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Topiramate use does not reduce flares of inflammatory bowel disease

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Abstract

Background—Additional medications are needed for inflammatory bowel disease (IBD), as existing therapies are incompletely effective and can be costly and toxic. Preclinical studies suggest that topiramate (an anticonvulsant) may have disease-modifying properties in IBD, but its efficacy in humans is unknown.

Aim—To evaluate whether topiramate use is associated with clinical benefit in IBD patients.

Methods—We conducted a retrospective cohort study using administrative claims data from the MarketScan databases. Persons with IBD were identified between 2000 and 2010. New users of topiramate were compared with users of other anticonvulsant and anti-migraine medications. The primary outcome was a new prescription for an oral steroid (≥14 days). Secondary outcomes included initiation of biologic agents, abdominal surgery, and hospitalization. Cox proportional hazard modeling was used to adjust for potential confounders.

Results—We identified 773 new users of topiramate and 956 users of comparator drugs. After adjusting for potential confounders, topiramate use was not associated with the primary outcome of steroid prescriptions (HR 1.14, 95% CI 0.74, 1.73). Results did not differ significantly by IBD subtype. There was no difference between topiramate users and users of comparator drugs with respect to post-exposure initiation of biologic agents (HR 0.93, 95% CI 0.35, 2.52), abdominal surgery (HR 1.22, 95% CI 0.70, 2.12), or hospitalization (HR 0.78, 95% CI 0.49, 1.26).

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Conclusion—In this large US administrative claims study, topiramate use was not associated with markers of IBD flares. These results cast doubt on whether topiramate may be an effective adjunct to current IBD therapy.

Keywords

Drug Repositioning [MeSH]; Colitis, Ulcerative [MeSH]; Crohn Disease [MeSH]; Inflammatory Bowel Diseases [MeSH]; Glucocorticoids [MeSH]; Cohort Studies [MeSH]

INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic condition that affects over a million Americans[1,2] and is associated with substantial morbidity, including frequent hospitalization and surgery [3], reductions in quality of life [4], and increased mortality [5]. Contemporary studies show that IBD is associated with significant healthcare expenditures, with estimated annual direct costs of over $6 billion in the US alone [6]. Current medical therapies for ulcerative colitis (UC) and Crohn's disease (CD) include drugs that are only modestly effective, have serious potential toxicities, are challenging to administer, or are very costly. Pharmacoepidemiology studies that explore novel uses of existing medications could lead to the identification of safe and inexpensive treatment options for patients with IBD. This “drug repositioning [7]” approach is particularly appealing for uncommon diseases like IBD, where traditional drug development approaches may not be as attractive for the pharmaceutical industry [8].

There are currently over 6,000 FDA-approved medications available in the US. The concept of drug repositioning involves identifying currently approved medications (regardless of indication) that may be useful for other disease processes. Given the substantial cost and time investment associated with *de novo* drug development, this concept has become attractive for industry, researchers, clinicians, and patients alike. Successful, high profile examples of drug repositioning include use of aspirin for prevention of cardiovascular disease [9], sildenafil for erectile dysfunction and pulmonary hypertension [10], thalidomide for multiple myeloma [11], and angiotensin II receptor blockers for Marfan's syndrome [12]. Uncommon diseases that are associated with high morbidity such as IBD are ideal candidates for drug repositioning research.

Topiramate (Topamax), an FDA-approved medication used primarily for seizure prophylaxis, was identified as a possible IBD treatment in a recent high profile study [13]. Using the Connectivity Map, Dudley et al. compared the gene expression signatures of a compendium of 164 drug compounds to that of IBD, and found that topiramate was associated with the strongest “therapeutic score” for both UC and CD, on par with prednisolone, an established IBD therapy. Furthermore, topiramate performed favorably in a preclinical rodent colitis model. However, the efficacy of topiramate in humans with IBD is uncertain and has not been studied previously. We aimed to conduct a pharmacoepidemiology study using administrative data to determine whether topiramate exposure is associated with a reduced rate of disease flares in subjects with IBD.

MATERIALS AND METHODS

Study design and data source

We conducted a retrospective cohort study using claims data from the MarketScan® databases (Truven Health Analytics Inc.). These US databases contain over 500 million claims on roughly 100 million individuals covered by employer-sponsored commercial health insurance from approximately 100 payers, including health plans, large employers, government and public organizations. Data elements include inpatient and outpatient diagnoses [International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes], procedures [Current Procedural Terminology, 4th Edition (CPT) codes], prescription records, demographic information, and enrollment details. Data from January 2000 to December 2010 were used in this study. This database has been used in other epidemiologic studies of IBD [14] and anticonvulsants [15], and is representative of the commercially-insured population of the US [16].

