Associations of Topiramate and Zonisamide Use With Kidney Stones: A Retrospective Cohort Study

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Rationale & Objective: Driven by expanding indications, topiramate and zonisamide utilization has increased over time, a trend that may be associated with greater occurrence of kidney stones given the effects of these medications on urine chemistries. We examined the relationship between topiramate and zonisamide use and kidney stone risk.

Study Design: Retrospective cohort study.

Setting & Participants: Individuals in Optum's deidentified Clinformatics Data Mart Database (CDM) and Medicare enrollees with at least 1 prescription filled for topiramate or zonisamide between January 1, 2011, and September 30, 2019, and age- and sex-matched controls.

Exposure: New topiramate or zonisamide use.

Outcome: Symptomatic stone event defined as an emergency department visit, hospitalization, or surgery for kidney stones.

Analytical Approach: Cox proportional hazards regression.

Results: Among 1,122,301 study participants, 187,032 filled a prescription for topiramate or zonisamide at some point during the study period. The unadjusted cumulative incidence of symptomatic stone events between 3 months and 3 years after the first filled prescription were 2.9% and 2.0% among users of topiramate or zonisamide versus 1.2% and 1.3% among nonusers in the CDM and Medicare cohorts, respectively ($P < 0.001$ for each comparison). After controlling for covariates, users had a significantly higher hazard than nonusers of experiencing a symptomatic stone event (CDM cohort: HR, 1.58 [95% CI, 1.49-1.68]; Medicare cohort: HR, 1.22 [95% CI, 1.11-1.34]). There was a stronger association with stone risk among younger adults receiving either topiramate or zonisamide and the hazard of a symptomatic stone event increased with higher topiramate doses.

Limitations: Potential bias in unmeasured differences between users of topiramate or zonisamide and nonusers. Participants may have been diagnosed with kidney stone disease before the study period.

Conclusions: Use of topiramate or zonisamide was associated with an increased hazard of symptomatic stone events. These findings inform the consideration of risks and benefits of these medications.

Visual Abstract online

Complete author and article information provided before references.

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Topiramate and zonisamide have been prescribed for over 2 decades to prevent epileptic seizures. More recently, their treatment indications have expanded to include new on- and off-label uses such as migraine prophylaxis and obesity management.[1-4] With this expansion, their utilization rates have risen such that topiramate is now the eleventh most commonly prescribed outpatient medication in the United States.[5,6] These utilization trends are concerning from a renal physiology standpoint because both medications inhibit carbonic anhydrase and cause a renal acidification defect that raises urine pH and lowers urine citrate, increasing calcium phosphate urinary supersaturation and possibly kidney stone risk.[7,8]

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However, prior empirical work supporting an association between kidney stone risk and topiramate and zonisamide use has been very weak. Studies to date have generally been limited to uncontrolled, single-center reports.[9-12] One of the only controlled studies included just 20 topiramate users.[13] Further, a larger population-based study from Taiwan showed no increased risk of stones associated with topiramate use.[14] What is more, there could be differences in risk by patient age given the higher prevalence of certain diseases in older adults that can also affect urine chemistries (eg, chronic kidney disease).[15-18] Additionally, emerging data suggest that migraines, which topiramate and zonisamide treat, may themselves be associated with kidney stone risk, independent of medication use.[19]

Given such medical uncertainty, we conducted a large retrospective cohort study. Specifically, we analyzed medical and pharmacy claims from working-age adults enrolled in a commercial health insurance plan as well as a national sample of older Medicare beneficiaries. After distinguishing the subpopulation who were new users of topiramate or zonisamide, we identified a set of age- and sex-matched nonusers. We then compared rates of symptomatic stone events over time in these 2 groups. Findings from this analysis are relevant to clinicians who prescribe these medications because kidney stones are a leading cause of unplanned emergency department (ED) visits and account for over $10 billion in annual health care spending.[20]

PLAIN-LANGUAGE SUMMARY

Topiramate and zonisamide are increasingly prescribed for uses other than seizure prophylaxis. These agents may cause kidney stones. In this retrospective cohort study of adults with either Medicare or commercial health insurance, we assessed the relationship between use of topiramate or zonisamide and kidney stone events requiring clinical intervention. Between 3 months and 3 years after first use of these drugs, stone events occurred more often among users of topiramate or zonisamide than nonusers. Our analysis also demonstrated a stronger association with stone risk among younger adults receiving either topiramate or zonisamide. These findings are consistent with the magnitude of association reported previously in the literature and the association was independent of treatment indication in younger adults.

