions	Topiramate (%, *N*=63,647)	Comparators[a] (%, *N*=59,012)	ASD[b] (%)
POS	7.7	7.3	1
CDHP	7.0	7.4	2
Other	10.5	10.3	1

Note: Concomitancy type and comorbidities with very low prevalence (myocardial infarction and AIDS) were not included in the propensity score model.

[a] Comparators included propranolol, metoprolol, amitriptyline, venlafaxine, or verapamil.

[b] ASD: Absolute Standardized Difference before propensity score adjustment. A value of <10% is generally interpreted as well-balanced between the two groups. All ASDs were <10% after propensity score weighting (eFigure 1).

[c] REMS: Risk Evaluation and Mitigation Strategy.

[d] HMO, health maintenance organization; PPO, preferred provider organization; POS, point of servic; CDHP, consumer driven high-deductible plan.

Table 2
Pregnancy events identified in each study cohort of oral hormonal contraceptive users with concomitant episodes of topiramate or other migraine prevention therapies (MarketScan 2005–2018)

Event	Topiramate (*N*=63,647)	Comparators[a] (*N*=59,012)
Full-term	85 (53.8)	68 (47.2)
Preterm	6 (3.8)	14 (9.7)
Postterm	0 (0.0)	1 (0.7)
Ectopic pregnancy	1 (0.6)	1 (0.7)
Stillbirth	0 (0.0)	4 (2.8)
Spontaneous abortion	34 (21.5)	26 (18.1)
Induced abortion	11 (7.0)	10 (6.9)
Prenatal visits	21 (13.3)	20 (13.9)
Total	158 (100)	144 (100)

[a] Comparators included propranolol, metoprolol, amitriptyline, venlafaxine, or verapamil. Numbers in parentheses are percentages within a cohort.

rate ratio remained close to the original analysis with confidence intervals crossing null (concomitancy gap: 0.92 [0.78, 1.07]; conception date + 14 days: 1.15 [0.88, 1.49]; conception date – 14: 1.05 [0.85, 1.30]; high-dimensional propensity score adjustment: 1.03 [0.81, 1.31]). Table 3 provides a summary of risk estimates across primary and sensitivity analyses.

4. Discussion

Our findings showed that concomitant use of low-dose topiramate and oral contraceptives was not associated with a higher risk of unintended pregnancy among patients with migraines or chronic headaches. Our sensitivity analyses confirmed the primary results.

Previous studies on the impact of topiramate on in-vitro CYP3A4 activity and plasma concentration of estrogen/progestin in the presence of concomitant use provide valuable context to our findings [12,13,20]. In an in-vitro study on human hepatocytes, topiramate increased CYP3A4 enzyme activity by 2 to 8 folds depending on the dose, albeit the induction was weaker than rifampicin (14–20 folds) [20]. A study on patients with epilepsy who were stable on valproic acid monotherapy and added topiramate 200, 400, or 800 mg/d suggested a dose-dependent, statistically significant 18% to 30% reduction in the AUC of the ethinyl estradiol component of norethindrone (1 mg)/ethinyl estradiol (35 mcg) product [13]. A follow-up study on the same contraceptive product investigated the concomitant use of 50, 100, and 200 mg/d of topiramate among healthy subjects. This investigation looked at patients with normal weight or obesity and used carbamazepine as a comparator drug. The authors concluded that topiramate with doses ≤200 mg/d seems to impact plasma levels of neither norethindrone nor ethinyl estradiol component [12].

Based on in-vitro and human data, CYP3A4 induction by topiramate appears to be dose-independent and insignificant if the dose is ≤ 200 mg/d, while the induction effect becomes dose-dependent and substantial with higher doses. Moreover, topiramate induction at high doses primarily impacts the estrogen component, which is more responsible for preventing breakthrough bleeding than ovulation and pregnancy prevention [6]. Still, none of these studies has provided evidence for the clinical implications of subtle changes in AUC on the unintended pregnancy outcome.

Our present study filled a knowledge gap related to mixed guidance for low-dose topiramate use with oral hormonal contraceptives. These results support current topiramate labeling based on pharmacokinetic studies that suggest no reduced contraception effectiveness at doses ≤200 mg [11]. Some recommendations state to avoid all oral hormonal contraceptives when treated with antiepileptic medications (i.e., an overall class effect). However, differentiating between strong and moderate CYP3A4 induction effects, progestin type, dose dependency, and potential teratogenicity risk may better inform prescribing choices.