Cohort identification and assessment of exposures

We selected IBD patients initiating topiramate therapy and a comparator group of IBD patients using other anticonvulsant and antimigraine drugs. First, the entire source population (n=104,951,068) was limited to those who met the IBD case definition: 1) at least 1 healthcare contact associated with an ICD-9-CM diagnosis code for CD (555.xx) or UC (556.xx) *and* 2) at least 1 pharmacy claim for any of the following IBD medications: mesalamine, olsalazine, balsalazide, sulfasalazine, 6-mercaptopurine, azathioprine, infliximab, adalimumab, certolizumab, natalizumab or enteral budesonide. To qualify for the study, exposed subjects had a new prescription (minimum 30 days supplied) for either topiramate, or one of the following comparator drugs: levetiracetam, phenytoin, lamotrigine, carbamazepine, oxcarbamazepine, valproate, or propranolol. This “active comparator, new user design” was used to minimize bias resulting from analysis of prevalent medication use compared with non-use such as the healthy user effect [17].

During a 6 month period prior to initiation of topiramate or a comparator drug, exclusion criteria were applied. Subjects were excluded if they did not meet the IBD diagnostic criteria. Other exclusion criteria included pre-exposure use of oral steroids (within 3 months of exposure), combination therapy with anticonvulsants, colectomy (for UC patients), and diagnoses of colorectal cancer, brain tumors, and esophageal varices. Subjects were also excluded if they did not have continuous health plan enrollment and pharmacy benefits during the 6 month pre-exposure period and the first month after drug exposure.

Assessment of covariates of interest

In addition to demographic information on age, sex, and geographic region (Northeast, North Central, South, and West based on US Census regions), data on potential confounders were measured based on claims during the 6 month pre-exposure period. These covariates included type of IBD (CD or UC, based on majority of diagnosis claims), use of other IBD medications [aminosalicylate drugs (mesalamine, olsalazine, balsalazide, sulfasalazine), 6-mercaptopurine (6-MP) or azathioprine, biologic agents (infliximab, adalimumab, certolizumab, and natalizumab), rectal steroids (enema, suppository, or foam), methotrexate,

or cyclosporine], markers of disease severity [weight loss (ICD-9 783.2), malnutrition (ICD-9 262.xx - 263.xx) and anemia (ICD-9 280.xx)], diagnosis of concomitant irritable bowel syndrome (IBS) (ICD-9 564.1), non-colectomy abdominal surgery (CPT 44500-44979, 49000-49999, 45000-45190, 45395-45999, 46020-46211, 46270-46288, 46700-46762, 46937-46942, 46999), comorbidities (Deyo modification of the Charlson comorbidity index [18]), claims for prescribing indications [seizure disorder (ICD-9 345.xx, 780.3, 781.0), migraine headaches (ICD-9 346.xx), bipolar disorder (ICD-9 296.xx), obesity (ICD-9 278.0), and peripheral neuropathy (ICD-9 337.0-1, 356.xx, 357.xx)], and markers of healthcare utilization [number of prescriptions, outpatient contacts, hospitalizations, and endoscopic procedures (upper or lower endoscopy, CPT codes: 43200-43259, 44360-44386, 44388-44397, or 45300-45392)].

Follow-up and outcomes

Participants were censored if they experienced a lapse in plan enrollment/pharmacy benefit > 1 month, if they stopped using topiramate or comparator drug (defined as a gap of >60 days beyond days supplied, according to a previously published definition [19]), or if they reached the end of study period (December 31, 2010). Subjects were censored at age 65 in conjunction with enrollment lapse and transition to Medicare.

The primary outcome for this study was defined as a 1st prescription for an oral steroid (days supplied ≥ 14), a marker of flare of disease [20]. Secondary outcomes included a 1) 1st use of any biologic agent (if not used in 6 months pre-exposure); 2) colectomy or other abdominal surgery (if no surgery 6 months prior to drug exposure, and excluding outpatient anal procedures such as hemorrhoidectomy); 3) first hospitalization, and 4) a composite outcome (i.e. any primary or secondary outcome).

Statistical Analysis

Sample size—Our sample size was not pre-specified, as we planned to include all subjects meeting the inclusion and exclusion criteria outlined above.

Bivariate analysis—Bivariate analysis was performed between covariates and the exposure (using chi-squared tests for categorical variables, or Student's t-tests for continuous variables), and the primary outcome (using Kaplan Meier plots and log rank tests). Covariates were evaluated for confounding and effect modification if they were significantly associated with the exposure and outcome at an alpha of ≤ 0.2, or if they were believed to be important confounders based on previously published data.

Survival and Multivariate analysis—Prior to inclusion in modeling, each variable was evaluated with log-log plots to ensure the proportional hazards assumption was not violated. First, Kaplan Meier plots were created for each outcome, without adjustment for covariates. Subsequently, Cox proportional hazard modeling was performed to estimate adjusted hazard ratios (aHR) for the association between topiramate use and the primary and secondary outcomes. To determine which covariates to include in the final multivariable models, a full model with all potential confounders was constructed. Covariates were then removed from the model using backwards elimination with a threshold of <10% change in beta coefficients

and a likelihood ratio test p value of >0.05. Because this process was repeated iteratively for each outcome, the adjustment set differed slightly for models for the primary and secondary outcomes. All analyses were performed with STATA version 10.1 (College Station, TX).