Methods

Data Sources and Study Population

In this retrospective cohort study, we examined medical and pharmacy claims from 2 sources. The first was the Optum Clinformatics Data Mart Database (CDM). The second was a 20% national sample of Medicare beneficiaries, including data from the Medicare Provider Analysis and Review, Outpatient, Carrier, and Part D Research Identifiable Files. We restricted our analysis to individuals 18 to 64 years of age (CDM) and 65 years and older (Medicare), who had a prescription drug benefit at any point between calendar years 2011 and 2019. We excluded from our analysis Medicare beneficiaries whose reason for entitlement was disability or end-stage renal disease. We also excluded those from the CDM and Medicare databases who were enrolled in Medicare Advantage during the study period because services provided to them are inconsistently captured in their claims.

Identifying Topiramate and Zonisamide Users and Nonusers

We used National Drug Codes (CDM) and generic drug names (Medicare) to identify individuals who had at least 1 prescription filled for topiramate or zonisamide between January 1, 2011, and September 30, 2019. Because our interest was in estimating kidney stone risk among new users, we ensured that these individuals had no prescription fills for either medication in the 6 months preceding their first fill during the study period. In an effort to capture new symptomatic stone events, we used published methods to exclude individuals who had a kidney stone episode (ie, outpatient evaluation and management or ED visit, hospitalization, or surgery for kidney stones) in the 12 months preceding and 3 months after their first prescription fill.[21,22] We also excluded individuals who died within 3 months after their first prescription fill.

We then identified sets of individuals in the CDM and Medicare databases without prescription fills for either medication during the study period to serve as controls. Anchoring on the date 3 months after each user's first prescription fill, we performed 5:1 matching based on nonusers' age (birthday within 1 year of the user to whom they were matched) and sex. We required all nonusers to meet the same medical and pharmacy enrollment criteria as the users to whom they were matched. They also could not have any outpatient evaluation and management or ED visits, hospitalizations, or surgery for kidney stones within the 12 months preceding and 3 months after the initial prescription fill for the user to whom they were matched. The matching process yielded 147,514 users and 737,570 nonusers in the CDM cohort and 39,518 users and 197,699 nonusers in the Medicare cohort.

Capturing Symptomatic Kidney Stone Events

Our primary outcome was a composite measure, indicating the occurrence of a symptomatic stone event. We defined this as an ED visit, hospitalization, or surgery for kidney stones. We assessed for the occurrence of an event among users and their matched nonusers beginning 3 months after each user's first prescription fill during the study period and extending through December 31, 2019. We censored participants at death or if they lost their health insurance coverage. For our secondary outcomes, we decomposed the composite measure, examining the first occurrence of an ED visit, hospitalization, and surgery for kidney stones separately, censoring at death or loss of health insurance coverage.

Statistical Analysis

For our initial analytic step, we measured the frequency of topiramate or zonisamide prescription in CDM and the national Medicare sample, evaluating for temporal trends over the study period. With the study participant serving as our unit of analysis, we then used parametric and nonparametric tests to compare topiramate or zonisamide users and their matched nonusers over a variety of baseline characteristics, including their age (measured at 3 months after a user's first prescription fill), sex, race and ethnicity, region of residence, and socioeconomic status (based on income relative to the federal poverty level and Medicare–Medicaid dual eligibility among CDM and Medicare participants, respectively). We also examined for differences in levels of comorbidity (assessed for the CDM and Medicare cohorts using the Charlson comorbidity index and hierarchical condition category methodologies, respectively[23,24]) and whether participants had a diagnosis placing them at higher risk for stone disease (assessed in the 12 months preceding the first prescription with a published algorithm[25]).

