

ORIGINAL ARTICLE

Differences between men and women in response to antiseizure medication use and the likelihood of developing treatment resistant epilepsy

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Abstract

Objective: The prevalence of epilepsy is slightly higher in women than in men and sensitivity to seizure stimuli differs between sexes. Some evidence suggests sex differences in response to antiseizure medications exist mainly due to inconsistent pharmacokinetic differences; however, there is a lack of real-world evidence examining differences in response to antiseizure medications between men and women.

Methods: This was a retrospective population-based cohort study in five large US healthcare databases. The population included adult patients with epilepsy, newly exposed to levetiracetam, and naive to antiseizure medication. The first exposure to levetiracetam was the index date. The requirement that all patients received the same medication was done to avoid potential confounding due to differences in index treatment. The outcome was the development of treatment resistant epilepsy (TRE), defined as having at least three distinct antiseizure medications in 1 year. The proportion of patients who developed TRE within 1 year following the index date was calculated. To compare the risk of developing TRE between sexes, relative risks (RR) and 95% confidence intervals (CI) were calculated, and estimates were pooled using meta-analytic techniques stratified by gender and age.

Results: A total of 147 334 subjects were included in the databases, 50.8% were women, and 4.27% developed TRE. The comorbid profile differed greatly between men and women; however, the types of epilepsy syndromes observed during baseline were similar between the two groups. Across all databases, women were more likely to develop TRE than men (pooled RR 1.27, 95% CI 1.17-1.38). Results remained similar when stratified by age.

Significance: This study assessed sex differences in response to antiseizure medications using the development of TRE as a proxy for effectiveness. Women newly exposed to levetiracetam were 27% more likely to develop TRE than men, independent of age.

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KEYWORDS

epilepsy, real-world evidence, sex differences, treatment resistance

1 | INTRODUCTION

Epilepsy is one of the most common neurological disorders in the USA with a prevalence of 411.8 per 100 000 people.¹ Epilepsy is also one of the most burdensome neurological conditions in terms of disability¹ and one of the leading medical conditions associated with poor health.²

The prevalence of epilepsy is slightly higher in women than in men^{3,4} and sensitivity to seizure stimuli, at least in animal models, differs between the sexes.^{5,6} There is some evidence suggesting that sex differences in response to antiseizure medications also exist, although mainly based on pharmacokinetic differences. These differences between men and women are inconsistent in direction. For example, there are reports suggesting that women have increased clearance of lamotrigine (in the presence of ethinyl estradiol) with the potential of loss of seizure control,⁷ or reports that carbamazepine plasma concentrations were higher in men than in women, whereas plasma concentrations of valproic acid and phenytoin were higher in women than in men.⁸

Differences in response between sexes are known to exist for other medications. For example, women experience more adverse events than men after short opioid exposure and require more opioids to achieve a similar degree of analgesia in the postoperative period,⁹ and in general, women report more adverse events after medication exposure.^{10,11} In some cases, sex differences have led health regulatory agencies to request changes in dosing of hypnotics in women after evidence surfaced that women were at higher risk for excessive daytime sedation and impaired driving proficiency with zolpidem than men.¹²

We sought to assess whether sex differences in response to antiseizure medications exist for patients with epilepsy in the real world, by focusing on individuals who initiate antiseizure therapy with the most commonly used antiseizure medication in the USA, levetiracetam.¹³ Healthcare databases contain data on millions of subjects allowing researchers to study conditions that are not common and conduct subgroup analyses that would be infeasible in traditional prospective studies. Although these databases do not have data on the number of seizures to assess effectiveness, the capture of prescriptions in these healthcare databases is very good.¹⁴ Thus, the development of treatment resistance can be used to assess antiseizure medication effectiveness since the

Key Points

- This study examined 147 334 patients diagnosed with epilepsy within five large US health-care databases
- All patients received levetiracetam to avoid potential confounding by differences in index treatment choice
- During a 1-year follow-up, women were 27% more likely to develop treatment resistant epilepsy than men, independent of age

number of antiepileptics received can be used as a proxy for medication response.

2 | MATERIAL AND METHODS

We conducted a retrospective cohort study utilizing observational administrative claims data in patients diagnosed with epilepsy and initiating levetiracetam.

