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The effect of levetiracetam and oxcarbazepine on 4-year fragility fracture risk among pre-pubertal and pubertal children with epilepsy

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Summary

Objective: The objective of this study was to determine if two of the commonly prescribed anti-seizure medications (ASM), levetiracetam (LEV) and oxcarbazepine (OXC), were associated with an increased risk of fragility fracture for children with epilepsy when initiating therapy during a crucial period of bone development; i.e., pre- and mid-puberty.

Methods: Claims data from 01/01/2009-12/31/2018 were extracted from Optum Clinformatics® Data Mart. Children aged 4-13 years at baseline with at least 5 years of continuous health plan enrollment were included to allow for a 1-year baseline (e.g., pre-ASM exposure) and 4-years of follow-up. Children with epilepsy that were ASM naïve were grouped based on whether ASM treatment initiation included LEV or OXC. The comparison group included children without epilepsy and without ASM exposure. Crude incidence rate (IR; n per 1,000 person years) and IR ratio (IRR and 95% confidence intervals [CI]) were estimated for non-trauma fracture (NTFx), a claims-based proxy for fragility fracture, for up to 4-years of follow-up. Cox proportional hazards regression estimated the hazard ratio (HR with 95% CI) after adjusting for demographic variables, motor impairment, and baseline fracture.

Results: The crude IR (95% CI) of NTFx was 21.5 (21.2-21.8) for non-ASM users without epilepsy (n=271,346), 19.8 (12.3-27.2) for LEV (n=358), and 34.4 (21.1-47.7) for OXC (n=203). Compared to non-ASM users, the crude IRR of NTFx was similar for LEV (IRR=0.92; 95%CI=0.63-1.34) and elevated for OXC (IRR=1.60; 95%CI=1.09-2.35); the crude IRR of NTFx was elevated for OXC compared to LEV (IRR=1.74; 95% CI=1.02-2.99). The findings were consistent after adjusting for covariates, except when comparing OXC to LEV (HR=1.71; 95%CI=0.99-2.93), which was marginally statistically insignificant (*P*=0.053).

Significance: Initiating OXC, but not LEV, therapy among 4-13 year olds with epilepsy is associated with an elevated risk of fragility fracture. Studies are needed to determine if these children could benefit from adjunct bone fragility therapies.

Keywords: epilepsy; anti-seizure medication; levetiracetam; oxcarbazepine; non-trauma fracture

Introduction

Anti-seizure medication (ASM) is a necessary and efficacious therapy to control seizures for individuals with epilepsy, but can create new medical problems, including bone fragility through a variety of mechanisms.[1-4] Many studies have found a robust association between ASM therapy and bone fragility for children and adults with epilepsy,[5-8] which may be related to the specific type of ASM,[5, 7] the number of concurrent ASMs used,[5] and the duration of ASM exposure.[9] Recent epidemiologic studies have reported that fragility fractures are associated with premature cardiorespiratory morbidity and mortality for adults with epilepsy,[10-12] underscoring the need to understand and counteract the ASM-induced bone fragility to maximize bone health throughout the lifespan for individuals with epilepsy.

Growth and development is an essential stage of life for accumulating bone mass and organizing architectural properties, especially around puberty,[13, 14] which collectively harmonize to establish a permanent skeletal framework.[15] ASM exposure could disrupt typical bone development and prevent essential bone growth, leading to an irreversible loss of bone strength and enhanced bone fragility in the adult years.[16] Studies examining the unique effect of ASM on bone turnover markers by pubertal status have found conflicting results, which may be due to the difference in the ASM and bone turnover markers that were investigated and the relatively small sample sizes.[17, 18] In a recent study of >1,200 children with epilepsy initiating ASM therapy, the 4-year risk of fragility fracture was elevated compared to a matched control group without ASM exposure, especially for children with epilepsy initiating ASM therapy around the time of puberty.[19] While these new findings suggest an age effect of initiating ASM therapy on bone fragility for children with epilepsy, ASM exposure was examined as a "catch all" group, and individual ASMs were not examined, which can have unique mechanisms of action impacting bone metabolism.

