Seizure: European Journal of Epilepsy 109 (2023) 20–25

Contents lists available at ScienceDirect

Seizure: European Journal of Epilepsy

journal homepage: www.elsevier.com/locate/seizure

Association of first anti-seizure medication choice with injuries in older adults with newly diagnosed epilepsy

Leah J. Blank [a,b,*], Parul Agarwal [a,b], Churl-Su Kwon [c], Nathalie Jetté [a,b]

[a] Department of Neurology, Division of Health Outcomes & Knowledge Translation Research, Icahn school of Medicine at Mount Sinai, One Gustave L. Levy Place, Box 1137, New York, NY, United States
[b] Department of Population Health and Policy, Institute for Healthcare Delivery, Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, Box 1077, New York, NY, United States
[c] Departments of Neurology, Epidemiology, Neurosurgery and the Gertrude H. Sergievsky Center, Columbia University, 622 West 168th Street, New York, NY PH19-106, United States

ARTICLE INFO

Keywords:
Seizure
Older adults
Polypharmacy
Injury
Falls

ABSTRACT

Background: Epilepsy incidence increases exponentially in older adults, who are also at higher risk of adverse drug effects. Anti-seizure medications (ASM) may be associated with sedation and injuries, but discontinuation can result in seizures. We sought to determine whether there was an association between prescribing non-guideline concordant ASM and subsequent injury as this could inform care models.
Methods: Retrospective cohort study of adults 50 years or older with newly-diagnosed epilepsy in 2015–16, sampled from the MarketScan Databases. The outcome of interest was injury within 1-year of ASM prescription (e.g., burns, falls) and the exposure of interest was ASM category (recommended vs. not recommended by clinical guidelines). Descriptive statistics characterized covariates and a multivariable Cox-regression model was built to examine the association between ASM category and subsequent injury.
Results: 5,931 people with newly diagnosed epilepsy were prescribed an ASM within 1-year. The three most common ASMs were: levetiracetam (62.86%), gabapentin (11.73%), and phenytoin (4.45%). Multivariable Cox-regression found that medication category was not associated with injury; however, older age (adjusted hazard ratio (AHR) 1.01/year), history of prior injury (AHR 1.77), traumatic brain injury (AHR 1.55) and ASM polypharmacy (AHR 1.32) were associated with increased hazard of injury.
Conclusions: Most older adults appear to be getting appropriate first prescriptions for epilepsy. However, a substantial proportion still receives medication that guidelines suggest avoiding. In addition, we show that ASM polypharmacy is associated with an increased hazard of injury within 1- year. Efforts to improve prescribing in older adults with epilepsy should consider how to reduce. both polypharmacy and exposure to medications that guidelines recommend avoiding.

1. Introduction

Anti-seizure medications (ASMs) are commonly prescribed in older adults as the risk of recurrent unprovoked seizures (epilepsy incidence) in the adult population increases exponentially in older age [1,2]. Resultantly, seizure prevalence approximately doubles between age 50 and 80 and commonly co-occurs with other comorbidities such as cerebrovascular or neurodegenerative disease [3]. Older adults may be particularly vulnerable to the side effects of ASMs because of aging-associated metabolic changes. In addition, they may have lower cognitive reserve, undetected/undiagnosed neurodegeneration and often take other central nervous system (CNS)-active medications. Even without these age-associated factors, adults with seizures are at a higher risk of injury and this may be compounded by medication choice [4–6].

Anti-seizure medications are the primary treatment modality for seizure. Over 95% of persons with epilepsy are on an ASM and attribute their improvement to medication [7]. The effectiveness of ASMs [8], combined with clinical inertia (the failure to intensify or de-intensify therapy when appropriate)[9] and the risk of recurrent seizures with drug switching or removal [10–13], mean that choosing the initial

* Corresponding author at: Department of Neurology, Division of Health Outcomes & Knowledge Translation Research, Icahn school of Medicine at Mount Sinai, One Gustave L. Levy Place, Box 1137, New York, NY, United States.
E-mail address: leah.blank@mssm.edu (L.J. Blank).

https://doi.org/10.1016/j.seizure.2023.05.006
Received 1 March 2023; Received in revised form 5 May 2023; Accepted 7 May 2023
Available online 7 May 2023

medication well is particularly important. Limited guidelines exist for ASM choice in older adults but recent studies show adherence to these is mixed [14–17].

In this study we sought to determine, in older adults, whether there was an association between prescribing a non-guideline concordant ASM for newly diagnosed epilepsy and subsequent injury.