Dosage, duration, and adherence analyses—To assess the possible contribution of dose, initial topiramate dose was categorized into ≤ 50mg/day and ≥100mg/day dose. Duration of topiramate therapy was dichotomized as ≤60 days vs. >60 days. In addition, the medication possession ratio [MPR calculated as: (sum of days supplied) ÷ (days of follow-up)] was categorized using cutoff of 0.90 to determine whether different levels of adherence modified the effect of topiramate use [21].

Sub-analyses—A number of secondary analyses were conducted to further evaluate our findings, including stratifying by gender and age (≤40 vs. >40 years), and restricting the population to: subjects with a diagnosis claim for seizure disorder, migraine headaches, or bipolar disorder. We also performed pairwise comparisons to analyze users of topiramate compared to each individual comparator drug.

Ethical considerations: The study protocol was granted an exemption by the Institutional Review Board at University of North Carolina because it involved the use of de-identified data.

RESULTS

Study population

Out of a total of 230,654 subjects with at least 1 IBD diagnosis and drug claim, we identified 775 topiramate exposed subjects and 958 subjects exposed to comparator drugs (Figure 1). Characteristics of each group are shown in Table 1. The mean age was similar in both groups (42 ± 12 for topiramate initiators, and 41 ± 14 for initiators of comparator drugs). Women represented a higher proportion of topiramate users (79% vs. 59%). IBD subtype did not differ between groups. With respect to indications for the drugs of interest, there was a higher proportion of topiramate users with migraine diagnoses (37 vs. 9%), and lower proportion with diagnoses of seizures or bipolar disorder (5 vs. 12% and 12 vs. 24% respectively). Mean Charlson comorbidity index scores were similar (0.45 ± 0.85 vs. 0.44 ± 1.01). IBD medication use in the pre-exposure period was similar between groups, though a slightly higher proportion of topiramate users were exposed to biologic agents (15 vs. 12%). In terms of healthcare utilization, topiramate users were less commonly hospitalized (17 vs. 25%), but had more outpatient contacts and prescriptions compared to users of comparator drugs (means 15 ± 11 vs. 13 ± 10 and 17 ± 11 vs. 13 ± 8, respectively).

Primary outcome

Over a median follow-up of 2.8 months, 115 patients filled a prescription for an oral steroid (primary outcome) for an overall incidence rate of 14 per 100 person years. The unadjusted Kaplan Meier survival was similar between groups (p=0.78) (Figure 2). Cox proportional hazards modeling revealed no significant difference between groups with respect to the primary outcome after adjustment for age, sex, region, pre-exposure diagnosis of seizures,

migraines, bipolar disorder, use of biologic agents, enteral budesonide, and number of prescriptions [aHR 1.14 (0.74, 1.73)] (Table 2). Stratification by disease subtype revealed similar findings [UC: aHR 1.06 (0.53, 2.13); Crohn's: aHR 1.23 (0.71, 2.11)].

Secondary outcomes

For initiation of anti-TNF therapy, abdominal surgery, hospitalization, and the composite outcome (any primary or secondary outcome), there was no difference in unadjusted survival (i.e. time until outcome occurrence) comparing topiramate users to the comparator group (Figure 3). Similarly, Cox proportional hazards modeling did not reveal any significant differences in the hazard of these outcomes comparing topiramate and comparator drug groups (Table 2).

Sub-analyses and dose response

Results of subanalyses are shown in Table 3. Stratification by age or gender did not change our results substantially. HR estimates tended to decrease with increasing dose, duration of use, and adherence to topiramate, but remained >1 and were not statistically significant. To investigate whether topiramate may act differently depending on the indication for its use, we examined whether limiting the population to those with a diagnosis of seizure disorder, migraine headache, or bipolar disorder changed the results, and it did not. Because IBD patients with concomitant irritable bowel syndrome may be more likely to be prescribed topiramate and may experience flares differently, we examined the effect of excluding subjects with a diagnosis of IBS and found no difference.

Pairwise comparisons

Because our comparator group included subjects exposed to a number of different medications which may have introduced heterogeneity, we examined the effect of varying the comparator group composition on our results. Results of pairwise comparisons of anticonvulsant and antimigraine drugs are shown in Table 3. For the most part, HR estimates were similar and not statistically significant, though comparison with levetiracetam yielded an elevated (but not statistically significant) HR estimate of 3.64 (0.93, 14.3).

DISCUSSION

In this retrospective cohort study, we found no evidence of a therapeutic benefit of topiramate in patients with IBD. We did not find evidence of differential efficacy (or lack thereof) based on gender, age, dose, duration of use, adherence, disease subtype, comorbidities or variations in the comparator group. This was an unequivocal negative study.