Next, we used the Kaplan-Meier method to generate the unadjusted cumulative incidences of symptomatic kidney

stone events for topiramate or zonisamide users and nonusers among our CDM and Medicare cohorts. We then fit multivariable Cox proportional hazards models for each cohort to estimate a participant's hazard of having a symptomatic kidney stone event as a function of topiramate or zonisamide exposure. Before modeling, we checked the proportional hazards assumptions by visual inspection of the log of negative log event-free survival versus the log of time. We included in our model controls for the various baseline characteristics described in the previous paragraph, as well as the calendar year at 3 months after a user's first prescription fill for topiramate or zonisamide. We also added an indicator variable, distinguishing whether users (and their matched nonusers) had a clinician-coded diagnosis of seizure disorder, migraines, or obesity (including type 2 diabetes and metabolic syndrome) on their first prescription fill date or in 12 months preceding it.

Finally, we conducted a series of post hoc sensitivity analyses to test the robustness of our findings. To examine whether the association between medication use and kidney stone risk among younger adults was modified by age, we fit a multivariable model on topiramate or zonisamide users and nonusers for the CDM cohort that included an interaction term between our exposure and increasing age strata. To evaluate for drug-specific differences in kidney stone risk, we re-estimated our regression models with a 3-level exposure variable that categorized participants as topiramate users, zonisamide users, or nonusers.

Given prior empirical work that suggests some conditions, which topiramate and zonisamide are used to treat, themselves may contribute to kidney stone risk, we tested for an interaction between our primary exposure and a variable specifying treatment indication in the CDM and Medicare cohorts. Because the interaction term was significant for the CDM cohort, we then repeated our analysis on this population, stratifying by the top 3 treatment indications: seizure disorder, migraines, and obesity. For a particular stratified analysis, users and nonusers had the condition of interest but neither of the other 2.

To assess the impact that drug dosage had on the association between topiramate use and kidney stone risk, we fit multivariable models for topiramate users, including a term for the prescribed tertile (high vs medium vs low). Because diuretics are a mainstay of kidney stone prevention strategies, their concomitant prescription, if differential between users and nonusers, could confound the association between topiramate/zonisamide receipt and symptomatic stone events. Therefore, we refit our multivariable models on the Medicare cohort, including an indicator that specified whether a participant was prescribed a thiazide or loop diuretic. This is the population among whom diuretic use was anticipated to be greatest due to their older age and higher levels of comorbid illness.

We conducted all analyses using SAS version 9.4 (SAS Institute). All our statistical tests were two-tailed, and we set the probability of type 1 error at 0.05. We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for reporting observational studies. Our study was based on deidentified data and, thus, deemed exempt from oversight by our institutional review board.

Results

In total, 1,122,301 participants were included in our study, 885,084 from the CDM cohort and 237,217 from the Medicare cohort. Between 2011 and 2019, rates of new prescription fills for topiramate or zonisamide increased significantly by 24.8% and 27.0% in the CDM database (Fig 1A) and the national Medicare sample (Fig 1B), respectively ($P < 0.001$ for the temporal trends). Indications for topiramate or zonisamide prescription differed between the CDM and Medicare cohorts. Namely, they were prescribed more often for migraines in the CDM cohort (62.2% vs 49.2% in Medicare) and obesity in the Medicare cohort (48.4% vs 31.9% in CDM). Rates of prescription for seizure disorder were 5.6% and 9.6% in the CDM and Medicare cohorts, respectively.