2. Materials and methods

2.1. Study design and data source

MarketScan's Commercial and Medicare Databases (2013–2017) was used to perform a retrospective observational study. MarketScan Databases are employer sponsored claims-based datasets that allow tracking of individuals across institutions and longitudinally over time through outpatient and inpatient medical claims, as well as pharmacy claims and enrollment information. The MarketScan Databases include patients from across the U.S. and across a variety of insurance types, from commercial insurance (typically working age individuals and their dependents) as well as Medicare (using the Medicare Supplemental Database). These databases provide data that are generalizable to the insured US population due to their broad geographic reach, insurance diversity, and number of individuals represented (more than 100 million lives).

2.2. Cohort identification

Adults 50 years of age or greater with newly diagnosed epilepsy were identified from Marketscan's Commercial and Medicare Databases 2015–16. Epilepsy was defined using a previously validated method: International Classification of Diseases, Ninth or Tenth Revision (ICD-9-CM or 10-CM) diagnosis codes for epilepsy or convulsion (345.xx/780.3x or G40.xx/R56.xx) and a minimum 30 day supply prescription filled for an ASM (lamotrigine, levetiracetam, zonisamide, carbamazepine, oxcarbazepine, esliscarbazepine, topiramate, lacosamide, brivaracetam, valproic acid, phenytoin, felbamate, phenobarbital, vigabatrin, rufinamide, clobazam, clonazepam, lorazepam, midazolam, diazepam, cannabidiol, gabapentin, pregabalin) within 1 year of the diagnosis [18,19]. To focus on newly diagnosed epilepsy, after identifying those who met the diagnostic criteria in 2015 or 2016, we then excluded anyone with an epilepsy-related diagnosis code or ASM prescription in the preceding 2 years (Fig. 1). In other sensitivity analyses (see Supplementary Table 2) we excluded only ASMs that are mostly used for epilepsy (lamotrigine, levetiracetam, zonisamide, carbamazepine, oxcarbazepine, esliscarbazepine, topiramate, lacosamide, brivaracetam, valproic acid, phenytoin, felbamate, phenobarbital, vigabatrin, rufinamide, clobazam) within the prior two years in order to see if excluding medications commonly prescribed for non-epilepsy indications was significantly influencing results.

2.3. Outcome measures

The primary outcome measured was injury within one year of ASM prescription. Injury was defined using previously published ICD-9-CM and ICD-10-CM codes for injuries, submersions, burns, accidental falls, and motor vehicle accidents (see Supplementary Table 1) [4,20].

2.4. Exposure of interest

Anti-seizure medications were categorized according to the American Academy of Neurology/ American Epilepsy Society guidelines for the Treatment of New-onset Epilepsy into a) "recommended" (gabapentin, lamotrigine, levetiracetam, zonisamide) b) "neutral" (brivaracetam, carbamazepine, eslicarbazepine acetate, pregabalin, lacosamide, oxcarbazepine, topiramate, valproic acid), c) "not recommended" (cannabidiol, felbamate, phenobarbital, phenytoin,