Drug repositioning is an important and burgeoning genre of pharmacoepidemiology research, and is particularly appealing for uncommon diseases such as IBD. The impetus for our research was a recent study in which topiramate was identified as an intriguing IBD therapeutic candidate based on its gene expression profile and pre-clinical data [13]. In light of this promising report, the lack of a demonstrable effect of topiramate in our study is disappointing. Nevertheless, we feel that this study illustrates the importance and feasibility

of using existing data to rapidly evaluate the potential effectiveness of promising drug repositioning candidates in order to identify those agents that merit further clinical investigation.

The strengths of this study bear mentioning. First, the size of the database allowed us to identify a large enough population of topiramate-exposed IBD patients to provide reasonable enough confidence that the negative findings observed here were not due to inadequate power or sample size. Indeed, the lower limit of the 95% confidence interval is compatible with a 25% reduction in the hazard of an IBD flare. While a weaker effect could theoretically exist, its clinical significance would be arguable. Importantly, most of our HR point estimates were greater than 1. Second, we used established administrative definitions for IBD and markers of flares, and assessed a number of different relevant outcomes. Additionally, we would expect high fidelity of drug exposure and primary outcome information (i.e. prescriptions filled, picked up, and paid for). Finally, we used an “active comparator, new user design” which is more methodologically sound comparing prevalent users of drugs with non-users.

In designing this study, we considered several possible “control” groups including all IBD subjects unexposed to topiramate and a control group of IBD subjects matched via propensity scores, but determined that a comparator group composed of users of peer medications would result in groups that were matched most closely with each other, apart from the specific drug exposures of interest. Adjusting for remaining differences between exposed and unexposed patients using multivariable modeling did not change the lack of association seen in this study. This is, in essence, a comparative effectiveness study. While it may not be typical for IBD patients to be prescribed anticonvulsants, we found that when they were, there was no difference in flares when they were prescribed topiramate vs. other agents. We therefore feel that these data provide good evidence that topiramate use among IBD patients is unlikely to be a highly effective disease-modifying agent. Nonetheless, it is possible that our comparator group selection led to some unforeseen bias, and unmeasured or residual confounding is always possible.

There are additional limitations associated with using administrative claims data that we attempted to address with our study design. As with any study using claims data, there exists the possibility of misclassification bias. In order to minimize misclassification of the study population, we used a previously reported administrative claims definition for IBD that is similar or more rigorous that others that have been reported or validated elsewhere [2,22]. The exposure and primary outcome were measured by prescriptions filled vs. patient report, which would be expected to minimize misclassification, but it is possible that some people who were prescribed topiramate actually did not take it, or took it only briefly. However, we found that even prolonged use and high adherence to topiramate were unassociated with reduced markers of disease flares. Given the lack of available clinical detail, we were unable to examine the potentially important effects of smoking history, disease phenotype, or use of non-prescription drugs such as over the counter analgesics, probiotics, fiber, etc. We also recognize that initiation of steroids may not be a perfect marker of flares of IBD, and it is possible that some steroid use in this population was related to non-IBD indications. However, even in absence of a 100% correlation with flare of disease, steroid use is an

important clinical outcome in itself given the associated toxicities of glucocorticoid therapy. Furthermore, follow-up may not have been long enough to capture all secondary outcome events (e.g. initiation of biologic agents), which could have biased these analyses toward the null. Regarding generalizability, we believe these results are applicable to commercially-insured patients in the US, but possibly not to other populations (e.g. elderly, uninsured, other nationalities). Lastly, data from this single study do not preclude the possibility that topiramate may be useful in aborting flares of IBD or in achieving other outcomes not studied here.

In summary, despite promise based on *in silico* and pre-clinical data, in this administrative claims study we found no evidence of a beneficial effect of topiramate in inflammatory bowel disease. This study highlights the important role of pharmacoepidemiology studies in drug repositioning research; shortly after topiramate was identified as a possible IBD therapy candidate, we were able to assess the potential efficacy of this agent using existing "real world" data from IBD patients taking this medication. While additional studies will be needed to confirm these results, our findings do not suggest that topiramate is likely to be a highly effective IBD therapy.

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Statement of authorship: SDC conceived of and designed the study, obtained funding, analyzed and interpreted the data, drafted and revised the manuscript. RS assisted with computer programming, acquisition of data, technical support, statistical analysis, and critical revision of manuscript. TS assisted with study concept and design and critical revision of manuscript. MDK assisted with study concept and design, analysis and interpretation of data, and critical revision of manuscript. All authors read and approved the final manuscript.