Levetiracetam (LEV) and oxcarbazepine (OXC) are the two most commonly prescribed ASMs to children and adolescents with epilepsy.[19, 20] Currently, data regarding the effect of LEV

and OXC on bone fragility among pre-pubertal and pubertal children with epilepsy is limited and contradictory. Several studies with small sample sizes in children with epilepsy treated with LEV reported un-altered biomarkers of bone metabolism and bone mass,[21-23] whereas a rat model treated with low-dose LEV reported reduced bone strength in the femoral neck, despite no changes in bone mass.[24] Studies have reported that OXC treatment may reduce levels of relevant bone metabolic biomarkers (e.g., osteocalcin, vitamin D)[18, 22, 25] and bone mass in children with epilepsy.[18] However, not all studies show a negative effect of OXC treatment on biomarkers or bone mass.[26, 27]

A major consequence of bone fragility is sustaining a fragility fracture. Determining the effect of LEV and OXC therapy on fragility fracture risk could help clinicians identify patients who may benefit from adjunct bone fragility therapies, especially for pre-pubertal and pubertal children with epilepsy who may be more susceptible to ASM-induced bone fragility due to the disruption of essential bone development.[19] The objective of this observational cohort study was to determine if the 4-year incidence of fragility fracture was increased for pre-pubertal and pubertal children with epilepsy that were initiating LEV or OXC therapy.

Methods

The data source used in this study does not contain information about the cause, energy, or event that lead to a fracture. Therefore, a proxy for a fragility fracture is derived from a fracture without accompanying trauma indicating high-impact (e.g., vehicle accident) and defined here as non-trauma fracture (NTFx).[10] While NTFx in the clinical setting can represent spontaneous and minimal-trauma fractures, NTFx in this study reflects a fracture without accompanying trauma codes.

Data source

This retrospective observational cohort study used individual-level claims from the full calendar years of 2009 to 2018, which was obtained from the Optum's de-identified Clinformatics® Data Mart Database. This is a U.S. national administrative claims database that contains medical and outpatient pharmacy claims from insured beneficiaries that have commercial or Medicare Advantage health plans.[28] For children to be enrolled in a private payer health plan, their caregiver can be of any age, disability status, or income, and either pays for

coverage out of pocket or is covered by their employer. Data are de-identified and the University Institutional Review Board approved this study as a non-regulated study.

Sample selection

All medical conditions, such as epilepsy and NTFx, were identified using the International Classification of Diseases, Ninth and Tenth Revision (ICD-9 and ICD-10), Clinical Modification codes, to account for the change in reporting ICD-10 codes that occurred nationally on October 1, 2015. Incidence of NTFx up to 4 years was examined in order to allow enough follow-up time to capture differences in NTFx incidence among groups. Given the greater potential for life-long adverse bone fragility effects by initiating ASM therapy prior to or during puberty, this study included children that were 4 to 13 years of age at baseline.[19] Children were included if they had at least 5 years of continuous health plan enrollment to obtain a 1-year baseline period prior to their start date of follow-up, which is a common time period used for claims-based research studies to obtain baseline data, and 4-years of follow-up for incidence of NTFx, as previously described.[19]

There were three groups: children with epilepsy that were new ASM users of (1) LEV or (2) OXC, and (3) children without epilepsy and that were not exposed to ASM for their entire 5-year study period, as ASM therapy can be used to clinically manage conditions other than epilepsy. The non-ASM users without epilepsy served as a comparison group reflecting the general pediatric population with private insurance, to determine how LEV or OXC initiation impacts NTFx incidence relative to what is typical.

Initiation of LEV or OXC therapy was identified by the first outpatient pharmacy claim for LEV and OXC in the calendar years of 2010 to 2014, and without an outpatient pharmacy claim for LEV and OXC in the 1-year prior in order to isolate treatment naïve children. Epilepsy was identified by ≥1 reimbursement claim (inpatient, outpatient, or emergency department) for "epilepsy and recurrent seizures", which coupled with ASM prescription, enhances specificity of epilepsy detection in administrative claims data up to 94%.[29] Further, the positive predictive value is up to 88% when using this study's algorithm of ≥1 claim for "epilepsy and recurrent seizures" and ≥1 claims for any ASM.[29] Unfortunately, administrative claims do not contain or reliably code data for the type, etiology, or duration of epilepsy (e.g., nearly 50% of a privately insured epilepsy cohort identified as having an "unspecified" epilepsy condition[10]). Therefore, it

was not possible to account for the clinically relevant types of epilepsy (e.g., generalized, focal). The start date of follow-up for new LEV or OXC users with epilepsy was the date of their first claim for LEV or OXC. The start date for the comparison group was randomly assigned between January 1, 2010 and December 31, 2014.