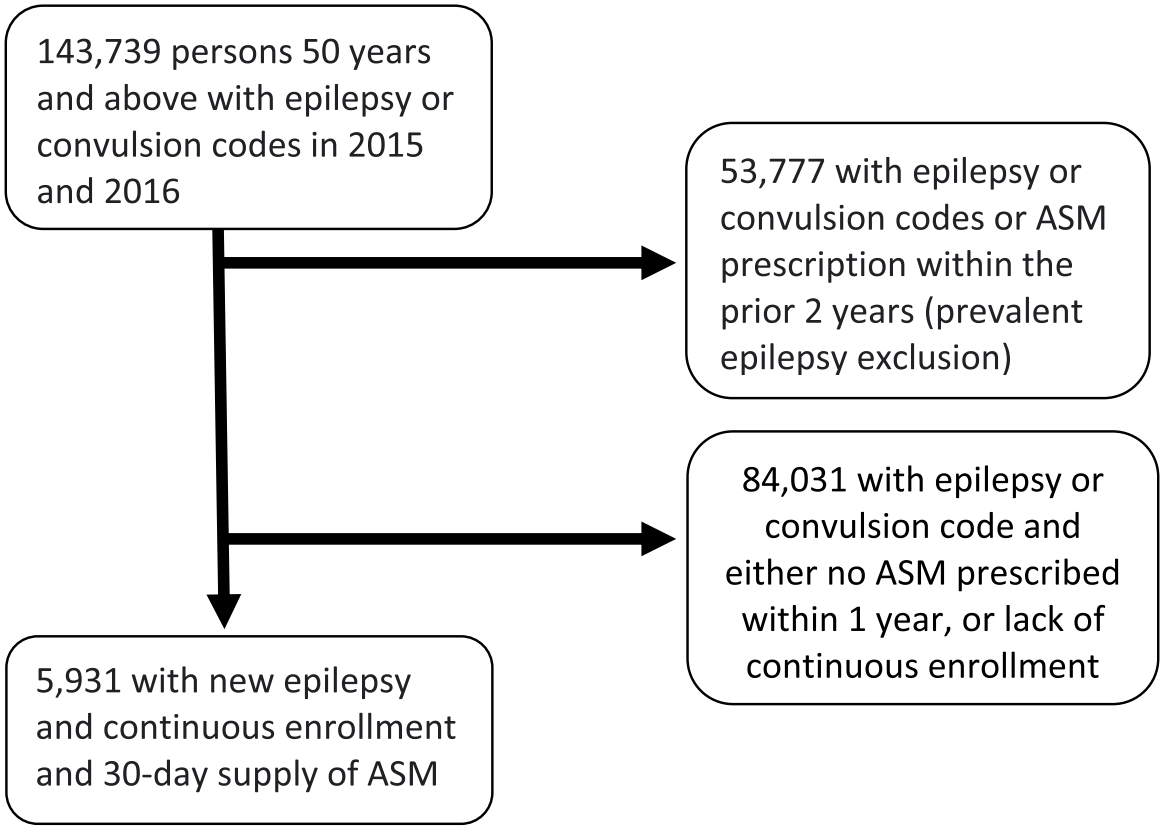

Fig. 1. Flow diagram of cohort inclusion.

primidone, rufinamide, vigabatrin), or d) "benzodiazepines."[17,21]

2.5. Other covariates

Covariates included: age, sex, Elixhauser comorbidity index[22], specific neurologic comorbidities (Alzheimer disease and related dementia, brain tumor, stroke or traumatic brain injury), ASM-polypharmacy, and prior injury. Polypharmacy was defined as being on at least two ASMs during the 1-year follow-up period [23]. Prior injury was defined as having had one of the injury codes in the 2 years prior to the initiation of the ASM. Specific neurologic comorbidities were also defined using the 2-year look-back period prior to epilepsy diagnosis and used previously published ICD-CM diagnostic codes (Supplementary Table 1) [24]. Finally, using the ICD-9/ICD-10-CM codes and Elixhauser comorbidity software, 29 Elixhauser comorbidities (Supplementary Table 1) were identified [25]. These comorbidities were transformed into a comorbidity index for each record.

2.6. Statistical analysis

Categorical variables were expressed as frequencies and percentages, and continuous variables as mean and range. Chi-square tests and Cox regression analyses were performed to identify the relationship between particular ASM choices and one-year injury. Hazard ratio and 95% confidence intervals were reported for the time to event analyses. As described in the cohort identification section, we performed a sensitivity analysis to ensure the robustness of our epilepsy case definition which included ASM-users in the prior 2 years on gabapentin, pregabalin, and benzodiazepines as these medications are more commonly used for non-seizure indications.

Statistical Analysis Software (SAS) version 9.4 was used to conduct all analyses (SAS Institute Inc., Cary, NC, USA).

2.7. Data availability statement

MarketScan Databases are accessible for purchase by researchers. The data user agreement limits release of data, and any requests should be made directly to MarketScan.

2.8. Standard protocol approvals, registrations and patient consent

The Icahn School of Medicine at Mount Sinai Institutional Review Board has reviewed and approved this project and waived need for individual consent.

3. Results

We identified 143,739 persons 50 years or older with a diagnosis code for epilepsy or convulsion in 2015–2016. Of these, 5931 met our definition of newly diagnosed epilepsy and were prescribed an ASM within one year (see Fig. 1). The three most commonly prescribed ASMs were levetiracetam (62.86%), gabapentin (11.73%), and phenytoin (4.45%) (see Table 1).

Patients who had a visit for injury within one year were statistically significantly more likely to be older, be treated with more than one ASM (polypharmacy), and have a history of prior injury (see Table 2). The following Elixhauser comorbidities were statistically significantly more common in the injury group including anemia, rheumatoid arthritis and collagen vascular disease, heart failure, chronic pulmonary disease, coagulopathies, depression and psychosis, diabetes, hypertension, liver disease, peripheral vascular disorders, renal failure and fluid and electrolyte disorders as well as weight loss. Neurologic comorbidities including Alzheimer and related dementia, stroke and traumatic brain disorder were also significantly more common in the injured group.

Multivariable Cox-regression models were built to examine the association between first drug prescribed and injury within one year (Table 3). Medication classes (recommended vs. neutral, not recommended or benzodiazepine) were not associated with hazard of injury. However, older age (adjusted hazard ratio (AHR) 1.01; 95% confidence interval (CI) 1.01–1.02 per year), history of prior injury (AHR 1.77, 95% CI 1.59–1.97), history of traumatic brain injury (AHR 1.55; 95%CI 1.40–1.72) and ASM polypharmacy (AHR 1.32; 95%CI 1.20–1.45) were all associated with increased hazard of injury. As it was the only potentially modifiable risk factor identified in our adjusted model, we looked at the ASM combinations seen most commonly in ASM polypharmacy in this cohort and found that the three most common ASM combinations were: levetiracetam and lorazepam (190 individuals), levetiracetam and gabapentin (188 individuals), levetiracetam and lacosamide (157 individuals) (see Table 4).