Table 1 displays similarities and differences between the topiramate or zonisamide users and nonusers. For both

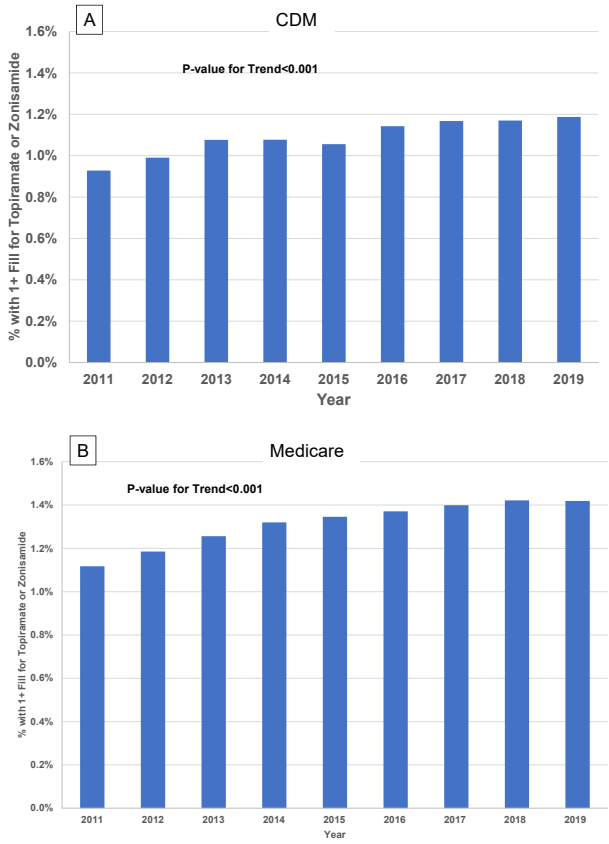

Figure 1. Rates of new prescription fills for topiramate and zonisamide in (A) CDM and (B) Medicare over the study period. Abbreviation: CDM, Clinformatics Data Mart.

cohorts, users and nonusers were similar with respect to their age at the time of initial prescription fill and sex distributions. However, compared with nonusers, a greater proportion of topiramate or zonisamide users tended to be White (CDM cohort: 75.0% vs 70.3%, $P < 0.001$; Medicare cohort: 89.6% vs 84.3%, $P < 0.001$), reside in the South (CDM: 49.9% vs 43.5%, $P < 0.001$; Medicare: 44.9% vs 37.7%, $P < 0.001$); and have higher levels of comorbid illness (CDM: mean Charlson score, 0.38 ± 0.93 [SD] vs 0.20 ± 0.74 [SD], $P < 0.001$; Medicare: mean hierarchical condition category score, 1.16 ± 1.10 [SD] vs 0.89 ± 0.97 [SD], $P < 0.001$). Topiramate or zonisamide users in both cohorts were also more likely to have a diagnosis that predisposed them to kidney stone formation. These included, but were not limited to, chronic urinary tract infection, gout, sarcoidosis, and gastrointestinal disease ($P < 0.05$ for all comparisons).

Figure 2 illustrates the unadjusted cumulative incidence of a symptomatic stone event for the CDM (Fig 2A) and Medicare (Fig 2B) cohorts. Between 3 months and 3 years of follow-up, the cumulative incidence was 2.9% and 2.0% for topiramate or zonisamide users versus 1.2% and 1.3% for nonusers in the CDM and Medicare cohorts, respectively ($P < 0.001$ for each comparison). Figure S1 illustrates the unadjusted cumulative incidences of our secondary outcomes. For both cohorts, the incidences of ED visit, hospitalization, and surgery for kidney stones between 3 months and 3 years of follow-up were also significantly higher for topiramate or zonisamide users than for nonusers ($P < 0.005$ for each comparison).

Table 2 shows findings from our multivariable models (full results available in Table S1). Topiramate or zonisamide users in both cohorts had a significantly higher hazard of a symptomatic stone event when compared with nonusers; however, the hazard was higher for participants in the CDM cohort (hazard ratio [HR], 1.58 [95% CI, 1.49-1.68]) than for those in the Medicare cohort (HR, 1.22 [95% CI, 1.11-1.34]). Table S2 highlights findings from our sensitivity analysis on the CDM cohort, examining whether the association between medication use and kidney stone risk among younger adults was modified by age. The test of the interaction was significant ($P < 0.001$). The table shows that the HR for users 39 years and younger to nonusers 39 years and younger (1.87 [95% CI, 1.72-2.03]) was substantially higher than that for users 55 years and older compared with nonusers 55 years and older (HR, 1.39 [95% CI, 1.24-1.56]).

