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Effectiveness of osteoporosis medication on site-specific fracture risk attenuation among adults with epilepsy

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Summary

Objective: The objective of this propensity score-matched, observational cohort study was to determine the effectiveness of osteoporosis medication on reducing the risk of non-trauma fracture (NTFx) among adults with epilepsy.

Methods: Data from 01/01/2012-09/30/2015 was extracted from Optum Clinformatics® Data Mart. NTFx risk attenuation from 12-months prior to 12-months after the individual's index date was examined for each group of adults ≥50 years of age as risk ratios (RR with 95% confidence intervals [CI]). Groups were stratified based on: (1) epilepsy status, as with vs. without epilepsy (EP); and (2) if and when osteoporosis medication was first prescribed, as new users (treatment naïve), consistent users (osteoporosis medication prescribed in pre-index period), and no users. Comparison groups were matched 1:1 to EP new users (n=828/group) for demographics, glucocorticoid and antiseizure medication, and the Elixhauser comorbidity index. Difference-in-difference analysis compared the change in pre- to post-index NTFx risk among groups as the ratio of the RR (RRR).

Results: The pre- to post-index NTFx risk at any site was reduced for EP new users (RR=0.49; 95%CI=0.40-0.61) and EP consistent users (RR=0.70; 95%CI=0.38-0.98), but non-significantly elevated for EP no users (RR=1.39; 95%CI=0.93-2.07)- findings were consistent for most sites (e.g., vertebral column). EP new users had a larger NTFx risk attenuation at any site compared to EP no users (RRR=0.35; 95%CI=0.23-0.54) and EP consistent users (RRR=0.70; 95%CI=0.51-0.97). EP consistent users had a larger NTFx risk attenuation at any site compared to EP no users (RRR=0.50; 95%CI=0.32-0.79). The extent of NTFx risk attenuation at any site was similar for new users with vs. without epilepsy (RRR=0.99; 95%CI=0.73-1.34) and consistent users with vs. without epilepsy (RRR=0.81; 95%CI=0.55-1.17). There was evidence of site-specific effects (e.g., hip).

Conclusion: Osteoporosis medication is associated with a clinically meaningful 12-month NTFx risk attenuation for adults with epilepsy, especially for those just starting osteoporosis medication.

Keywords: epilepsy; osteoporosis medication; fracture

Introduction

Skeletal fragility is a major problem for individuals with epilepsy across the lifespan. Children with epilepsy have lower bone mineral density and an elevated frequency of fractures compared to children without epilepsy.[1, 2] Approximately three out of four adults with epilepsy have low bone mineral density or osteoporosis, [3, 4] leading to an increased risk for fracture.[5] Non-trauma fracture (NTFx), an indicator of skeletal fragility, is present in one out of five adults ≥18 years of age with epilepsy, which is 3.2 times higher compared to the general adult population without epilepsy.[6]

Recently, a large cohort study reported that after accounting for demographics and several chronic diseases, the adjusted rate of 12-month mortality was 70% higher for adults with epilepsy that sustained an NTFx as compared to adults with epilepsy that did not sustain an NTFx, and 41% higher compared to adults without epilepsy that sustained an NTFx.[6] While the cause and effect has yet to be elucidated, the elevated risk of post-NTFx mortality may be driven by development of cardiorespiratory diseases,[7-9] which are among the leading causes of premature mortality for individuals with epilepsy.[10-13] Taken together, these new findings could suggest a greater post-NTFx disease and survival burden for adults with epilepsy, and underscores the importance of maximizing skeletal health throughout the lifespan and attenuating the risk of NTFx in the adult years.

Despite the significant need, there is a dearth of empirical evidence about the effectiveness of osteoporosis medication therapy on skeletal health for individuals with epilepsy. Lazzari and colleagues[14] started to address this knowledge gap and performed a 2-year double-blind, randomized placebo controlled study that included male veterans with epilepsy that were taking antiseizure medication, had normal calcium and vitamin D levels, were not taking glucocorticoid medication, and did not have osteoporosis at baseline, among other exclusion criteria. The authors reported that treatment with risedronate- an antiresorptive bisophosphonate agent- improved bone mineral density and reduced the incidence of fractures compared to the placebo group.[14] While fundamental to the field, the sample size was small (treatment group, n=27; placebo group, n=26) and may not be generalizable to the greater population with epilepsy given the strict inclusion criteria that often accompanies randomized controlled trials. Further, in general, inferences about the effectiveness of osteoporosis medication on fracture risk attenuation are limited from randomized controlled trials,[15] as they may not represent the heterogeneity observed in clinical settings for medication adherence, patient populations, and

medication prescriptions. Therefore, the purpose of this propensity score-matched, observational cohort study was to determine if osteoporosis medication was associated with NTFx risk attenuation among adults with epilepsy.