Abbreviations

IBD	inflammatory bowel disease
UC	ulcerative colitis
CD	Crohn's disease
FDA	US Food and Drug Administration
ICD-9-CM	International Classification of Diseases, 9th Revision, Clinical Modification
CPT	Current Procedural Terminology code
HR	hazard ratio
aHR	adjusted hazard ratio
CI	confidence interval
IBS	irritable bowel syndrome
6-MP	6-mercaptopurine

NE	no estimate
MPR	medication possession ratio
Dx	diagnosis
Rx	prescription

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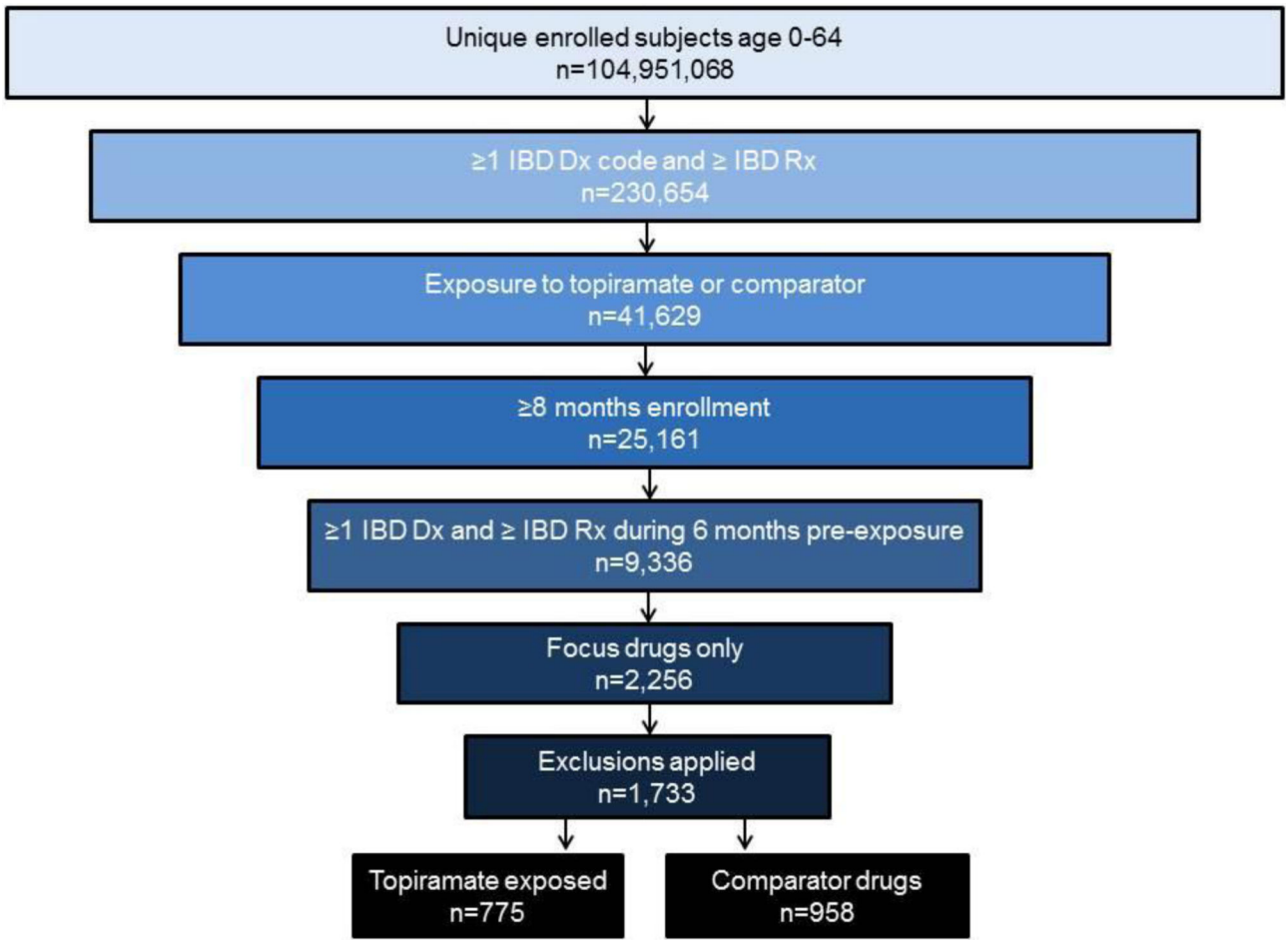

Figure 1.

Flow diagram for identification of study population.

IBD Dx: ICD-9 CM diagnosis code for an inflammatory bowel disease; IBD Rx: prescription for IBD specific medication (see text for details).