2.1 | Inclusion criteria

Adult patients (≥ 18 years old) newly exposed to levetiracetam who had at least one diagnosis of epilepsy prior to the start of the medication were included. The SNOMED-CT (Systematized Nomenclature of Medicine-Clinical Terms) concepts used to identify epilepsy are listed in [Table A1](#) in [Appendix 1](#). SNOMED-CT is a standardized, multilingual vocabulary of clinical terminology used by healthcare providers for the electronic exchange of clinical health information.¹⁵ The ICD-9 and ICD-10 codes which map to the SNOMED-CT concepts have been used to identify epilepsy and validated for identifying patients with epilepsy in administrative health databases.¹⁶ Levetiracetam was selected as the antiseizure medication of interest as it is the most commonly used. Approximately 44% of commercially insured subjects are exposed to levetiracetam as the first line of treatment for epilepsy.¹³

Patients were required to have at least 1 year of continuous enrollment in the database prior to and after the first exposure to levetiracetam. The first exposure to levetiracetam was considered the index date.

2.2 | Exclusion criteria

Patients were excluded if they had a dispensing for any antiseizure medication 1 year before the index date; and therefore, the included patients were considered “naive” to any antiseizure medication. To increase the likelihood that patients were truly treatment resistant patients, we also excluded patients with a diagnosis of refractory epilepsy prior to the index date.

2.3 | Outcome

The outcome was the development of treatment resistant epilepsy (TRE) defined as receiving at least three distinct antiseizure medications in 1 year. Although TRE is defined as the persistence of seizures despite adequate doses of two antiseizure medications,^{17,18} assessing the reason for stopping the medication (lack of effect vs adverse events) is challenging in administrative databases.^{19,20} Therefore, a conservative approach was taken in defining the outcome by requiring at least three distinct antiseizure medications within 1 year. A similar definition has been validated in administrative databases for treatment resistant depression.²¹

2.4 | Time at risk

The time at risk started on the index date and ended 365 days following the index date.

2.5 | Data sources

The study was conducted in five US healthcare databases. Each database contains data from adjudicated health insurance claims (eg, inpatient hospitalizations, emergency department/outpatient/office visits, and outpatient pharmacy) and health plan enrollment information. Briefly, the five databases included in this study were as follows.

IBM MarketScan® Commercial Database (CCAЕ): Included data from 155 million individuals enrolled in employer-sponsored insurance health plans. Data spanned from January 1, 2000 to October 31, 2020.

IBM® MarketScan® Multi-State Medicaid Database (MDCD): A claims database for 31 million Medicaid enrollees from multiple states. Data spanned from January 2006 to December 30, 2019.

IBM® MarketScan® Medicare Supplemental Database (MDCR): Included data for more than 10 million retirees with primary or Medicare supplemental coverage through

privately insured fee-for-service, point-of-service, or capitated health plans. Data spanned from January 2000 to October 31, 2020.

Optum® De-Identified Clinformatics® Data Mart Database: Included 102 million members with private health insurance who are fully insured in commercial plans or Medicare Advantage. Data spanned from May 2000 to March 31, 2020.

The IQVIA® Adjudicated Health Plan Claims Data (formerly PharMetrics Plus): Included information of over 70 contributing health plans and self-insured employer groups throughout the USA for over 100 million unique enrollees. Data spanned from July 2015 to July 2020.

Data elements in these databases were outpatient pharmacy dispensing claims (coded with National Drug Codes), inpatient and outpatient medical claims that provide diagnosis codes (coded in the International Classification of Diseases [ICD], Ninth Revision, Clinical Modification [ICD-9-CM] or ICD Tenth Revision, Clinical Modification [ICD-10-CM]) associated with a visit.

As observational data sets vary in content and format, code written to develop models on one database often cannot be shared to run on another database. To overcome this issue, the Observational Medical Outcomes Partnership (OMOP) common data model²² was developed. All the data sources were mapped from their raw format into the OMOP common data model.

2.6 | Baseline characteristics

To describe the baseline characteristics of men and women included in the study, we identified medical conditions present in the database 1 year before or at the index date using the systematized Nomenclature of Medicine-Clinical Terms (SNOMED CT). SNOMED is a standardized, multilingual vocabulary of clinical terminology that is used by physicians and other healthcare providers for the electronic exchange of clinical health information.¹⁵ The SNOMED classification allows mapping of various diagnostic languages, including ICD-9-CM and ICD-10-CM, to a single standardized set of concepts, and is used in the OMOP common data model.

Since a comparison of medical comorbidities could include thousands of variables, we prioritized the reporting to characteristics that could not only affect the development of TRE such as the type of epilepsy syndrome²³ but also included the most commonly observed medical conditions. In addition, we calculated the Charlson comorbidity index. This index is a weighted sum of the presence of 19 medical conditions that affect the risk of mortality.²⁴

2.7 | Analysis

To compare the baseline characteristics between men and women, we calculated standardized mean differences (SMD). SMD is the difference in prevalence of a specific characteristic in the two cohorts divided by the pooled standard deviation of the two groups. A large absolute value SMD on a covariate is an indication of a significant disparity in the proportion of patients with the covariate between the two groups. An SMD more than 0.1 has been used as an ad hoc heuristic for what constitutes “large”.²⁵

We calculated the proportion of subjects who developed TRE 1 year after the index date (number of subjects who developed TRE/total number of subjects at risk) and stratified by gender and age. Three age categories were created 18-40, 41-65, >65 years. This age categorization permitted us to separate women with different female hormone profiles at baseline (eg, menopausal women).²⁶ The CCAE database does not contain subjects 65 years or older and the MDCR database does not contain subjects 40 years or younger.