Methods

Data source

Claims data was ascertained from January 1, 2012 to September 30, 2015 from Optum Clinformatics® Data Mart Database (OptumInsightTM, Eden Prairie, MN, USA). This national single private payer administrative claims database contains medical and outpatient pharmacy information from privately insured or Medicare Advantage beneficiaries in the United States and has been described previously in detail.[16] Since data are de-identified, the University Institutional Review Board approved this study as non-regulated.

Sample selection

All medical conditions were identified using the International Classification of Diseases (ICD), Ninth Revision, Clinical Modification codes. As there was a national change in reporting ICD-9 to ICD-10 codes on October 1, 2015, this study ended at September 30, 2015 to limit bias from unknown differences in detection of medical conditions.

Individuals were initially considered for this study if they were ≥50 years of age, had at least 12-months of continuous enrollment in the pre-index period to ascertain baseline data, had at least 12-months of continuous enrollment in the post-index period for the outcome, and utilized healthcare services at least 2 days in the pre-index period (to limit detection bias due to lack of clinician interaction). Epilepsy was identified by at least one reimbursement inpatient, outpatient, or emergency department claim for "epilepsy and recurrent seizures" on at least two separate days within the 12-month pre-index period, as previously described.[6] The 2+ claim algorithm has a positive predictive value of ~70-100% for epilepsy.[17] Reimbursement claims do not contain or reliably code information for etiology, type, or duration of epilepsy. For example, 46% of this cohort had an "unspecified" epilepsy condition. Therefore, stratification or statistical adjustment for clinically relevant variables pertaining to the epilepsy condition was not performed.

The first outpatient pharmacy claim for osteoporosis medication was identified between January 1, 2012 and September 30, 2014 (to allow 12-months of follow-up for the outcome), and included at least one osteoporosis medications, as guided by previous studies.[18, 19] The index date for those prescribed an osteoporosis medication on or after January 1, 2013 was the date of the first outpatient pharmacy claim for an osteoporosis medication. The index date for those prescribed an osteoporosis medication in the calendar year 2012 was January 1, 2013. The index date for those not prescribed an osteoporosis medication was a randomly assigned date within the study period.[9]

The osteoporosis medication groups were categorized as "new" and "consistent" users to examine the effect of chronicity of osteoporosis medication exposure. For example, new users may have a larger effect on NTFx risk attenuation. New users were defined as individuals that had no outpatient pharmacy claims for osteoporosis medication in the 12-month pre-index period and were considered treatment naïve.[19] Consistent users were defined as individuals that had one or more outpatient pharmacy claims for osteoporosis medication in the 12-month pre-index period.

The sample was categorized into 5 groups based on the status of epilepsy (EP) and osteoporosis medication prescription: adults with epilepsy that were (1) new users (EP new users), (2) consistent users (EP consistent users), and (3) not prescribed osteoporosis medication (EP no users), and adults without epilepsy that were (4) new users (w/o EP new users) and (5) consistent users (w/o EP consistent users). EP new users were the primary group of interest and all other groups were considered comparison groups.

Fracture

Fracture occurring at the vertebral column, hip (including proximal femur), non-proximal femur, tibia or fibula, humerus, ulna or radius, or at an unspecified site that did not have corresponding trauma codes (e.g., car accident) 7 days before to 7 days after the index date of the fracture event was defined as an NTFx, as previously described.[6, 20-22] All other fractures were considered to be trauma related. Fractures in the pre-index time period were not distinguished as trauma or non-trauma, because collectively, fracture regardless of energy level increases risk for subsequent fractures.[23] However, in the post-index period, only fractures that were non-traumatic (i.e., NTFx) were examined.

In the post-index period, the first NTFx was examined. To be sure that the first NTFx event in the post-index period was indeed an incident fracture for those with a pre-index fracture, it was required that the post-index period NTFx event was at a new site or there was a gap of at least 6 months from the previous NTFx event if at the same site. The 6-month gap requirement is a conservative approach compared to the 3-month gap used in previous claims-based studies.[15, 18, 19]

Prevalence of fracture was examined in the pre-index period as measures were not taken to identify new onset fracture (i.e., required another lookback period) and incidence of fracture was examined in the post-index period.