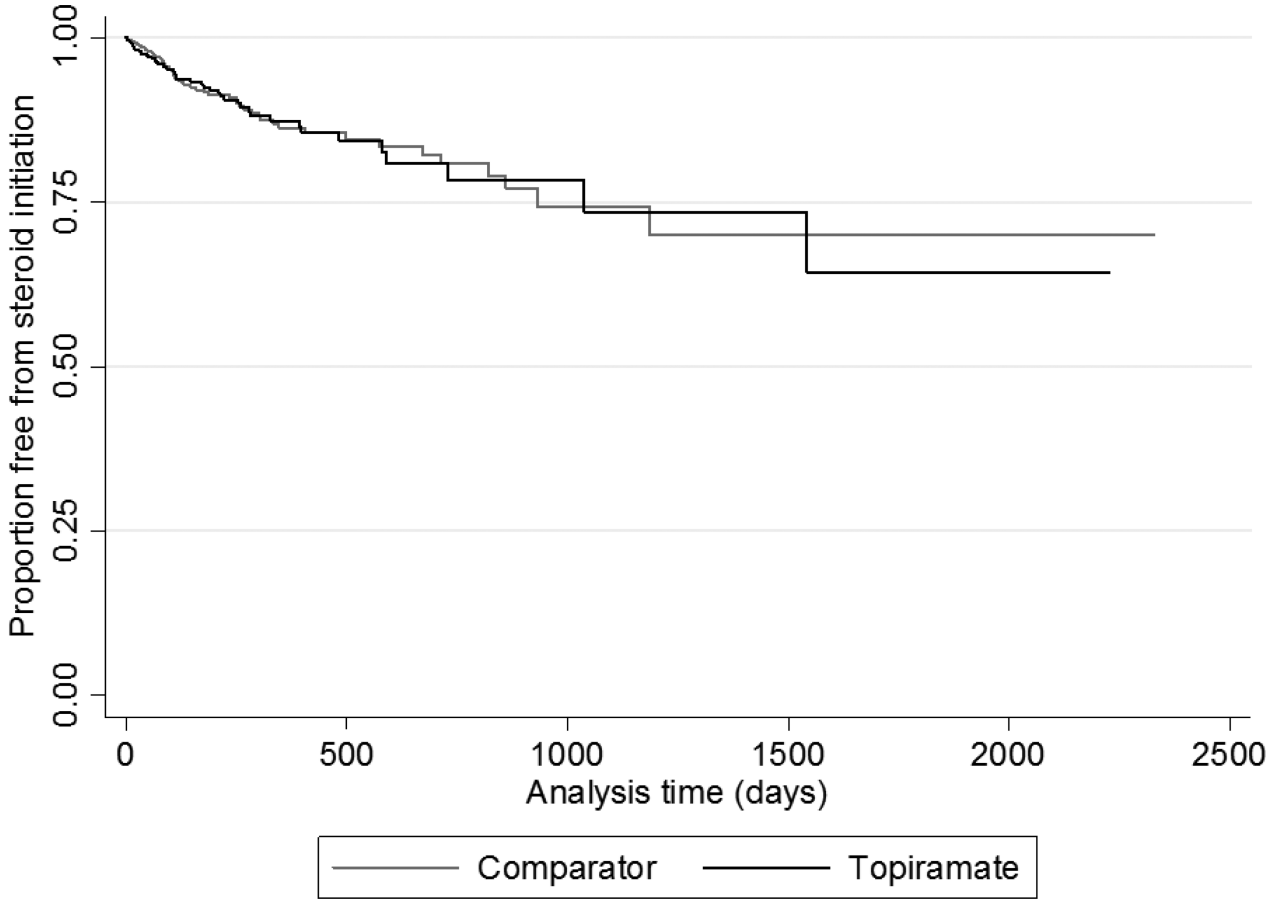

Figure 2.

Kaplan-Meier survival graph for primary outcome (steroid prescription ≥14 days) comparing new users of topiramate (black line) and comparator drugs (gray line).(p=0.78)