Outcome: 4-year incidence of NTFx

Incidence of NTFx up to 4-years was identified as a fracture that occurred at the vertebral column, hip (including proximal femur), non-proximal femur, tibia/fibula, humerus, ulna/radius, or an unspecified site that did not have an accompanying code indicating trauma (e.g., car accident) 7 days before to 7 days after the fracture claim date.[10, 11, 30, 31] Children that did not sustain an NTFx were right censored at the end of the 4-year follow-up period.

Covariates

Covariates were selected based on the relevance to epilepsy, bone fragility, and availability and reliability in claims databases. Demographic variables included age, sex, race/ethnicity, and U.S. region of residence. Pre-existing bone fragility was accounted for by all-cause fracture of any location in the 1-year baseline period and evidence of motor impairment. Motor impairment cannot be directly measured from individual claims. Therefore, a proxy for motor impairment was developed, which included the presence of co-occurring cerebral palsy, spina bifida, or use of a wheelchair using ICD codes.[32] Guided by previous studies,[12, 30] osteoporosis medications were examined in the 1-year baseline period and during the 4-year follow-up (medications listed in reference[19]). However, since there was no evidence of an outpatient pharmacy prescription of osteoporosis medication throughout each person's 5-year study period, this variable was not carried forward in the analysis.

Statistical analysis

Baseline descriptive characteristics were summarized for each group and compared using the Chi-Squared test for categorical variables or the independent t-test for continuous variables. The crude incidence rate (IR) with 95% confidence interval (CI) of any NTFx was calculated for each group as the number of NTFx events divided by the amount of person years and expressed as n per 1,000 person years. The crude IR ratio (IRR) with 95% CI[33] of any NTFx was estimated

for the LEV and OXC groups separately, comparing to non-ASM users without epilepsy. Secondary analysis compared the crude IRR between LEV and OXC groups. Due to the small number of NTFx events, site-specific NTFx incidence was not examined and sex effects were unable to be examined. However, in our previous study using a similar methodology and sample, there was no evidence of an effect by sex for ASM and NTFx risk for children with vs. without epilepsy.[19]

Cox proportional hazards regression was used to estimate the hazard ratio (HR) of NTFx incidence after adjusting for covariates, comparing the LEV and OXC groups to non-ASM users without epilepsy. Secondary analysis compared the HR between LEV and OXC groups. Since NTFx is a relatively rare outcome leading to statistical limitations on the number of covariates that can be used in a single statistical model,[34] only covariates that were significantly different between groups were included for adjustment, as it was not possible to adjust for all covariates in a single model. Possible interactions between group with age and sex were examined by conducting separate analyses for age or sex (to estimate group effects) and including the product terms in the Cox model (to test for interactions).

Sensitivity analysis

Accounting for potential confounding can be challenging in pediatric fracture incidence studies due to the inability to statistically adjust for a large number of covariates, which could lead to biased regression coefficients. In order to account for covariates that may influence the association between group with incidence of NTFx without the need for statistically adjusting for several covariates, two propensity score matched groups were constructed using non-ASM users without epilepsy as the comparison group for the LEV and OXC groups separately. Therefore, LEV had its own matched group ($LEV_{matched}$) and OXC had its own matched group ($OXC_{matched}$), pulling from the same comparator group (i.e., non-ASM users without epilepsy). Propensity scores were computed based on age, sex, race/ethnicity, U.S. region of residence, motor impairment, and baseline fracture using the PSMATCH procedure in SAS 9.4 (SAS Institute, Cary, NC, USA), as described previously.[12, 19] The groups were each matched 1:2 (case:control) in a random fashion using a standard caliper of ≤0.25, without losing any participants from the LEV or OXC groups to limit bias. Balance in matching was assessed using a standardized mean difference of ≤0.10 and compared using the Chi-Squared test for categorical variables or the

independent t-test for continuous variables to ensure balance in matching. The crude IR of any NTFx was estimated for each group as described above, and the crude IRR of any NTFx was estimated comparing LEV to $LEV_{matched}$ and OXC to $OXC_{matched}$. To visually represent the incidence of any NTFx for the groups, Kaplan-Meier plots (with 95% CI) were constructed, as the crude IRR is a numerical approximation of the unadjusted HR.

Analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, USA) and $P<0.05$ was considered statistically significant.

Results

Baseline descriptive characteristics of children with epilepsy initiating LEV (n=358) or OXC (n=203) therapy, and non-ASM users without epilepsy (n=271,346) are presented in **Table 1**. Compared to non-ASM users without epilepsy, LEV and OXC groups had a significantly higher prevalence of motor impairment, while LEV had a significantly higher proportion of Black children and OXC had a significantly higher proportion of boys (all $P<0.05$). Compared to LEV, OXC had a higher proportion of boys ($P<0.05$). While not presented to preserve patient de-identification, very few children in the LEV (1.4%) and OXC (2.5%) groups initiating ASM therapy showed evidence that initiation was polytherapy.

In the 4-year follow-up, there were 27 (7.5%) NTFx events from the LEV group, 26 (12.8%) NTFx events in the OXC group, and 22,304 (8.2%) NTFx events from non-ASM users without epilepsy. The mean (standard deviation) follow-up time was 1,393 (261) for LEV, 1,358 (307) for OXC, and 1,395 (247) for non-ASM users without epilepsy. The distribution of NTFx by site was similar between groups, with the majority occurring at the forearm for LEV (55.1%), OXC (63.0%), and non-ASM users without epilepsy (54.6%), followed by the tibia/fibula (17.2%, 22.2%, and 20.1%, respectively).

The crude IR and IRR of any NTFx are presented in **Table 2**. Compared to non-ASM users without epilepsy, the incidence of any NTFx was similar for LEV (IRR=0.92; 95% CI=0.63-1.34) and 60% higher for OXC (IRR=1.60; 95% CI=1.09-2.35). Compared to LEV, the incidence of any NTFx was 74% higher for OXC (IRR=1.74; 95% CI=1.02-2.99).

The HR of any NTFx after adjusting for covariates that were significantly different between groups is presented in **Table 3**. After adjusting for race/ethnicity and motor impairment,

the incidence of NTFx was not different between LEV and non-ASM users without epilepsy (HR=0.90; 95% CI=0.62-1.32). After adjusting for sex and motor impairment, the incidence of NTFx was elevated for OXC compared to non-ASM users without epilepsy (HR=1.51; 95% CI=1.03-2.22). After adjusting for sex, the incidence of NTFx was elevated for OXC compared to LEV (HR=1.71; 95% CI=0.99-2.93), but this was marginally statistically insignificant (*P*=0.053).

Sensitivity analysis

Balanced matching was achieved using a 1:2 matching ratio for all variables for both sets of matched groups (i.e., LEV and $LEV_{matched}$; OXC and $OXC_{matched}$) (**Table 4**). The crude IR and IRR of any NTFx are presented in **Table 5** and visually presented in **Figure 1**. The comparison of LEV and $LEV_{matched}$ is consistent with the primary analysis (IRR=0.91; 95% CI=0.58-1.44). However, the comparison of OXC and $OXC_{matched}$ differed slightly from the primary analysis, in that after balancing covariates between groups, the incidence of NTFx was more elevated for OXC as compared to $OXC_{matched}$ (IRR=2.07; 95% CI=1.20-3.57). To be sure this was not an issue of selection bias when matching participants from non-ASM users without epilepsy group to the OXC group, we re-randomized the order of the non-ASM users without epilepsy and performed analyses nine additional times. There was balance in matching all variables each time. All ten analyses lead to the same conclusion showing a large effect estimate suggesting an elevated incidence of NTFx for OXC compared to $OXC_{matched}$, with crude IRRs ranging from 1.43 to 2.17, which is consistent with the conclusion drawn from the primary analysis.

Discussion

The main finding from this study is that initiating OXC therapy, but not LEV therapy, was associated with an elevated 4-year risk of NTFx among pre-pubertal and pubertal children with epilepsy, even after accounting for demographics, motor impairment, and fracture history in the 1-year baseline period.