Covariates

Covariates were selected based on their relevance to epilepsy or NTFx and availability and reliability in claims databases. Sociodemographic variables included age, sex, race, and U.S. region of residence. Glucocorticoid medications and antiseizure medications were identified by at least one outpatient pharmacy claim for relevant medications anywhere in the 12-month pre-index period to 2 weeks after the individual's index date, to capture individuals that may have been prescribed these medications around the time of the osteoporosis medication prescription. A modified version of the validated Elixhauser comorbidity index was computed. The original Elixhauser comorbidity index includes a score (yes or no) for 30 comorbidities.[24] As there is some overlap with epilepsy, paralysis and other neurological disorders (which contain epilepsy codes) were omitted for this study. Co-occurring cerebral palsy is common among individuals with epilepsy and is strongly associated with skeletal fragility.[9, 22, 25-29] Therefore, cerebral palsy was added as its own comorbidity to account for health and disease status, which made the total count of 29 for the modified Elixhauser comorbidity index used in this study.

Propensity-score matching

One-year incidence of NTFx is typically a rare outcome in research and may limit the interpretability of covariate adjusted regression models when there is a need for adjustment of several covariates. Therefore, to account for confounders that may influence the associations of interest, the 4 comparison groups were each matched to the primary group of interest, EP new users, at a 1:1 matching ratio using a propensity score computed by the PSMATCH procedure in

SAS version 9.4 (SAS Institute, Cary, NC, USA). We employed the greedy nearest neighbor method after randomizing the order of the comparator groups, required a standard caliper of 0.25, and initially considered all covariates to create the propensity score. Balance in matching was examined and if not met, alternative approaches were taken.

Statistical analysis

Descriptive characteristics were presented for each group. 95% binomial confidence intervals (CI) for the prevalence of pre-index fracture and incidence of post-index NTFx were calculated as the sample proportion ± the margin of error with a z-value of 1.96.[30]

To estimate the change in NTFx risk from pre- to post-index periods for each group, risk ratios (RR) and 95% CI were estimated. To determine if the change in NTFx risk was different across groups, a difference-in-difference analysis was conducted. Specifically, a generalized linear model with repeated measures and a log link function was used for NTFx as any site and then for each site separately. Each participant had two observations in the difference-in-difference analysis: presence of pre-index fracture and presence of post-index NTFx. The interpretation of these analyses were focused on the relative change for the entire group which is assessed by taking the ratio of the RR (RRR) from the groups being compared. The RRR is a numerical approximation of the time by exposure variable interaction. In real world settings, the differences in pre-treatment profiles for those treated and not treated can impact interpretations regarding the effectiveness of a treatment (e.g., osteoporosis medication) on an outcome (e.g., change in NTFx risk).[15] By examining the longitudinal change in fracture prevalence using a within-person design, bias due to confounding is mitigated as each group serves as their own internal control, making this analytic approach a strength for addressing the research question.

Sensitivity analysis

Antiseizure medication can lead to skeletal fragility through a variety of mechanisms.[31] To determine if the change in pre-index fracture to post-index NTFx differed by status of antiseizure medication exposure, unadjusted RR for NTFx at any site was examined after stratifying each group by antiseizure medication exposure in the 12.5-month pre-index period. Site-specific effects were not examined due to the small sample size.

Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

Prior to matching, 9.1% out of 52,398 adults ≥50 years of age with epilepsy that met all other eligibility criteria were prescribed an osteoporosis medication (n=828 for new users, n=3,940 for consistent users), which was 1.69 times higher (95% CI=1.64-1.73) than the 5.4% out of 4,329,365 adults without epilepsy.

Balanced matching without omitting any participant from the primary group of interest, EP new users, was not possible when U.S. region of residence and race was included. Upon further examination, U.S. region of residence was omitted and race was re-categorized as White, Black, and everything else, and successful matching for all groups was achieved. Descriptive characteristics from the pre-index period for all groups (n=828/group) is presented in **Table 1**. Using the Chi-square test, there were significant group differences for U.S. region of residence (P<0.001) and race when examined as the original categories (P=0.005), but not for race when re-categorized (P=0.533) due to matching; no other group differences were observed. Approximately 96-97% of the osteoporosis medication groups were prescribed an antiresorptive agent and the remaining 3-4% were prescribed an anabolic agent.