Table 1
Number and proportion of first anti-seizure medication prescribed in 2015–2016 by injury status.

	Total		Injury		No Injury	
Anti-seizure medication	N	%	N	%	N	%
Levetiracetam	3728	62.86	1323	62.91	2405	62.83
Gabapentin	696	11.73	264	12.55	432	11.29
Phenytoin	264	4.45	104	4.95	160	4.18
Topiramate	215	3.63	59	2.81	156	4.08
Lamotrigine	197	3.32	59	2.81	138	3.61
Lacosamide	173	2.92	76	3.61	97	2.53
Clonazepam	159	2.68	46	2.19	113	2.95
Lorazepam	155	2.61	59	2.81	96	2.51
Oxcarbazepine	89	1.50	28	1.33	61	1.59
Carbamazepine	68	1.15	20	0.95	48	1.25
Pregabalin	59	0.99	26	1.24	33	0.86
Diazepam	44	0.74	13	0.62	31	0.81
Zonisamide	40	0.67	N.R.	N.R.	30	0.78
Valproic Acid	26	0.44	N.R.	N.R.	17	0.44
Eslicarbazepine Acetate	N.R.	N.R.	N.R.	N.R.	N.R.	N.R.
Phenobarbital	N.R.	N.R.	N.R.	N.R.	N.R.	N.R.

N.R. = not reportable due to cell size.

4. Discussion

In this study we show that ASM polypharmacy is associated with an increased hazard of injury within one year of ASM-prescription in older adults with epilepsy. This finding reinforces the likely deleterious effects of polypharmacy in older adults which has previously been associated with fall risk [26,27]. Anti-seizure medications are among a number of classes of medications that have their main effects in the central nervous system (CNS) [28]. Prior studies suggest that CNS-active medications such as ASMs may be particularly dangerous in relation to injuries, although many of these studies were conducted when older generation ASMs were more commonly prescribed [6,29-31]. Anti-seizure medications are also commonly co-prescribed with other CNS-active medications including anti-depressants and anti-psychotics which may also increase risk of injury [28,32,33]. Furthermore, epilepsy itself places individuals at higher risk of injury[4,5] making parsimonious drug selection particularly important in this group.

Our study reassuringly showed that the majority of older adults are started on recommended first-line medications (levetiracetam and gabapentin were the two most commonly prescribed). However, there is still a sizeable proportion started on suboptimal medications including over 6% on benzodiazepines or barbiturates [34], and another 5–6% on enzyme-inducing ASMs. These are potentially inappropriate drugs that carry known short-term (e.g., delirium, falls, fractures, and motor vehicle crashes) and long-terms risks (e.g., osteomalecia and dyslipidemia), and that have long been recommended to not be prescribed, in particular in older adults [34,35].

Interestingly, our final models did not show a difference in hazard of injury by guideline medication category (recommended, not recommended, neutral or benzodiazepine). Our initial models suggested an

Table 2
Baseline characteristics of persons with newly diagnosed epilepsy and new anti-seizure medication use in 2015–2016 by injury status.