Table 3 reveals findings from the other 4 sensitivity analyses that we performed. When we examined topiramate or zonisamide separately, the 95% CIs around their respective HRs overlapped in both the CDM and Medicare cohorts. When we stratified by treatment indication in the CDM cohort, the higher hazard of a symptomatic stone event persisted. When we examined the dose of topiramate initially prescribed, we observed a dose–response relationship such that participants in the highest dose tertile had the highest hazard of a symptomatic kidney stone event. Finally, when we refit our multivariable models, including an indicator that specified concomitant thiazide or loop diuretic use in the Medicare cohort, we observed little difference in our parameter estimate for topiramate/zonisamide receipt. However, diuretic use was independently associated with a lower hazard of a symptomatic stone event (HR, 0.76 [95% CI, 0.70-0.83]).

Discussion

Our analysis has 3 key findings. First, although we found a higher hazard of symptomatic kidney stone events associated with topiramate or zonisamide use in the CDM and Medicare cohorts, the magnitude of the association was greater for younger adults. Second, the hazard of a symptomatic stone event among topiramate or zonisamide users was independent of the treatment indication only in the CDM cohort. Third, there appeared to be a dose–response relationship such that higher dosages of topiramate were associated with higher hazards. Based on these findings, we estimate that for every 144 and 391 participants in CDM and Medicare, respectively, exposed to topiramate or zonisamide, one will experience a symptomatic stone event at 3 years, which they would not otherwise. For context, this would translate into somewhere between 1,800 and 4,900 additional ED visits, hospitalizations, and surgical procedures for kidney stones annually among the 2.1 million topiramate users in the United States.

Our analysis is not the first to demonstrate an association between topiramate use and future stone events. A prior systematic review identified 10 studies, reporting on the same association that included a total of 1,264 topiramate users.[12] In comparison, we examined symptomatic stone events among 140 times as many topiramate users, as well as over 9,000 zonisamide users. Pooled data from the systematic review showed an overall annual incidence of 2.1% for symptomatic kidney stones events, which is comparable to what we observed in both the CDM and Medicare cohorts. Importantly, our analysis not only confirms the magnitude of association but also reveals it to be independent of the treatment indication in younger adults.

Findings from our analysis have physiologic feasibility given topiramate and zonisamide's mechanism of action. Namely, they both inhibit renal carbonic anhydrase, resulting in the inability to excrete titratable acid that leads to a lower pH. Pooled data from 6 studies show a significant reduction in serum bicarbonate levels after 3 months of topiramate use.[12] Moreover, there are multiple reports of falling levels of urine citrate excretion after the initiation of topiramate.[12] Such an environment predisposes to calcium phosphate stone formation.[7,8] The dose–response relationship we found could be explained by higher doses of topiramate being associated with larger metabolic abnormalities and hence a greater risk of kidney stone formation.[10]

Table 1. Bivariate Comparisons Between Topiramate and Zonisamide Users and Nonusers