Prevalence of pre-index fracture and incidence of post-index NTFx

Notably, EP new users had a higher prevalence of pre-index fracture at any site compared to all comparison groups and pre-index fracture at each site compared to all comparison groups (all P<0.05) except w/o EP new users (similar prevalence at each site) and EP consistent users for the lower extremities (similar prevalence) (**Table 2**). In the post-index period, the differences were less pronounced, but EP users still had a higher incidence of NTFx at any site compared to all comparison groups (all P<0.05) except w/o EP new users (similar incidence). For site-specific effects in the post-index period, EP new users had a similar NTFx incidence for each site compared to EP consistent users, higher incidence of NTFx at the vertebral column and hip compared to EP no users (both P<0.05), and higher incidence of NTFx at the hip compared to w/o EP new and consistent users (both P<0.05).

Since matching was not performed for U.S. region of residence or race when examined as the full original categorization, logistic regression models were developed to determine if these

variables confounded the group comparisons. The results were the same as the unadjusted comparisons when adjusting for U.S. region of residence or race (results not shown).

Change in pre-index fracture to post-index NTFx

The change in pre-index fracture to post-index NTFx risk is visually presented in **Figure 1** for any site and the unadjusted RR is presented in **Table 2**. The unadjusted RR was significantly lower for any site and each site for EP new users, EP consistent users (except for the upper extremities), and w/o EP new users, suggesting robust risk attenuation of NTFx for these groups. The unadjusted RR was non-significantly elevated for any site and each site (except for the hip) for EP no users.

The RRR for NTFx at any site was significantly lower for EP new users compared to EP no users (RRR=0.35; 95% CI=0.23-0.54) and EP consistent users (RRR=0.70; 95% CI=0.51-0.97) suggesting a larger risk attenuation of NTFx, but was similar compared to w/o EP new users (RRR=0.99; 95% CI=0.73-1.34) (**Table 3**). The RRR for NTFx at any site was significantly lower for EP consistent users compared to EP no users (RRR=0.50; 95% CI=0.32-0.79), but was similar to w/o EP consistent users (RRR=0.81; 95% CI=0.55-1.17). The results were the same after adjusting the models for U.S. region of residence and race (data not shown).

When risk attenuation of NTFx at specific sites was examined, the pattern of results was the same for NTFx of the vertebral column as NTFx at any site, but no significant findings were observed in NTFx risk attenuation of the hip across groups. Both EP new users and EP consistent users showed significant NTFx risk attenuation of the lower extremities compared to EP no users (both RRR=0.28, $P<0.05$), but the change was similar between EP new and consistent users (RRR=1.01; 95% CI=0.42-2.44). EP new users had a significantly lower RRR for NTFx of the upper extremities compared to EP no users (RRR=0.36; 95% CI=0.14-0.91). The results were the same after adjusting the models for U.S. region of residence and race (data not shown).

Sensitivity analysis

The prevalence of pre-index fracture and incidence of post-index NTFx was higher for those exposed to antiseizure medication in the 12.5-month pre-index period for the osteoporosis medication groups, but only reached statistical significance for pre-index fracture for w/o EP consistent users (**Table 4**). The unadjusted RR was similar for those exposed and not exposed to

antiseizure medication within each group except for EP consistent users, where those exposed to antiseizure medication had a significantly lower RR (RR=0.63; 95% CI=0.44-0.91) but those not exposed did not have a significantly lower RR (RR=0.91; 95% CI=0.50-1.65).

Discussion

The findings from this study suggest that osteoporosis medication is associated with a clinically meaningful 12-month NTFx risk attenuation among adults with epilepsy, which mirrored that of the general population without epilepsy. The beneficial effect of osteoporosis medication for adults with epilepsy was observed for all sites, including the vertebral column, hip, lower extremities, and upper extremities. Further, the effect of osteoporosis medication was not altered by exposure to antiseizure medication for adults with epilepsy that were new users of osteoporosis medication. It is important to note that causation cannot be derived from an observational study, especially for determining effectiveness of treatment due to a variety of factors, including unmeasured confounding. Further, this observational study did not examine adverse events or side effects associated with osteoporosis medication. Taken together, study findings provide real world evidence about the effectiveness of osteoporosis medication on site-specific NTFx risk attenuation among a large privately insured cohort of adults ≥50 years of age with epilepsy. However, prior to changing clinical practice and osteoporosis medication prescription, future studies are needed to determine safety and efficacy of osteoporosis medication in relation to the medical and pharmacological complexities associated with epilepsy.