	Injury		No Injury		
	N	%	*N*	%	*p-value*
Total	2103	35.46	3828	64.54	
Age *mean (*min, max*)*	68	(50, 100)	66	(50,98)	<0.0001
Age group					<0.0001
50–54	309	31.15	683	68.85	
55–64	681	31.14	1506	68.86	
65 and older	1113	40.44	1639	59.56	
Sex					0.99
Male	1044	35.45	1901	64.55	
Female	1059	35.47	1927	64.53	
Region					0.0001
Northeast	497	36.46	866	63.54	
North Central	638	39.43	980	60.57	
South	727	32.07	1540	67.93	
West	N.R.	N.R.	N.R.	N.R.	
Unknown	N.R.	N.R.	N.R.	N.R.	
Polypharmacy	680	40.62	994	59.38	<0.0001
Prior Injury	1616	42.16	2217	57.84	<0.0001
Elixhauser Comorbidities					
AIDS/HIV	N.R.	N.R.	N.R.	N.R.	0.52
Alcohol abuse	383	38.45	613	61.55	0.03
Anemia	604	42.09	831	57.91	<0.0001
Rheumatoid arthritis/ collagen vascular diseases	206	45.27	249	54.73	<0.0001
Blood loss anemia	60	39.47	92	60.53	0.29
Chronic heart failure	433	42.74	580	57.26	<0.0001
Chronic pulmonary disease	688	39.54	1052	60.46	<0.0001
Coagulopathy	224	44.71	277	55.29	<0.0001
Depression	564	40.69	822	59.31	<0.0001
Diabetes, uncomplicated	422	40.27	626	59.73	0.0003
Diabetes, complicated	722	38.71	1143	61.29	0.0004
Drug abuse	94	44.98	115	55.02	0.003
Hypertension	1692	37.24	2852	62.76	<0.0001
Hypothyroidism	529	39.51	810	60.49	0.00043
Liver disease	207	43.76	266	56.24	<0.0001
Lymphoma	39	40.63	57	59.38	0.29
Fluid and electrolyte disorders	870	41.00	1252	59.00	<0.0001
Metastatic cancer	94	32.98	191	67.02	0.37
Other neurological disorders	2099	35.43	3825	64.57	0.23
Obesity	378	36.24	665	63.76	0.56
Paralysis	300	39.47	460	60.53	0.01
Peripheral vascular disorders	571	41.59	802	58.41	<0.0001
Psychoses	367	41.90	509	58.11	<0.0001
Pulmonary circulation disorders	169	42.46	229	57.54	0.002
Renal failure	382	41.75	533	58.25	<0.0001
Solid tumor without metastasis	377	37.14	638	62.86	0.22
Peptic ulcer disease	16	36.36	28	63.64	0.90
Valvular Disease	593	38.81	935	61.19	0.002
Weight loss	287	43.42	374	56.58	<0.0001
Elixhauser Index *mean (*min, max*)*	15	(−19, 67)	12	(−19, 67)	<0.0001
Neurologic comorbidity					
Alzheimer and related dementias	515	41.63	722	58.37	<0.0001
Brain tumor	92	34.59	174	65.41	0.76
Stroke	1227	39.19	1904	60.81	<0.0001
Traumatic brain injury	607	52.37	552	47.63	<0.0001

N.R. = not reportable due to cell size.

increased odds of injury when first prescribed a benzodiazepine (Supplementary Table 2). However, when we added the polypharmacy term, a traumatic brain injury TBI term, required a full year of follow-up and excluded all prior ASM users (as opposed to epilepsy-specific prior ASM users), there was no longer an association between first drug choice and injury. These findings highlight the relative importance of polypharmacy in this population and therefore the importance of optimizing first drug choice so additional ASMs do not need to be added/tried. These findings further support the typical practice of serial monotherapy in epilepsy. In other words, if seizures do not stop with the first medication trial, a second medication should be added and the initial ineffective medication removed [36].

Table 3
Multivariable Cox-regression examining the association between anti-seizure medication (ASM) and 1-year injury in persons with newly diagnosed epilepsy and new ASM use.

Covariates	HR	95% CI		p-value
Age (increasing by 1 year)	1.01	1.01	1.01	<0.0001
Male sex	1.05	0.96	1.14	0.28
Polypharmacy	1.32	1.20	1.45	<0.0001
Prior injury	1.77	1.59	1.97	<0.0001
Elixhauser Comorbidity index (increasing by 1 point)	1.01	1.00	1.01	0.013
Neurologic comorbidity:				
Alzheimer and related dementias	0.97	0.87	1.08	0.56
Brain tumor	0.93	0.75	1.15	0.49
Stroke	1.10	1.00	1.20	0.06
Traumatic brain injury	1.55	1.40	1.72	<0.0001
Anti-seizure medication category				
Benzodiazepine	0.92	0.77	1.12	0.41
Neutral	1.01	0.88	1.17	0.85
Not recommended	1.01	0.83	1.24	0.90
Recommended	*Reference*			

CI = confidence interval; HR = hazard ratio.

Prior injury, as has been seen in other epilepsy cohorts and other disorders was unsurprisingly associated with subsequent injury [37,38]. Interestingly, the neurologic comorbidities we examined were not all associated with increased hazard of injury within one year: only TBI and stroke were associated while brain tumor or dementia diagnoses were not. This was unexpected, as prior studies have suggested an increased risk of fall in patients with dementia[39,40] and brain tumors [41] and may reflect different or more intensive caregiving in the setting of these conditions and seizures. Consistent with prior studies, increasing age was also associated with increasing hazard of injury [39,42,43]. This expected finding of increasing age being tied to injury emphasizes the need for thoughtful medication selection in this higher risk group.