Participant Characteristics	CDM			Medicare		
	Users (n = 147,514)	Nonusers (n = 737,570)	SMD	Users (n = 39,518)	Nonusers (n = 197,699)	SMD
Age, y	41.6 ± 11.7	41.6 ± 11.7	0.000	74.1 ± 6.4	74.1 ± 6.4	0.00119
Female	117,496 (79.7%)	587,480 (79.7%)	0.000	28,360 (71.8%)	141,859 (71.8%)	0.00022
Race			0.160			0.18425
White	110,628 (75.0%)	518,674 (70.3%)		35,396 (89.6%)	166,634 (84.3%)	
Black	16,716 (11.3%)	76,905 (10.4%)		2,022 (5.1%)	14,127 (7.1%)	
Other race	20,170 (13.7%)	141,991 (19.3%)		2,100 (5.3%)	16,938 (8.6%)	
Region of residence			0.169			0.14961
Midwest	38,421 (26.0%)	192,183 (26.1%)		8,711 (22.0%)	45,953 (23.2%)	
Northeast	10,375 (7.0%)	69,899 (9.5%)		6,231 (15.8%)	38,245 (19.3%)	
South	73,606 (49.9%)	320,507 (43.5%)		17,728 (44.9%)	74,527 (37.7%)	
West	25,112 (17.0%)	154,981 (21.0%)		6,801 (17.2%)	38,530 (19.5%)	
Income <400% of FPL	994 (0.7%)	3,249 (0.4%)	−0.031	NA	NA	NA
Medicare-Medicaid dual eligible	NA	NA	NA	6,580 (16.7%)	34,024 (17.2%)	0.01492
Charlson score	0.38 ± 0.93	0.20 ± 0.74	−0.205	NA	NA	NA
HCC score	NA	NA	NA	1.16 ± 1.10	0.89 ± 0.97	−0.26225
High-risk condition						
Chronic urinary tract infections	19,389 (13.1%)	55,400 (7.5%)	−0.186	5,180 (13.1%)	16,506 (8.3%)	−0.15423
Disorder of purine metabolism/gout	2,920 (2.0%)	8,058 (1.1%)	−0.072	2,124 (5.4%)	8,625 (4.4%)	−0.04704
Sarcoidosis	418 (0.3%)	1,106 (0.1%)	−0.029	112 (0.3%)	435 (0.2%)	−0.01265
Osteoporosis/pathological fractures	20,783 (14.1%)	67,245 (9.1%)	−0.156	10,707 (27.1%)	43,751 (22.1%)	−0.11543
Gastrointestinal disease/surgery	40,204 (27.3%)	98,783 (13.4%)	−0.350	7,331 (18.6%)	20,891 (10.6%)	−0.22783
Hypertension	52,311 (35.5%)	153,007 (20.7%)	−0.332	31,905 (80.7%)	139,323 (70.5%)	−0.24070
Hyperparathyroidism	826 (0.6%)	2,172 (0.3%)	−0.041	585 (1.5%)	2,278 (1.2%)	−0.02879
Immobilization	1,288 (0.9%)	2,976 (0.4%)	−0.059	292 (0.7%)	768 (0.4%)	−0.04682
Renal abnormalities	273 (0.2%)	667 (0.1%)	−0.026	49 (0.1%)	162 (0.1%)	−0.01311
Obesity	53,490 (36.3%)	105,814 (14.3%)	−0.521	9,923 (25.1%)	24,102 (12.2%)	−0.33632
Type 2 diabetes	19,221 (13.0%)	55,713 (7.6%)	−0.181	13,787 (34.9%)	57,034 (28.8%)	−0.12987
Any high-risk condition	104,196 (70.6%)	326,321 (44.2%)	−0.554	36,304 (91.9%)	161,398 (81.6%)	−0.30522
Indication						
Headache	91,682 (62.2%)	57,729 (7.8%)	−1.386	19,453 (49.2%)	16,210 (8.2%)	−1.01741
Weight loss	47,045 (31.9%)	89,674 (12.2%)	−0.490	19,126 (48.4%)	70,423 (35.6%)	−0.26106
Seizures	8,204 (5.6%)	4,244 (0.6%)	−0.292	3,794 (9.6%)	3,968 (2.0%)	−0.32914

Values are given as mean ± SD for continuous variables and as number (percentage) for categorical variables. Abbreviations: CDM, Clinformatics Data Mart; FPL, federal poverty limit; HCC, hierarchical condition category; NA, not applicable; SMD, standardized mean difference.