In this sample of privately insured adults ≥50 years of age, 9.1% of the epilepsy group was prescribed an osteoporosis medication. Although 1.69 times higher compared to the group without epilepsy, this is still not addressing the pharmacological needs to augment skeletal robustness for this population. Previous research suggests that one in five adults ≥18 years of age with epilepsy has a prevalent NTFx[6] and three to four out of five adults with epilepsy have low bone mineral density.[3, 4] Importantly, a recent claims-based study using private insurance found that NTFx is associated with an accelerated rate of mortality among adults with epilepsy (70% higher) and compared to adults without epilepsy (41% higher) before and after accounting for potential confounders.[6] In that study,[6] site-specific effects were examined. Although the hip was the most commonly fractured site (consistent with the current study for EP no users), it elicited a significant, although weaker, unadjusted and adjusted association with 12-month mortality for

adults with epilepsy compared to other sites (adjusted hazard ratio [HR]=1.15; $P<0.05$). The lower extremities had the strongest unadjusted and adjusted effect with 12-month mortality (adjusted HR=1.92), followed by the upper extremities (adjusted HR=1.79) and the vertebral column (adjusted HR=1.30) (all $P<0.05$). While osteoporosis medication is prescribed to reduce the risk of NTFx, it is associated with lower risk of mortality.[32] This additional benefit is important for adults with epilepsy given the excessive burden of premature mortality[10-13] that may be exacerbated by NTFx.[6]

In the current study, when examining group specific changes (i.e., RR), significant risk attenuation of NTFx of the vertebral column, hip, lower extremities, and upper extremities was observed for adults with epilepsy that were new users, whereas the same was observed for consistent users with epilepsy except for the upper extremities. Adults with epilepsy that were not prescribed osteoporosis medication is a useful group to examine what would happen to fracture risk without any intervention. This group exhibited an increase in NTFx risk for the vertebral column, lower extremities, and upper extremities, but a decrease in NTFx risk of the hip; although, all these changes were not statistically significant.

When comparing the RRR, or the extent of change in NTFx risk across groups, study findings suggest that newly prescribed osteoporosis medication is associated with a robust decrease in NTFx risk in epilepsy and consistent users with epilepsy still exhibit a clinically meaningful NTFx risk attenuation compared to adults with epilepsy that were not prescribed osteoporosis medication. However, since it was not possible to determine chronicity of osteoporosis medication exposure, results from this group should be interpreted with caution.

For site-specific effects, new users with epilepsy had a larger NTFx risk attenuation at all sites compared to adults with epilepsy that were not prescribed an osteoporosis medication except for the hip. Interestingly, while the change in NTFx risk of the vertebral column, lower extremities, and upper extremities for new users with epilepsy mirrored that of the new users without epilepsy, the change in NTFx risk of the hip was 95% higher for new users with vs. without epilepsy (RRR=1.95). Although not statistically significant, this finding suggests that the NTFx risk attenuation associated with new osteoporosis medication use for this important fracture site is approximately half for adults with vs. without epilepsy. This finding should be interpreted with caution as it is possible that prescription of osteoporosis medication may have

been driven by the type and location of fracture, thus leading to bias from unmeasured confounding.

The causes and pathophysiological mechanisms leading to fractures in epilepsy are complex and multifactorial. For example, seizures account for a considerable portion of fractures (~25%), but the burden of fracture is still elevated for patients with vs. without epilepsy when excluding seizure-related fractures.[33, 34] Antiseizure medications are commonly prescribed to individuals with epilepsy and are well-established risk factors for skeletal fragility,[35] possibly due to a variety of direct and indirect effects on skeletal metabolism, such as altered vitamin D and calcium metabolism, neurological side effects (e.g., gait instability, falls), endocrine disruption, and altered bone turnover.[31] In the current study, the findings were similar for new users with epilepsy when stratified by 12.5-month exposure to antiseizure medication. Interpretations regarding the association with antiseizure medication for the other groups should be done so with caution, as this study was designed to match based on several covariates to EP new users which included antiseizure medication. Therefore, while the EP new user group can be considered representative of this privately insured sample, the other groups may not, especially for the groups without epilepsy. Future studies are needed to determine the efficacy of osteoporosis medication based on the varying pathophysiology leading to skeletal fragility, and if different classes of osteoporosis medication (e.g., bisphosphonates, RANKL inhibitor) elicits differential skeletal effects among adults with epilepsy.