4.2. Limitations

This study is unique in that it uses a large national database to show factors associated with injury in older adults with new epilepsy. This study, however, has several possible limitations. First, our study assessed the U.S. population during 2013–2017 (with cases sampled from 2015 to 2016), and may not reflect the current experience. In addition, administrative claims data are produced for billing purposes, and so, do not allow for a detailed examination of socioeconomic background, healthcare attitudes, medication adherence, functional status, or disease severity all of which might impact decisions as to which medications to prescribe as well as likelihood of injury. Additionally, it does not allow for a detailed examination of the injury event; for example, we cannot determine whether the injury was due to a seizure, medication side effect or something else. We used validated ICD-CM codes for epilepsy, but despite being widely used, not all of the injury codes have been specifically validated in this population. Marketscan Databases also do not include individual mortality data which might be important to understand the relationship between ASM, injury and mortality in future studies. Finally, the MarketScan Databases are large (more than 100 million lives) with broad geographic reach and insurance diversity but require insurance so are thought to be generalizable only to the insured US population.

Table 4
Anti-seizure medication (ASM) co-prescription in 1674 persons with newly diagnosed epilepsy and multiple ASM use.

	CBZ	CLZ	DZP	ESL	GBP	LCM	LTG	LEV	LZP	OXC	PHB	PHT	PGB	TPM	VPA	ZNS
Carbamazepine (CBZ)		N.R.	N.R.	N.R.	N.R.	N.R.	N.R.	N.R.	N.R.	N.R.	0	N.R.	N.R.	N.R.	0	0
Clonazepam (CLZ)	N.R.		N.R.	N.R.	20	N.R.	N.R.	16	N.R.	N.R.	0	N.R.	N.R.	N.R.	N.R.	0
Diazepam (DZP)	0	N.R.		0	19	N.R.	N.R.	25	N.R.	0	N.R.	0	N.R.	N.R.	0	N.R.
Eslicarbazepine (ESL)	0	0	0		N.R.	N.R.	0	0	0	0	0	0	0	N.R.	0	N.R.
Gabapentin (GBP)	N.R.	N.R.	15	0		N.R.	N.R.	48	15	N.R.	N.R.	N.R.	20	11	N.R.	N.R.
Lacosamide (LCM)	N.R.	N.R.	N.R.	N.R.	12		11	50	15	N.R.	N.R.	N.R.	N.R.	N.R.	N.R.	N.R.
Lamotrigine (LTG)	N.R.	N.R.	N.R.	N.R.	13	N.R.		28	13	N.R.	0	N.R.	0	N.R.	N.R.	N.R.
Levetiracetam (LEV)	27	70	79	18	188	157	152		190	76	N.R.	98	25	70	N.R.	32
Lorazepam (LZP)	N.R.	20	N.R.	N.R.	34	N.R.	N.R.	55		N.R.	0	N.R.	0	N.R.	0	N.R.
Oxcarbazepine (OXC)	0	N.R.	0	0	N.R.	N.R.	N.R.	18	10		N.R.	0	N.R.	N.R.	0	N.R.
Phenobarbital (PHB)	0	N.R.	N.R.	0	0	0	0	1	0	0		N.R.	0	N.R.	0	0
Phenytoin (PHT)	N.R.	N.R.	N.R.	0	17	N.R.	10	88	16	N.R.	N.R.		N.R.	N.R.	N.R.	N.R.
Pregabalin (PGB)	0	0	N.R.	0	N.R.	0	N.R.	N.R.	N.R.	N.R.	0	0		0	0	N.R.
Topiramate (TMP)	N.R.	N.R.	N.R.	N.R.	17	N.R.	N.R.	N.R.	N.R.	N.R.	0	N.R.	N.R.		0	N.R.
Valproic Acid (VPA)	0	N.R.	N.R.	0	N.R.	N.R.	0	N.R.	N.R.	0	0	0	0	0		0
Zonisamide (ZNS)	0	0	N.R.	0	N.R.	N.R.	N.R.	N.R.	0	0	0	0	0	0	0	

>100 persons
11-100 persons
0-10 persons
N.R. = not reportable due to cell size

N.R. = not reportable due to cell size.

5. Conclusions

We present data on prescribing and injury in newly diagnosed epilepsy in older adults. While the majority of persons with epilepsy appear to be getting appropriate first prescriptions, there is still a substantial proportion getting medication that guidelines suggest may be inappropriate. In addition, we show that ASM polypharmacy in particular is associated with an increased hazard of injury within one year. Efforts to improve prescribing in older adults with epilepsy should consider both avoidance of potentially inappropriate therapies as well as avoidance of polytherapy.

Author contributions

LJB and NJ conceptualized and refined the research ideas. LJB, CSK and NJ obtained the dataset. PA performed the statistical analysis. All authors contributed to the interpretation of the results. LJB wrote the first draft of the manuscript and all authors contributed to subsequent drafts.

Role of the funding source

The American Epilepsy Society, the Epilepsy Foundation and NIA (5P30AG028741-11 and T32AG066598) helped fund portions of this work. These sponsors did not have any role in the design, methods, subject recruitment, data collections, analysis or preparation of this manuscript.