We used a nationwide private health insurance claims database in the U.S. that provided an ample sample size to study this potential drug-drug interaction. Our previous seminal study successfully implemented a pharmacoepidemiologic approach to assess drug-drug interactions with hormonal contraceptives by recovering the real-world clinical effect of concomitancy with strong CYP3A4 inducers [15]. In our present study, we implemented a similar evaluation with an active comparator group to minimize confounding due to factors with weak measurement in claims databases, such as sexual activity, smoking, and obesity [21].

There are several limitations in our approach and data source. Drug use is measured based on pharmacy dispensing claims and the days of supply. Adherence to either topiramate or oral contraceptive is likely imperfect in this setting; however, we expect a similar pattern in the control group. Patients in the real world may also discontinue oral contraceptives before the supply is exhausted to plan for pregnancy. This behavior would result in overestimating the contraception failure rate, but the magnitude of misclassification would likely be similar in both study cohorts. We showed in our previous study that the impact of exposure misclassification on estimated risk is likely insignificant [15].

Measuring pregnancy events and their respective conception date is a complex task in health insurance data [16,22]. We may have missed some pregnancy events with no interactions with the healthcare system, which impacted the sensitivity of the outcome measure, potentially underestimating the contraception failure rate in both cohorts. This limitation could be more significant for abortions where out-of-pocket pay with no insurance claims is expected and is potentially a more common pregnancy outcome when taking a teratogenic medication. Therefore, our findings may be subject to differential outcome misclassification that could bias results toward the null effect. We should also note that contraception failure rates based on the Pearl Index or typical-use condition may not be directly compared with our findings, as our study population was unique with at least a migraine or chronic headache diagnosis. In addition, the denominator in the Pearl Index formula considers months with sexual activity, which we could not discern in our data source, resulting in fundamental differences in contraception failure rate definition. As such, there is a need to establish a formal definition for “real-world” contraception failure separate from the available definitions.

Another limitation of the pregnancy measurement approach in this study is that the exact time of conception or last menstrual period is not available in our database. The algorithms we have used to estimate conception date have high accuracy for live births (>90% within 2 weeks of the actual date) and modest accuracy for other end points (60%–80%) [17,18,23]. Therefore, the specificity of the outcome measure is also imperfect, and the overall outcome misclassification bias may have obscured a true positive associa-

Table 3
Primary and sensitivity analyses of the association between concomitant use of low-dose topiramate and oral hormonal contraceptives and the unintended pregnancy outcome (MarketScan 2005–2018)

Primary analysis				
Medication	Events	Person-years (PY)	Rate (per 100 PY, adjusted), 95% CI	Rate Ratio (adjusted), 95% CI
Topiramate	158	11,882	1.3 (1.1–1.6)	1.02 (0.81–1.28)
Comparators[a]	144	11,033	1.3 (1.1–1.6)	Ref.
Sensitivity analyses				
Sensitivity analysis conducted			Rate ratio (adjusted), 95% CI	
Required at least one diagnosis visit			0.92 (0.78–1.07)	
Reduced concomitancy gap to 1 d			0.92 (0.73–1.15)	
Changed conception date + 14			1.15 (0.88–1.49)	
Changed conception date - 14			1.05 (0.85–1.30)	
High-dimensional propensity scores			1.03 (0.81–1.31)	
Restricted to topiramate daily dose ≤200mg			1.00 (0.80–1.27)	
Restricted to episodes longer than 56 d			1.05 (0.77, 1.42)	

CI, confidence interval; PY, person-years.
[a] Comparators included propranolol, metoprolol, amitriptyline, venlafaxine, or verapamil.

tion. However, our sensitivity analyses varied the estimated conception date by 2 weeks in both directions, and we observed a minimal impact on risk estimates.

Our study did not limit drug exposure to a specific estrogen/progestin product or dosing schedule. Any combined oral contraceptive or progestin-only product, except high-dose estrogen products (>50 mcg) and emergency pills, was considered eligible for exposure. We implemented this approach to achieve adequate statistical power, and our findings shall be the average effect across all such products. A growing body of evidence supports differential effects on progestin components within contraceptives via CYP3A4-mediated drug interactions, and this would be an avenue for future studies [24]. We have also shown that the contraceptive route of administration is an additional important factor in the risk of unintended pregnancy due to drug-drug interactions [25].

Our study provided the first insight into real-world outcomes of a potential drug-drug interaction between topiramate and oral contraceptives. Based on our findings and the human data from clinical pharmacology trials, the totality of evidence suggests that low-dose topiramate may not influence oral contraceptive effectiveness in preventing unintended pregnancies. The teratogenic nature of this drug may still necessitate double-method or long-acting reversible contraception. These findings can aid clinical decision-making in diverse clinical uses of topiramate where benefit-risk balance requires meticulous individualization.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.contraception.2023.109953.

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