In addition to the observational cohort design leading to potential bias from unmeasured confounding, this study has other limitations. First, information regarding the type, etiology, or time since diagnosis of epilepsy was not possible. Further, accuracy of identifying epilepsy cases in administrative claims data can be less than ideal. Algorithms to identify epilepsy that rely solely on electromyography or magnetic resonance imaging tend to have low positive predictive value, whereas the codes used in the current study tend to have higher positive predictive value.[36, 37] Further, the number of occurrences of the claim with a respective epilepsy code further enhances the positive predictive value;[37] for this study, the positive predictive value is estimated to be ~70-100% based on previous validation studies.[17, 36, 38] Nevertheless, it is possible that some cases were misclassified and the conclusions drawn from this study should be made with caution. Second, chronicity of osteoporosis medication or antiseizure medication was not possible. Third, claims data provides a date of when a prescription was ordered and filled,

but not if the patient took the medication or adhered to the medication dosage and timing. Further, antiseizure medications alone are unable to classify epilepsy status as these medications can be used clinically to treat or manage other conditions, such as neuropathic pain, mood disorders, and other central nervous system disorders. However, it is possible that some individuals in the without epilepsy groups were misclassified, thus diluting the comparisons between epilepsy and non-epilepsy groups. Fourth, there may have been additional intervention or counseling around the time of the first osteoporosis medication prescription. For example, healthcare providers may have talked with the patient or provided information leading to changes in nutrition, smoking, alcohol use, avoidance of risky behaviors, exercise, and rehabilitation. This type of intervention(s) would be less likely to occur for the EP no users group. However, since new and consistent users were compared by status of epilepsy (e.g., new users with vs. without epilepsy), most comparisons were unaffected by this potential issue. Fourth, over-the-counter medications cannot be accounted for using claims data, such as vitamin and/or mineral supplements. Lastly, this study did not examine specific medications or classes of antiseizure medication, such as enzyme-inducing agents, which may have a differential effect on skeletal fragility. Future studies are needed to address this knowledge gap.

In conclusion, osteoporosis medication among privately insured adults ≥50 years of age with epilepsy is associated with a clinically meaningful risk attenuation of NTFx, especially for treatment naïve individuals, which mirrored that of adults without epilepsy. For treatment naïve adults with epilepsy, the beneficial effect was not influenced by a recent 12.5-month exposure to antiseizure medication and was observed at the vertebral column, hip, lower extremities, and upper extremities. Future studies are needed to determine safety, efficacy, timing, and dosing of osteoporosis medication to reduce NTFx risk for all adults with epilepsy.

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Conflict of interest

The author has no conflict of interest to disclose.

Key points

- Skeletal fragility is a major problem for adults with epilepsy; yet, the real world effectiveness of pharmacological osteoporosis therapy is not well-known
- This private claims-based study found that osteoporosis medication was associated with risk attenuation of non-trauma fractures (NTFx) for adults with epilepsy
- The NTFx risk attenuation was present for the vertebral column, hip, lower extremities, and upper extremities
- Treatment naïve adults with epilepsy had the largest risk attenuation of NTFx
- The extent of NTFx risk attenuation was similar to adults without epilepsy

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Figure 1. Unadjusted prevalence of pre-index fracture and incidence of post-index non-trauma fracture (and 95% confidence interval) at any site for propensity matched adults (1:1 matching ratio) by status of epilepsy (EP) and new, consistent, or no users of osteoporosis medication.

Table 1. Baseline descriptive characteristics of propensity matched participants (1:1, n=828/group) by status of epilepsy (EP) and new, consistent, or no users of osteoporosis medication.

	EP new users	EP consistent users	EP no users	w/o EP new users	w/o EP consistent users
	%	%	%	%	%
Age, mean (SD)	69.9 (10.1)	69.6 (9.7)	70.1 (10.2)	70.5 (10.0)	70.3 (10.2)
50-64 years	31.4	32.7	31.5	29.1	31.0
65-79 years	47.6	48.0	46.5	48.0	45.8
≥80 years	21.0	19.3	22.0	23.0	23.2
Sex					
Women	82.1	85.1	82.1	82.0	82.0
Men	17.9	14.9	17.9	18.0	18.0
Race					
White	64.9	66.6	67.6	67.3	65.8

Black	7.3	5.7	6.0	5.6	4.7
Hispanic	11.1	10.8	9.2	12.7	12.1
Asian	2.8	4.0	2.1	2.9	5.6
Unknown/missing	14.0	13.0	15.1	11.6	11.8
US region					
West	34.9	28.5	25.7	32.9	29.8
Midwest	13.9	18.0	20.7	15.5	17.0
South	36.8	35.0	39.1	40.7	40.5
Northeast	14.4	18.5	14.5	11.0	12.7
Elixhauser comorbidity index					
Mean (SD)	4.4 (3.1)	4.4 (3.1)	4.3 (2.8)	4.5 (3.0)	4.3 (2.9)
Median (IQR)	4.0 (2.0-6.0)	4.0 (2.0-6.0)	4.0 (2.0-6.0)	4.0 (2.0-6.0)	4.0 (2.0-6.0)
Glucocorticoid medications	25.2	24.4	23.7	26.3	23.2
Antiseizure medications	64.3	66.7	65.6	64.3	64.6
Osteoporosis medication					
Antiresorptive agents	96.6	97.1	0	95.7	97.3
Anabolic agents	3.4	2.9	0	4.3	2.7

SD, standard deviation; IQR, interquartile range.