There are a variety of mechanisms in which ASMs may alter bone metabolism, including catabolism of vitamin D, increasing parathyroid hormone levels,[1] exhibiting adverse effects on sex steroids,[2] having a direct link and influence on bone cells,[3] and increasing levels of homocysteine,[4] which has been shown to reduce bone strength through a cascade of biological

events.[35] It is generally believed that OXC is a weak inducer of liver enzymes and alters thyroid function,[21] leading to secondary hyperparathyroidism via altered metabolism of vitamin D, calcium, and phosphorous. If LEV interacts with bone metabolism, the mechanisms of action are not well known. In regards to development, Lin et al.[36] has shown that treatment after 1 year with OXC and/or valproate was associated with reduced growth velocity among children with epilepsy aged 1-18 years, with evidence of dysregulated bone turnover. This is consistent with a previous study that found long-term treatment with ASM led to suppressed linear bone growth and formation; although, the ASM was neither LEV or OXC.[37] Further, rat growth plate chondrocytes cultured with various ASMs found that valproic acid, but not LEV or OXC, lead to increased chondrocyte apoptosis,[38] which may be an additional mechanism in which some ASMs can hinder bone growth.

While it is important to know which ASMs disrupt bone metabolism, knowing when during growth that ASMs play a more deleterious and lasting role on bone fragility is also of clinical relevance. The hypothesis is that initiating some ASMs, such as OXC, may disrupt essential bone growth, especially around puberty, leading to an un-recoverable deficit in certain structural properties leading to permanently weak bones. Bone strength can be operationalized as the interplay among several bone properties, such as, but not limited to, bone architecture, size, shape, mass, and material qualities.[39] Unfortunately, much of the bone-focused research for children with epilepsy has been confined to bone mass and biomarkers of bone metabolism. While these bone properties are important, relying on these measures alone provides an incomplete assessment of the structural and biological mechanisms that explain bone strength and fragility for this pediatric population. Future research is needed to understand how certain ASMs impact bone fragility beyond bone mass and the underlying biological influence (e.g., excess resorption and/or inadequate formation), and how to best counteract the iatrogenic mechanism (e.g., targeting bone formation mid-puberty to promote periosteal expansion).

Consistent with our previous study,[19] we found no evidence of osteoporosis medication for any participant, but especially for children in the OXC group, to supplement the potential iatrogenic association of OXC on bone fragility. However, many osteoporosis medications would be off-label in children <18 years old. Additionally, vitamin D and calcium supplements were not examined in the current study as these supplements are often obtained “over the counter”, which is information not available in claims data. We were therefore unable to identify

if the clinical team caring for the child with epilepsy recommended vitamin D and/or calcium supplementation to counteract the negative effect of ASM, especially OXC, on bone fragility. This is important as it is not uncommon for children with epilepsy to have co-occurring neurodevelopmental conditions, such as cerebral palsy.[40] Children with cerebral palsy have notable bone fragility, with the extent of fragility associated with the severity of cerebral palsy.[41, 42] The difficulty in managing epilepsy in children with cerebral palsy is that, while LEV may be a good option to not exacerbate their bone fragility, side effects of LEV include altering mood, anxiety, and irritability. Mental health disorders are also a major problem for the population with cerebral palsy,[43, 44] in which clinicians should be aware of when deciding on a treatment course. A study in children with severe cerebral palsy that had epilepsy and were taking ASMs >2 years reported that vitamin D and calcium supplementation improved bone mass compared to controls.[45] The children were taking a variety of combinations of many ASMs, which did not include LEV or OXC. It is therefore unknown if the supplementation "rescued" ASM-induced altered vitamin D metabolism, or if the bone mass gain was due to other effects. More work is needed to understand how best to manage epilepsy and support bone growth during the critical period of pubertal bone gain, especially for children with co-occurring neurodevelopmental conditions or who are non-ambulatory.

The major strength of this study is the relatively large sample size that allowed for analysis of the effect of initiating specific ASMs on fracture incidence for children. While it is not possible to account for all relevant factors (e.g., activity, body composition, diet) in a single study due to statistical and claims-data limitations, the large sample size allowed for us to account for several relevant factors via two complementary analytic designs (i.e., covariate-adjustment and matching), which found similar results. This is a strength given that bone-focused studies in the field are often limited in their ability to account for several relevant factors due to a restricted sample size.