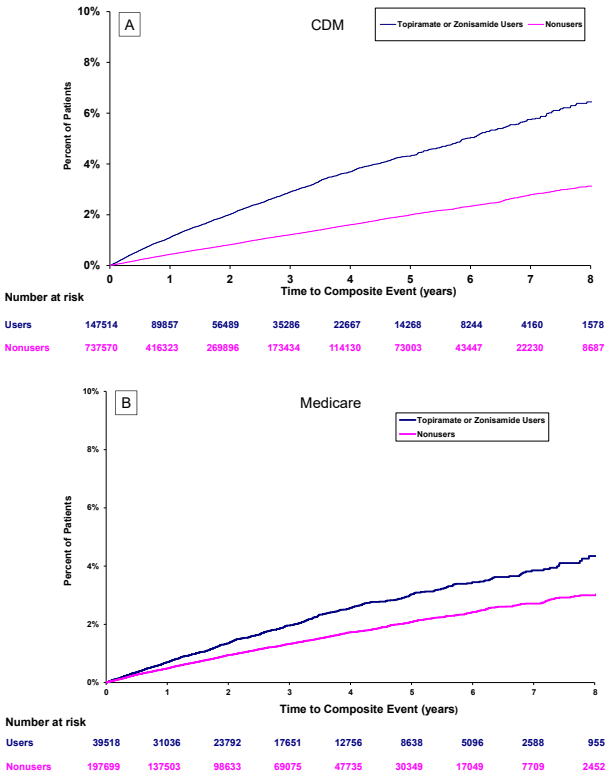

Figure 2. Unadjusted cumulative incidence of a symptomatic stone event among topiramate or zonisamide users (blue) versus nonusers (pink) in (A) CDM and (B) Medicare. Abbreviation: CDM, Clinformatics Data Mart.

The difference in risk between older and younger adults also has biologic plausibility when considering the higher prevalence of certain diseases in the former that can also affect urine chemistries. For instance, chronic kidney disease is more common in older adults,[15] and it leads to reduced ability to concentrate urine and lower urinary calcium excretion,[16,17] which might offset some of the changes caused by topiramate and zonisamide. Type 2 diabetes is also more prevalent in older adults (Table 1),[15] which lowers patients' urine pH.[18] Consequently, older adults with type 2 diabetes may not experience the same increase in urine pH as younger adults without it do after starting topiramate or zonisamide.

Our analysis has some limitations that merit discussion. First and foremost, we acknowledge the possibility of unmeasured differences between the users and nonusers that could confound the observed association. For example, although we excluded those who had had a kidney stone episode within the 12 months preceding and 3 months after their first prescription fill for topiramate or zonisamide, we do not know whether the participants included in our study had had a kidney stone disease diagnosis before the study period, which would predispose them to recurrence. Having said that, for our results to be biased there would have to be an imbalance in the proportions of users and nonusers with a history of kidney stone disease, which we have no reason to suspect.

Second, we did not account in our modeling approach for nonusers who were prescribed topiramate or zonisamide after baseline. This decision may result in the misclassification of some nonusers, but we would argue that any measurement error resulting from it would bias our results toward the null.

Third, we recognize the potential for confounding by contraindication. Insofar as participants with conditions for which topiramate or zonisamide are used as treatments, who also have a history of urolithiasis, are less likely to be prescribed these medications because they may increase recurrence risk, we could be underestimating the association between treatment and outcome.

Fourth, our analysis may underestimate kidney stone risk among users. Specifically, our outcome of interest was the occurrence of a symptomatic stone event, which we identified using medical claims data to determine whether a given participant had an ED visit, hospitalization, or surgery for kidney stones. However, some patients may develop asymptomatic kidney stones or pass a stone with minimal discomfort on their own, never seeing a clinician. But we would argue that symptomatic stone events are

Table 2. Multivariable Model Findings on the Association Between Topiramate/Zonisamide Receipt and the Hazard of a Symptomatic Stone Event