Table 2. Risk and unadjusted risk ratio (RR) of pre- and post-index fracture among propensity matched participants (1:1, n=828/group) by status of epilepsy (EP) and new, consistent, or no users of osteoporosis medication.

	EP new users	EP consistent users	EP no users	w/o EP new users	w/o EP consistent users
Pre-index period	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)

Any site	26.1 (23.1, 29.1)	10.8 (8.6, 12.9)	4.7 (3.3, 6.2)	19.3 (16.6, 22.0)	8.1 (6.2, 9.9)
Vertebral column	13.7 (11.3, 16.0)	5.2 (3.7, 6.7)	1.3 (0.5, 2.1)	10.9 (8.7, 13.0)	4.7 (3.3, 6.2)
Hip	7.0 (5.3, 8.7)	3.5 (2.2, 4.8)	1.9 (1.0, 2.9)	4.0 (2.7, 5.3)	1.0 (0.3, 1.6)
Lower extremities	5.0 (3.5, 6.4)	2.8 (1.7, 3.9)	0.9 (0.2, 1.5)	4.0 (2.7, 5.3)	1.5 (0.6, 2.3)
Upper extremities	5.8 (4.2, 7.4)	2.1 (1.1, 3.0)	1.3 (0.5, 2.1)	3.7 (2.4, 5.0)	1.1 (0.4, 1.8)
Post-index period	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)
Any site	12.8 (10.5, 15.1)	7.5 (5.7, 9.3)	6.5 (4.8, 8.2)	9.5 (7.5, 11.5)	7.0 (5.3, 8.7)
Vertebral column	4.8 (3.4, 6.3)	3.1 (2.0, 4.3)	2.3 (1.3, 3.3)	4.6 (3.2, 6.0)	3.6 (2.3, 4.9)
Hip	2.9 (1.8, 4.0)	1.6 (0.7, 2.4)	1.0 (0.3, 1.6)	0.9 (0.2, 1.5)	1.0 (0.3, 1.6)
Lower extremities	2.2 (1.2, 3.2)	1.2 (0.5, 2.0)	1.3 (0.5, 2.1)	1.5 (0.6, 2.3)	0.9 (0.2, 1.5)
Upper extremities	2.3 (1.3, 3.3)	1.3 (0.5, 2.1)	1.5 (0.6, 2.3)	1.8 (0.9, 2.7)	1.1 (0.4, 1.8)
RR (pre- to post-index)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
Any site	0.49 (0.40, 0.61)	0.70 (0.51, 0.95)	1.39 (0.93, 2.07)	0.49 (0.38, 0.64)	0.87 (0.62, 1.21)
Vertebral column	0.35 (0.25, 0.50)	0.61 (0.38, 0.98)	1.73 (0.83, 3.61)	0.42 (0.29, 0.61)	0.77 (0.48, 1.23)
Hip	0.41 (0.26, 0.66)	0.45 (0.24, 0.86)	0.50 (0.22, 1.16)	0.21 (0.09, 0.48)	1.00 (0.38, 2.65)
Lower extremities	0.44 (0.25, 0.76)	0.44 (0.21, 0.91)	1.57 (0.61, 4.03)	0.36 (0.19, 0.70)	0.58 (0.23, 1.47)
Upper extremities	0.40 (0.24, 0.67)	0.65 (0.31, 1.37)	1.09 (0.48, 2.46)	0.48 (0.26, 0.89)	1.00 (0.40, 2.51)

CI, confidence interval.

Table 3. The ratio of the risk ratio (RRR) of pre- to post-index fracture among propensity matched participants (1:1, n=828/group) by status of epilepsy (EP) and new, consistent, or no users of osteoporosis medication.