The study limitations must be discussed. First, we were unable to examine analyses by sex. While there are sex differences in how and when bone develops, we found no statistical evidence of a sex interaction in the current study, which is consistent with our previous study using a similar methodology with a "catch all" ASM exposure group.[19] Second, claims data provides information on whether or not a prescription was filled, but not whether the child took the medication and adhered to the guidelines. Further, we did not account for medication

persistence. While it is not uncommon for individuals with epilepsy to discontinue, switch, or augment (e.g., polytherapy) their ASM therapy, a previous claims-based study found that ASM persistence was highest when first-line treatment was with LEV or OXC, but that study included individuals across the lifespan and was not specific to children.[20] Nevertheless, if medication persistence was poor resulting in discontinuation or switching to LEV, the estimates reported in this study would be conservative for OXC. On the other hand, if OXC switched to other ASMs known to negatively impact bone metabolism, such as some potent enzyme-inducing ASMs, that would inflate the present findings for OXC, but this is anticipated to be unlikely; other enzyme inducing ASMs are often avoided in clinical practice in the pediatric population when possible. Additionally, vitamin D and calcium supplementation was not included as they are not able to be accurately captured using claims data. For example, many individuals taking a supplement may obtain them over the counter and not through a physician's prescription, decreasing sensitivity of capturing supplementation using claims data. Third, since the data was ascertained from a privately insured sample, the findings may not be generalizable to other insured (e.g., Medicaid) or uninsured children with epilepsy, as they may represent a slightly more affluent sector of the U.S. population.

In conclusion, the 4-year incidence of fragility fracture is elevated for pre-pubertal and pubertal children with epilepsy initiating OXC therapy, but not LEV therapy. While OXC treatment is often necessary for managing seizures, clinicians should be aware of the iatrogenic association of OXC on fragility fracture risk for pre-pubertal and pubertal children with epilepsy. Future studies are needed to determine if pre-pubertal and pubertal children with epilepsy initiating OXC therapy could benefit from adjunct therapies to augment bone development.

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Conflict of interest

None of the authors has any conflict of interest to disclose.

Key Points

- Some anti-seizure medications can impede bone metabolism leading to increased fracture risk, especially during development when bone is rapidly growing
- Levetiracetam (LEV) and oxcarbazepine (OXC) are often prescribed for treating epilepsy; yet, data regarding their effect on bone fragility is limited
- Pre-pubertal and pubertal children with epilepsy initiating OXC, but not LEV, had an elevated 4-year incidence of fragility fracture
- Pre-pubertal and pubertal children with epilepsy initiating OXC therapy may benefit from adjunct bone fragility therapies
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Figure 1. Kaplan-Meier plots (lines) and 95% confidence limits (shaded area) of 4-year incidence of non-trauma fracture among 4-13 year olds with epilepsy (blue) initiating (A) levetiracetam or (B) oxcarbazepine as compared to their own propensity score matched group (1:2 matching ratio) of children without epilepsy and without anti-seizure medication exposure (red).

Table 1. Baseline descriptive characteristics of children with epilepsy initiating levetiracetam (LEV) or oxcarbazepine (OXC), and children without epilepsy and anti-seizure medication (ASM) exposure.

	LEV (n=358)	OXC (n=203)	Non-ASM users without epilepsy (n=271,346)

	% (n)	% (n)	% (n)
Age, mean (SD)	8.6 (3.0)	8.7 (2.7)	8.7 (2.9)
4-6 years	30.5 (109)	23.7 (48)	27.6 (74848)
7-10 years	38.8 (139)	48.8 (99)	39.9 (108232)
11-13 years	30.7 (110)	27.6 (56)	32.5 (88266)
Sex		[1,2]	
Girls	46.1 (165)	37.0 (75)	48.7 (132146)
Boys	53.9 (193)	63.0 (128)	51.3 (139200)
Race/ethnicity	[1]		
White	68.2 (244)	69.5 (141)	67.5 (183105)
Black	10.3 (37)	6.4 (13)	6.3 (17197)
Hispanic	8.1 (29)	9.9 (20)	11.2 (30288)
Asian	3.9 (14)	6.9 (14)	5.7 (15568)
Other/unknown	9.5 (34)	7.4 (15)	9.3 (25188)
US region			
West	19.0 (68)	18.2 (37)	22.0 (59563)
Midwest	29.9 (107)	28.1 (57)	28.9 (78355)
South	41.3 (148)	44.3 (90)	39.4 (106900)
Northeast	9.8 (35)	9.4 (19)	9.8 (26528)
Motor impairment	9.8 (35)[1]	12.3 (25)[1]	0.3 (828)
Baseline fracture	3.1 (11)	[3]	2.5 (6658)

SD, standard deviation. [1]$P<0.01$ compared to non-ASM users without epilepsy. [2]$P<0.05$ compared to LEV. [3]N≤10 cases and not presented for de-identification purposes.