Declaration of Competing Interest

LJB received grant support from the American Epilepsy Society, the Epilepsy Foundation and NIA (Mount Sinai Claude D. Pepper Older Americans Independence Center, 5P30AG028741–11 and T32AG066598). NJ was the Bludhorn Professor of International Medicine and received grant funding paid to her institution for grants unrelated to this work from NINDS (NIH U24NS107201, NIH IU54NS100064, 3R01CA202911–05S1, R21NS122389, R01HL161847). She also receives an honorarium for her work as an Associate Editor of *Epilepsia*. The other authors report no conflicts of interest.

Funding sources

American Epilepsy Society, the Epilepsy Foundation and NIA (5P30AG028741-11 and T32AG066598).

Acknowledgments

We confirm that we have listed everyone who has contributed significantly to this work.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.seizure.2023.05.006.

References

[1] Hauser WA, Annegers JF, Kurland LT. Incidence of epilepsy and unprovoked seizures in Rochester, Minnesota: 1935-1984. Epilepsia 1993;34:453–68.
[2] Hesdorffer DC, Logroscino G, Benn EK, Katri N, Cascino G, Hauser WA. Estimating risk for developing epilepsy: a population-based study in Rochester, Minnesota. Neurology 2011;76:23–7.
[3] de la Court A, Breteler MM, Meinardi H, Hauser WA, Hofman A. Prevalence of epilepsy in the elderly: the Rotterdam Study. Epilepsia 1996;37:141–7.
[4] Kwon CS, Liu M, Quan H, et al. The incidence of injuries in persons with and without epilepsy—a population-based study. Epilepsia 2010;51:2247–53.
[5] Kwon CS, Agrawal P, Goldstein J, Dhamoon M, Mazumdar M, Jette N. Risk of readmission for injury in patients with epilepsy in the United States—a population-based study. Epilepsy Behav 2020;102:106651.
[6] Asadi-Pooya AA, Nikseresht A, Yaghoubi E, Nei M. Physical injuries in patients with epilepsy and their associated risk factors. Seizure 2012;21:165–8.
[7] Josephson CB, Patten SB, Bulloch A, et al. The impact of seizures on epilepsy outcomes: a national, community-based survey. Epilepsia 2017;58:764–71.
[8] Kwan P, Brodie MJ. Early identification of refractory epilepsy. N Engl J Med 2000;342:314–9.
[9] Phillips LS, Branch WT, Cook CB, et al. Clinical inertia. Ann Intern Med 2001;135:825–34.