	Any site	Vertebral column	Hip	Lower extremities	Upper extremities
	RRR (95% CI)	RRR (95% CI)	RRR (95% CI)	RRR (95% CI)	RRR (95% CI)
EP new users vs. EP no users	0.35 (0.23, 0.54)	0.21 (0.10, 0.44)	0.83 (0.22, 1.13)	0.28 (0.09, 0.83)	0.36 (0.14, 0.91)
EP consistent users vs. EP no users	0.50 (0.32, 0.79)	0.35 (0.16, 0.77)	0.89 (0.33, 2.41)	0.28 (0.09, 0.90)	0.60 (0.21, 1.75)
EP new users vs. EP consistent users	0.70 (0.51, 0.97)	0.58 (0.35, 0.97)	0.92 (0.45, 1.90)	1.01 (0.42, 2.44)	0.61 (0.25, 1.47)

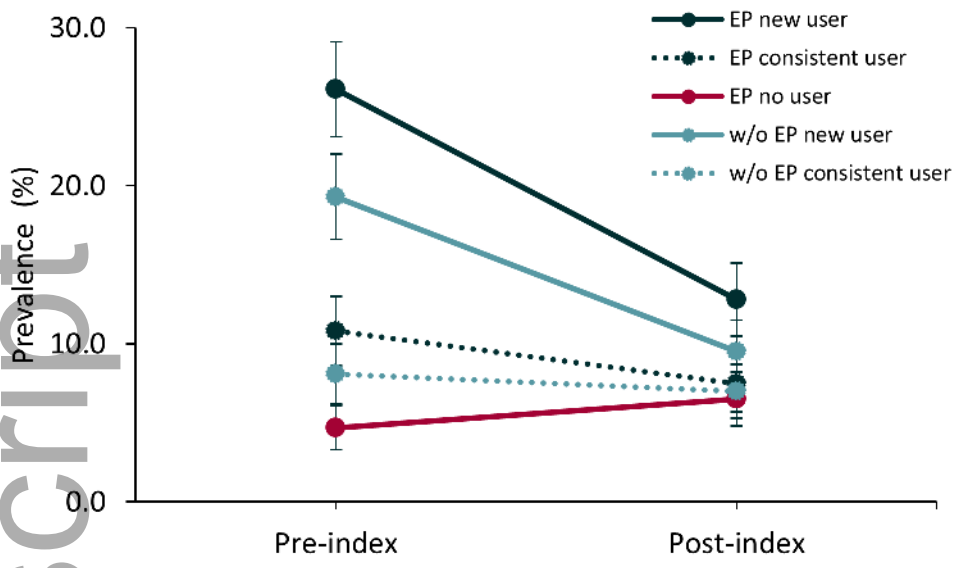
New users, EP vs. w/o EP	0.99 (0.73, 1.34)	0.84 (0.52, 1.35)	1.95 (0.77, 4.92)	1.20 (0.54, 2.70)	0.82 (0.39, 1.72)
Consistent users, EP vs. w/o EP	0.81 (0.55, 1.17)	0.79 (0.46, 1.35)	0.45 (0.16, 1.24)	0.74 (0.25, 2.19)	0.65 (0.23, 1.85)

CI, confidence interval.

Table 4. Risk and unadjusted risk ratio (RR) of pre- and post-index fracture at any site by status of antiseizure medication (ASM) exposure, epilepsy (EP), and new, consistent, or no users of osteoporosis medication.

	EP new users	EP consistent users	EP no users	w/o EP new users	w/o EP consistent users
Pre-index period	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)
ASM exposure					
No	22.6 (17.9, 27.4)	7.6 (4.5, 10.7)	5.6 (2.9, 8.3)	19.3 (14.8, 23.8)	4.8 (2.3, 7.2)
Yes	28.0 (24.2, 31.8)	12.3 (9.6, 15.1)	4.2 (2.5, 5.9)	19.4 (16.0, 22.7)	9.9 (7.4, 12.4)
Post-index period	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)
ASM exposure					
No	11.5 (7.9, 15.1)	6.9 (3.9, 9.9)	7.7 (4.6, 10.8)	7.8 (4.7, 10.8)	4.4 (2.1, 6.8)
Yes	13.5 (10.6, 16.4)	7.8 (5.6, 10.0)	5.9 (3.9, 7.9)	10.5 (7.9, 13.1)	8.4 (6.1, 10.8)
RR (pre- to post-index)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
ASM exposure					
No	0.51 (0.35, 0.74)	0.91 (0.50, 1.65)	1.38 (0.74, 2.56)	0.40 (0.26, 0.64)	0.93 (0.44, 1.94)
Yes	0.48 (0.38, 0.62)	0.63 (0.44, 0.91)	1.39 (0.83, 2.35)	0.54 (0.41, 0.74)	0.85 (0.58, 1.24)

CI, confidence interval.



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