	CDM Cohort		Medicare Cohort	
	Users (n = 147,514)	Nonusers (n = 737,570)	Users (n = 39,518)	Nonusers (n = 197,699)
Median follow-up time, y	1.5	1.3	2.7	2.0
No. of events				
Composite	2,896	5,905	752	2,180
ED visit	2,562	5,006	442	1,307
Hospitalization	267	502	116	317
Surgery for kidney stones	1,032	2,170	513	1,415
Unadjusted HR (95% CI)	2.35 (2.24-2.45)	1.00 (ref)	1.45 (1.34-1.58)	1.00 (ref)
Adjusted HR (95% CI)[a]	1.58 (1.49-1.68)	1.00 (ref)	1.22 (1.11-1.34)	1.00 (ref)

Abbreviations: CDM, Clinformatics Data Mart; ED, emergency department; HR, hazard ratio; ref, referent.
[a]Adjusted for age, sex, race, region of residence, socioeconomic status, level of comorbidity, concomitant diagnoses associated with increased stone risk, calendar year, and treatment indication.

Table 3. Findings From Post Hoc Sensitivity Analyses

Analysis	CDM HR (95% CI)	Medicare HR (95% CI)
Drug type (ref, nonuser)		
Topiramate	1.57 (1.48-1.66)	1.20 (1.08-1.32)
Zonisamide	1.91 (1.62-2.26)	1.51 (1.18-1.94)
Treatment indication (ref, nonuser)		
Headache	1.49 (1.34-1.66)	—
Weight loss	1.49 (1.33-1.68)	—
Seizure	3.06 (1.80-5.20)	—
Topiramate dose tertile (ref, low tertile)		
High	1.19 (1.01-1.39)	1.34 (1.04-1.73)
Medium	1.14 (1.05-1.23)	1.03 (0.87-1.22)
Concomitant diuretic use (ref, nonuser)	—	1.23 (1.11-1.35)

Abbreviations: CDM, Clinformatics Data Mart; HR, hazard ratio; ref, referent.

generally more meaningful to patients and the clinicians who care for them.

Fifth, the CDM cohort is a convenience sample, and Medicare beneficiaries are mainly older Americans. This limits our findings' generalizability. Nonetheless, our analysis is, by far, the largest to examine the association between kidney stone risk and topiramate and zonisamide use to date.

Limitations notwithstanding, our analysis has important potential clinical implications. In particular, it suggests that patients treated with topiramate or zonisamide for a variety of indications, especially younger adults and those with diagnoses associated with kidney stone formation, are at an increased risk of symptomatic kidney stone events. These findings should inform the risk-reward assessments of use of these drugs for a wide variety of conditions.

Supplementary Material

Supplementary File (PDF)

Figure S1: Unadjusted cumulative incidence of a stone-related ED visit, hospitalization, and surgery among topiramate and zonisamide users (blue) versus nonusers (pink) for the CDM and Medicare cohorts.

Table S1: Full multivariable model, revealing factors independently associated with a patient's hazard of a symptomatic stone event.

Table S2: Results from the multivariable model involving the CDM cohort, examining whether age moderates the association between medication use and kidney stone risk.

Article Information

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Associations of Topiramate and Zonisamide Use With Kidney Stones

Setting & Population

Retrospective cohort study

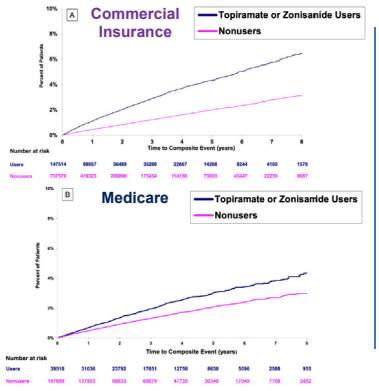
2011-2019

N = 1,122,301

Exposure:
New topiramate or zonisamide use

Outcome:
Symptomatic stone event

Findings



Unadjusted Cumulative Incidence of Symptomatic Stone Events

	Follow-up	
	3 Months	3 Years
Users	2.9	2.0
Nonusers	1.2	1.3

Hazard of Stone Event Among Users

Cohort	aHR (95% CI)
Commercial Insurance	1.58 (1.49-1.68)
Medicare	1.22 (1.11-1.34)

CONCLUSION: Use of topiramate or zonisamide was associated with an increased hazard of symptomatic stone events.

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