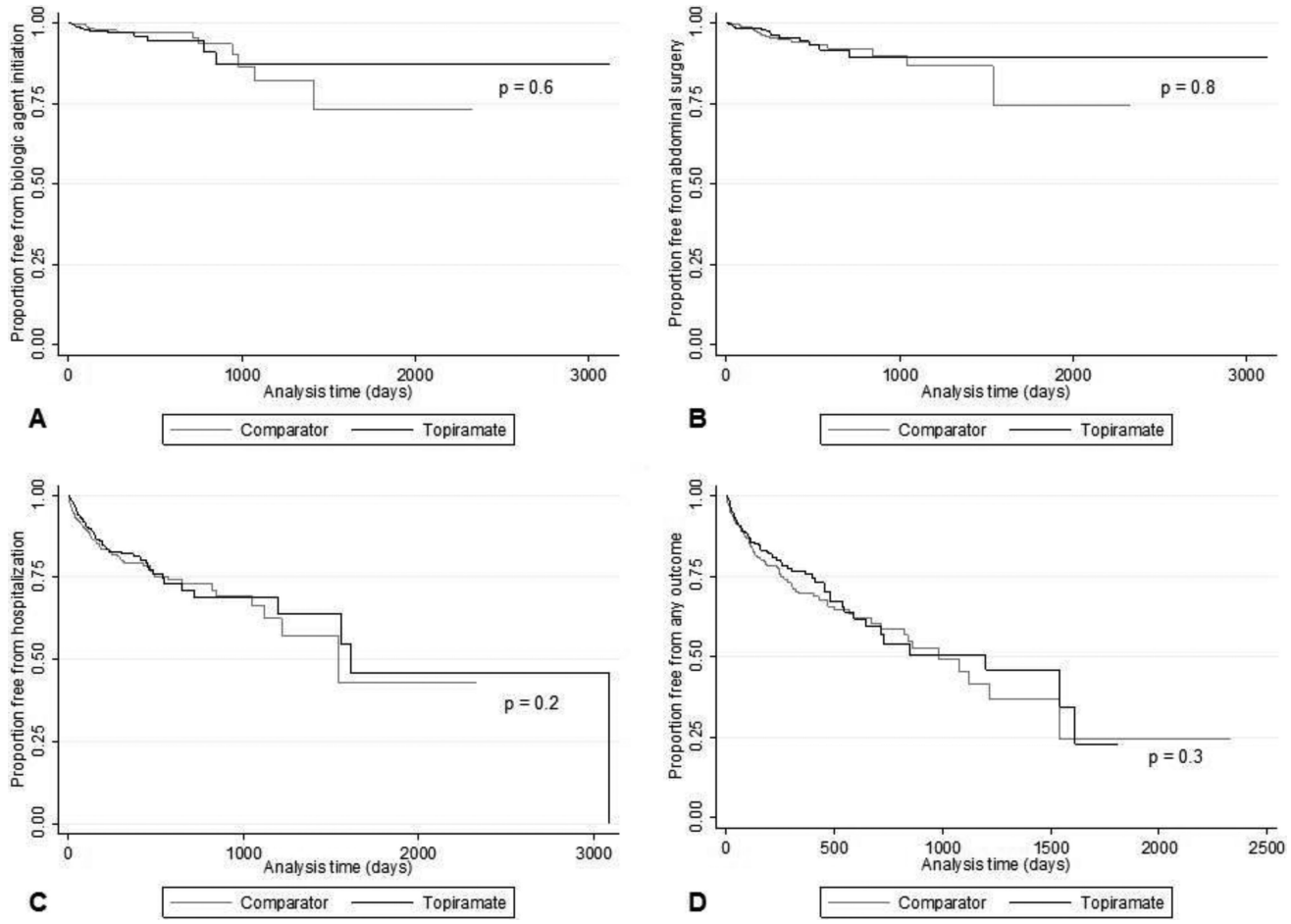

Figure 3.

Kaplan Meier graphs for secondary outcomes including (A) initiation of biologic agents, (B) abdominal surgery, (C) hospitalization, (D) composite outcome (any primary or secondary outcome) comparing new users of topiramate (black lines) and comparator drugs (gray lines).

Table 1

Characteristics of cohort based on claims in 6 month pre-exposure period

Characteristics		Topiramate (n = 775) n (%) or mean ± SD	Comparator group (n = 958) n (%) or mean ± SD	p value*
Drug exposure				n/a
	Topiramate	775 (100)	0 (0)	
	Levetiracetam	0 (0)	61 (6)	
	Phenytoin	0 (0)	47 (5)	
	Carbamazepine/oxcarbazepine	0 (0)	77 (8)	
	Lamotrigine	0 (0)	255 (27)	
	Valproic Acid	0 (0)	127 (13)	
	Propranolol	0 (0)	391 (41)	
Age	0-20	41 (5)	78 (8)	0.07
	21-40	309 (40)	368 (38)	
	41-64	425 (55)	512 (53)	
Sex	Female	615 (79)	563 (59)	<0.001
	Male	160 (21)	395 (41)	
Region	Northeast	89 (11)	138 (14)	<0.001
	North Central	187 (24)	305 (32)	
	South	382 (49)	380 (40)	
	West	115 (15)	132 (14)	
IBD type				1.0
	Crohn's	428 (55)	527 (55)	
	UC	337 (43)	418 (44)	
	Indeterminate	10 (1)	13 (1)	
Comorbidities				
	Seizure diagnosis	40 (5)	114 (12)	<0.001
	Migraine	284 (37)	88 (9)	<0.001
	Bipolar disorder	91 (12)	230 (24)	<0.001
	Obesity	20 (3)	12 (1)	0.04
	Peripheral neuropathy	23 (3)	8 (1)	0.001
	Congenital brain abnormality	2 (0.3)	2 (0.2)	0.8
	IBS	48 (6)	51 (5)	0.4
	Weight loss	9 (1)	21 (2)	0.1
	Malnutrition	6 (<1)	9 (<1)	0.7
	Anemia	39 (5)	54 (6)	0.6
Charlson index†		0.45 ± 0.85	0.44 ± 1.01	0.7
IBD drugs				