Table 2. Crude incidence rate (IR) and IR ratio (IRR) for non-trauma fracture (NTFx) among children with epilepsy initiating levetiracetam (LEV) (n=358) or oxcarbazepine (OXC) (n=203), and children without epilepsy and anti-seizure medication (ASM) exposure (n=271,346).

	NTFx cases	Crude IR	Crude IRR	Crude IRR
	n	N per 1,000 person years (95% CI)	IRR (95% CI)	IRR (95% CI)
Non-ASM users	22,304	21.5 (21.2, 21.8)	Reference	-

without epilepsy				
LEV	27	19.8 (12.3, 27.2)	0.92 (0.63, 1.34)	Reference
OXC	26	34.4 (21.2, 47.7)	1.60 (1.09, 2.35)	1.74 (1.02, 2.99)

CI, confidence interval.

Table 3. Adjusted hazard ratio (HR) for non-trauma fracture (NTFx) among children with epilepsy initiating levetiracetam (LEV) (n=358) or oxcarbazepine (OXC) (n=203), and children without epilepsy and anti-seizure medication (ASM) exposure (n=271,346).

	Model 1	Model 2	Model 3
	HR (95% CI)	HR (95% CI)	HR (95% CI)
Non-ASM users without epilepsy	Reference	Reference	-
LEV	0.90 (0.62, 1.32)	-	Reference
OXC	-	1.51 (1.03, 2.22)	1.71 (0.99, 2.93)

CI, confidence interval. Model 1 adjusted for race/ethnicity and motor impairment. Model 2 adjusted for sex and motor impairment. Model 3 adjusted for sex.

Table 4. Baseline descriptive characteristics of children with epilepsy initiating levetiracetam (LEV) or oxcarbazepine (OXC) and their propensity score matched (1:2) comparison group.

	LEV (n=358)	$LEV_{matched}$ (n=716)	OXC (n=203)	$OXC_{matched}$ (n=406)
	% (n)	% (n)	% (n)	% (n)
Age, mean (SD)	8.6 (3.0)	8.8 (3.0)	8.7 (2.7)	8.9 (2.7)
4-6 years	30.5 (109)	28.1 (201)	23.7 (48)	21.9 (89)
7-10 years	38.8 (139)	39.3 (281)	48.8 (99)	48.0 (195)
11-13 years	30.7 (110)	32.7 (234)	27.6 (56)	30.1 (122)
Sex				
Female	46.1 (165)	43.2 (309)	37.0 (75)	37.0 (150)
Male	53.9 (193)	56.8 (407)	63.0 (128)	63.0 (256)
Race/ethnicity				
White	68.2 (244)	69.0 (494)	69.5 (141)	70.0 (284)