[10] Finamore JM, Sperling MR, Zhan T, Nei M, Skidmore CT, Mintzer S. Seizure outcome after switching antiepileptic drugs: a matched, prospective study. Epilepsia 2016;57:1294–300.
[11] Wang SP, Mintzer S, Skidmore CT, et al. Seizure recurrence and remission after switching antiepileptic drugs. Epilepsia 2013;54:187–93.
[12] Hansen RN, Campbell JD, Sullivan SD. Association between antiepileptic drug switching and epilepsy-related events. Epilepsy Behav 2009;15:481–5.
[13] Zachry 3rd WM, Doan QD, Clewell JD, Smith BJ. Case-control analysis of ambulance, emergency room, or inpatient hospital events for epilepsy and antiepileptic drug formulation changes. Epilepsia 2009;50:493–500.
[14] Ertl J, Hapfelmeier J, Peckmann T, Forth B, Strzelczyk A. Guideline conform initial monotherapy increases in patients with focal epilepsy: a population-based study on German health insurance data. Seizure 2016;41:9–15.
[15] Pickrell WO, Lacey AS, Thomas RH, Lyons RA, Smith PE, Rees MI. Trends in the first antiepileptic drug prescribed for epilepsy between 2000 and 2010. Seizure 2014;23:77–80.
[16] Faught E, Helmers S, Thurman D, Kim H, Kalilani L. Patient characteristics and treatment patterns in patients with newly diagnosed epilepsy: a US database analysis. Epilepsy Behav 2018;85:37–44.
[17] Kanner AM, Ashman E, Gloss D, et al. Practice guideline update summary: efficacy and tolerability of the new antiepileptic drugs I: treatment of new-onset epilepsy: report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Neurology 2018;91:74–81.
[18] Moura LM, Price M, Cole AJ, Hoch DB, Hsu J. Accuracy of claims-based algorithms for epilepsy research: revealing the unseen performance of claims-based studies. Epilepsia 2017;58:683–91.
[19] Moura L, Smith JR, Blacker D, et al. Epilepsy among elderly medicare beneficiaries: a validated approach to identify prevalent and incident epilepsy. Med Care 2019; 57:318–24.
[20] Kwon C, Liu M, Quan H, Thoo V, Wiebe S, Jette N. Motor vehicle accidents, suicides, and assaults in epilepsy: a population-based study. Neurology 2011;76: 801–6.
[21] Vu LC, Piccenna L, Kwan P, O'Brien TJ. New-onset epilepsy in the elderly. Br J Clin Pharmacol 2018;84:2208–17.
[22] Moore BJ, White S, Washington R, Coenen N, Elixhauser A. Identifying increased risk of readmission and in-hospital mortality using hospital administrative data: the AHRQ elixhauser comorbidity index. Med Care 2017;55:698–705.
[23] Masnoon N, Shakib S, Kalisch-Ellett L, Caughey GE. What is polypharmacy? A systematic review of definitions. BMC Geriatr 2017;17:230.
[24] St Germaine-Smith C, Metcalfe A, Pringsheim T, et al. Recommendations for optimal ICD codes to study neurologic conditions: a systematic review. Neurology 2012;79:1049–55.
[25] Elixhauser A, Steiner C, Harris DR, Coffey RM. Comorbidity measures for use with administrative data. Med Care 1998;36:8–27.
[26] Dhalwani NN, Fahami R, Sathanapally H, Seidu S, Davies MJ, Khunti K. Association between polypharmacy and falls in older adults: a longitudinal study from England. BMJ Open 2017;7:e016358.
[27] Fried TR, O'Leary J, Towle V, Goldstein MK, Trentalange M, Martin DK. Health outcomes associated with polypharmacy in community-dwelling older adults: a systematic review. J Am Geriatr Soc 2014;62:2261–72.
[28] BtAGSBCUE Panel. American Geriatrics Society 2019 updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. J Am Geriatr Soc 2019;67:674–94.
[29] Ensrud KE, Blackwell TL, Mangione CM, et al. Central nervous system-active medications and risk for falls in older women. J Am Geriatr Soc 2002;50:1629–37.
[30] Cumming RG. Epidemiology of medication-related falls and fractures in the elderly. Drugs Aging 1998;12:43–53.
[31] Gur-Ozmen S, Mula M, Agrawal N, Cock HR, Lozsadi D, von Oertzen TJ. The effect of depression and side effects of antiepileptic drugs on injuries in patients with epilepsy. Eur J Neurol 2017;24:1135–9.
[32] Maust DT, Strominger J, Kim HM, et al. Prevalence of central nervous system–active polypharmacy among older adults with dementia in the US. JAMA 2021;325:952–61.
[33] Hart LA, Marcum ZA, Gray SL, Walker RL, Crane PK, Larson EB. The association between central nervous system-active medication use and fall-related injury in community-dwelling older adults with dementia. Pharmacother. 2019;39:530–43.
[34] By the American Geriatrics Society Beers Criteria Update Expert P. American Geriatrics Society 2015 updated Beers Criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc 2015;63:2227–46.
[35] Brodie MJ, Mintzer S, Pack AM, Gidal BE, Vecht CJ, Schmidt D. Enzyme induction with antiepileptic drugs: cause for concern? Epilepsia 2013;54:11–27.
[36] St Louis EK, Rosenfeld WE, Bramley T. Antiepileptic drug monotherapy: the initial approach in epilepsy management. Curr Neuropharmacol 2009;7:77–82.
[37] Fulton J, Wright K, Kelly M, et al. Injury risk is altered by previous injury: a systematic review of the literature and presentation of causative neuromuscular factors. Int J Sports Phys Ther 2014;9:583–95.
[38] Asiri S, Al-Otaibi A, Al Hameed M, et al. Seizure-related injuries in people with epilepsy: a cohort study from Saudi Arabia. Epilepsia Open 2022;7:422–30.
[39] Meuleners LB, Hobday MB. A population-based study examining injury in older adults with and without dementia. J Am Geriatr Soc 2017;65:520–5.
[40] Chen R, Chien WC, Kao CC, et al. Analysis of the risk and risk factors for injury in people with and without dementia: a 14-year, retrospective, matched cohort study. Alzheimers Res Ther 2018;10:111.
[41] Stone CA, Lawlor PG, Savva GM, Bennett K, Kenny RA. Prospective study of falls and risk factors for falls in adults with advanced cancer. J Clin Oncol 2012;30: 2128–33.
[42] Talbot LA, Musiol RJ, Witham EK, Metter EJ. Falls in young, middle-aged and older community dwelling adults: perceived cause, environmental factors and injury. BMC Public Health 2005;5:86.
[43] Nilsson M, Eriksson J, Larsson B, Oden A, Johansson H, Lorentzon M. Fall risk assessment predicts fall-related injury, hip fracture, and head injury in older adults. J Am Geriatr Soc 2016;64:2242–50.