Characteristics		Topiramate (n = 775) n (%) or mean ± SD	Comparator group (n = 958) n (%) or mean ± SD	p value*
	5-ASA‡	563 (73)	721 (75)	0.2
	6MP/AZA	219 (28)	268 (28)	0.9
	Methotrexate	20 (3)	18 (2)	0.3
	Cyclosporine	6 (<1)	3 (<1)	0.2
	Enteral budesonide	103 (13)	109 (11)	0.2
	Rectal steroid	36 (5)	47 (5)	0.8
	Any biologic	166 (21)	166 (17)	0.03
	Infliximab	115 (15)	117 (12)	0.1
	Adalimumab	46 (6)	46 (5)	0.3
	Certolizumab	5 (<1)	8 (<1)	0.8
	Natalizumab	3 (<1)	1 (<1)	0.2
Healthcare utilization				
	Any hospitalization	131 (17)	242 (25)	<0.001
	Outpatient visits	15 +/− 11	13 +/−10	<0.001
	Number of Rx	17 +/− 11	13 +/− 8	<0.001
Endoscopy				
	EGD	99 (13)	106 (11)	0.3
	Colonoscopy	237 (31)	276 (29)	0.4
	Any endoscopy	291 (38)	345 (36)	0.5

*p values obtained via Chi-squared tests or Student's t-tests

†Deyo modification of Charlson comorbidity index

‡5-ASA includes prescription for sulfasalazine, mesalamine, olsalazine, or balsalazide

Table 2

Cox proportional hazards model estimates for primary and secondary outcomes, overall and stratified by disease subtype.

	Primary outcome	Secondary outcomes			
Estimates	**Steroid prescription HR (95% CI)**	**Initiation of biologic agent HR (95% CI)**	**Abdominal surgery HR (95% CI)**	**Hospitalization HR (95% CI)**	**Composite outcome HR (95% CI)**
Unadjusted HR					
all IBD	1.05 (0.73, 1.52)	1.23 (0.61, 2.49)	1.33 (0.27, 6.61)	0.83 (0.63, 1.10)	0.86 (0.66, 1.13)
Crohn's	1.26 (0.78, 2.04)	1.26 (0.56, 2.87)	1.37 (0.28, 6.80)	0.82 (0.57, 1.17)	0.80 (0.55, 1.18)
UC	0.81 (0.45, 1.46)	1.22 (0.31, 4.89)	NE	0.78 (0.49, 1.26)	0.89 (0.61, 1.32)
Adjusted HR*					
all IBD	1.14 (0.74, 1.73)	0.93 (0.39, 2.19)	1.04 (0.17, 6.41)	0.86 (0.62, 1.19)	0.96 (0.71, 1.31)
Crohn's	1.23 (0.71, 2.11)	0.94 (0.35, 2.52)	1.20 (0.20, 7.09)	0.81 (0.54, 1.20)	0.82 (0.53, 1.26)
UC	1.06 (0.53, 2.13)	1.18 (0.22, 6.39)	NE	0.93 (0.52, 1.65)	1.16 (0.73, 1.85)

HR: Hazard ratio; IBD: Inflammatory bowel disease; UC: ulcerative colitis; NE: No estimate (e.g. too few events)

*Adjusted for age, sex, region, and pre-exposure dx of seizure, migraine, bipolar disorder, use of enteral budesonide, use of biologic agents (except for this outcome), and number of prescriptions in pre-exposure period.

Table 3

Subanalyses for primary outcome examining effects of gender and age, dose response, and variations in study population and comparator group.

Subanalysis	Steroid prescription aHR* (95% CI)
Gender	
Males only	1.37 (0.65, 2.90)
Females only	1.18 (0.70, 1.99)
Age	
0-40 years	1.20 (0.66, 2.19)
>40 years	1.09 (0.60, 1.99)
Study population	
Limit to seizure diagnosis	2.64 (0.83, 8.38)
Limit to migraine diagnosis	1.78 (0.58, 5.54)
Limit to bipolar diagnosis	1.31 (0.46, 3.67)
Exclude diagnosis IBS	1.18 (0.77, 1.82)
Dose response	
Dosage: 15-50mg/day	1.14 (0.74, 1.76)
100-200mg/day	1.04 (0.40, 2.68)
Duration: ≤60 days	1.33 (0.61, 2.89)
>60 days	1.10 (0.70, 1.71)
Adherence: MPR <90%	1.24 (0.71, 2.15)
MPR ≥90%	1.08 (0.68, 1.73)
Pairwise comparisons	
Topiramate vs. all	1.14 (0.74, 1.73)
vs. all AEDs†	1.20 (0.71, 2.01)
vs. Levetiracetam	3.64 (0.93, 14.3)
vs. Phenytoin	0.91 (0.27, 3.10)
vs. Carbamazepine‡	1.05 (0.41, 2.70)
vs. Lamotrigine	1.38 (0.71, 2.67)
vs. Valproate	1.57 (0.61, 4.02)
vs. Propranolol	0.97 (0.57, 1.63)

IBS: irritable bowel syndrome; MPR: medication possession ratio = (total days supplied)/(days in study); AED: anti-epileptic drugs

*Hazard ratio for all inflammatory bowel disease subjects, adjusted for age, sex, region, and pre-exposure dx of seizure, migraine, bipolar disorder, use of enteral budesonide, use of anti-TNF agent, and number of prescriptions in pre-exposure period. Referent (i.e. HR 1.0) is comparator group for all analyses.

†excludes propranolol users

‡Also includes oxcarbamazepine