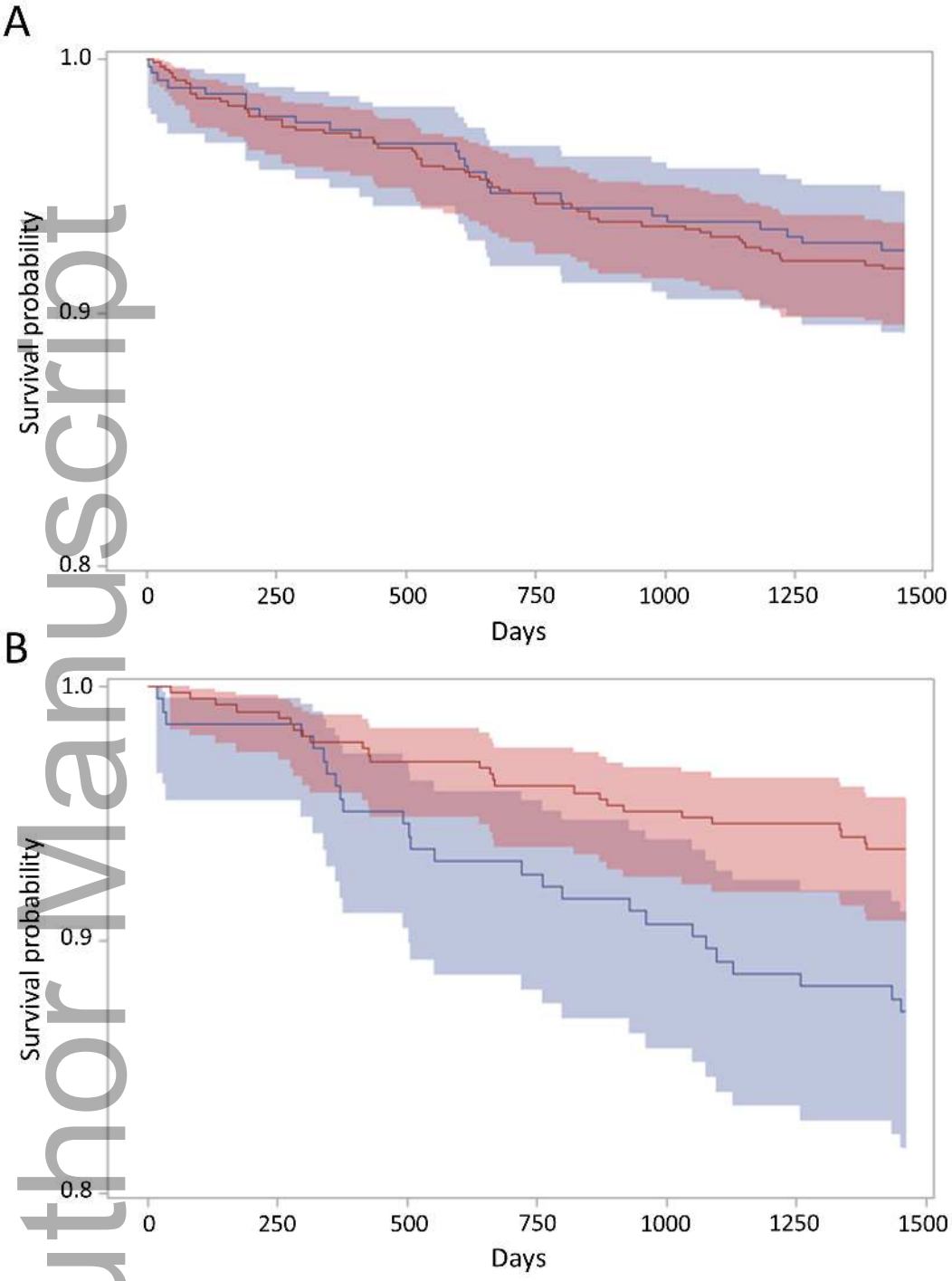
Black	10.3 (37)	9.5 (68)	6.4 (13)	6.4 (26)
Hispanic	8.1 (29)	9.5 (68)	9.9 (20)	9.6 (39)
Asian	3.9 (14)	5.2 (37)	6.9 (14)	5.2 (21)
Other/unknown	9.5 (34)	6.8 (49)	7.4 (15)	8.9 (36)
US region				
West	19.0 (68)	19.0 (136)	18.2 (37)	18.0 (73)
Midwest	29.9 (107)	30.0 (215)	28.1 (57)	28.1 (114)
South	41.3 (148)	41.5 (297)	44.3 (90)	44.1 (179)
Northeast	9.8 (35)	9.5 (68)	9.4 (19)	9.9 (40)
Motor impairment	9.8 (35)	9.8 (70)	12.3 (25)	12.3 (50)
Baseline fracture	3.1 (11)	3.1 (22)	[1]	2.7 (11)

SD, standard deviation. [1]N≤10 cases and not presented for de-identification purposes. All variables are balanced between the respective groups with $p>0.05$.

Table 5. Crude incidence rate (IR) and IR ratio (IRR) for non-trauma fracture (NTFx) among children with epilepsy initiating levetiracetam (LEV) (n=358) or oxcarbazepine (OXC) (n=203) and their propensity score matched (1:2) comparison group.

	NTFx cases	Crude IR	Crude IRR
	n	N per 1,000 person years (95% CI)	IRR (95% CI)
$LEV_{matched}$	59	21.7 (16.1, 27.2)	Reference
LEV	27	19.8 (12.3, 27.2)	0.91 (0.58, 1.44)
$OXC_{matched}$	26	16.6 (10.2, 23.0)	Reference
OXC	26	34.4 (21.2, 47.7)	2.07 (1.20, 3.57)

CI, confidence interval.



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