To compare the risk of developing TRE between men and women, we calculated relative risks (RR) and 95% confidence intervals (CI). RRs >1 indicate a higher risk of developing TRE in women. Since five databases were included, we pooled the estimates using meta-analytic techniques. We utilized a random effects model using the DerSimonian and Laird method.

The use of the IBM® MarketScan and Optum claims databases was reviewed by the New England Institutional Review Board (IRB) and was determined to be exempt from broad IRB approval, as this research project did not involve human subjects research.

3 | RESULTS

A total of 147 334 subjects newly exposed to levetiracetam who had no prior antiseizure medication use and a diagnosis of epilepsy were identified, and, overall, 50.8% were women.

The baseline characteristics of men and women in each database are described in Table 1. The age of men and women were similar in each database. The type of epilepsy syndromes (according to the SNOMED-CT classifications) were also very similar between men and women at baseline in all databases. Women were more likely to have prior diagnoses for infectious disease of the genitourinary system, osteoporosis, hypothyroidism, depression, anxiety, or arthropathy. On the other hand, men were more likely to have been diagnosed with drug dependency, including alcoholism, and coronary atherosclerosis. Charlson comorbidity index score was similar in men

and women in all the databases, although the score was a bit higher in men in MDCR.

A total of 6290 (4.27%) individuals met the criteria for TRE. Of the subjects who developed TRE, 56.4% were women.

In all databases, women were more likely to develop TRE than men. For example, in MDCD, 3.15% of men developed TRE vs 4.86% of women, Table 2. The pooled RR was 1.27 (95% CI 1.17-1.38). The magnitude of the RR was higher in Medicaid as compared to the other databases (1.54 vs 1.21-1.24, respectively) (Figure 1).

Results remained similar when stratified by age (Table 2), and women had a higher risk of developing TRE than men in all the databases, independent of age (Figure 2).

4 | DISCUSSION

This population-based study assessed sex differences in response to antiseizure medications using the development of TRE as a proxy for effectiveness. Differences between men and women in response to antiseizure therapy exist, with women newly exposed to levetiracetam more likely to develop TRE than men, independent of age.

The higher risk for women developing TRE in this study was consistent in all five databases and in all age groups. The sex differences observed are likely due to both pharmacokinetics and pharmacodynamic differences. Pharmacokinetics differences would be due to women receiving more medications that could affect metabolism/elimination of the antiseizure medication due to drug interactions or women receiving relatively higher medication doses (eg, mg/kg dose), since women generally have a lower body weight than males. Pharmacodynamic differences could be explained by sex hormones²⁷⁻²⁹ since these hormones can influence hyperexcitability in the brain. Or it could be driven by differences in endogenous neurosteroids protection against neuronal excitability, differences in the distribution of brain steroids receptors, differences in plasticity in GABA receptor structure and function,^{6,30} or by sexual dimorphism of cerebral connectivity.

There is very limited prior evidence assessing the effect of sex on response to antiseizure medications. A small study in patients with autism spectrum disorder found that women had higher risk of TRE than men.³¹ With scant evidence of these differences to guide study design, it was necessary to assess differences between men and women under as similar conditions as possible. We sought to control for potential confounding by indication by limiting the study population to those who initiated treatment with levetiracetam. It may be of interest for future research to examine patients who initiate treatment for

TABLE 1 Characteristics of men and women included in the study

	OPTUM			MDCD			MDCR			CCAIE			IQVIA		
	Men	Women	SMD	Men	Women	SMD	Men	Women	SMD	Men	Women	SMD	Men	Women	SMD
Demographics															
Number of subjects	19983	20533		9000	11197		6128	6762		18003	17486		10898	9764	
Age years (mean ±SD)	61.3±19.5	64.0±19.6	-0.10	45.9±17.4	44.8±18.6	0.04	77.1±7.6	79.1±8.0	-0.18	43.1±15.3	42.9±14.7	0.01	44.8±17.0	44.4±16.7	0.01
Charlson index (mean ±SD)	4.9±3.9	4.8±3.8	0.01	3.7±3.7	3.5±3.8	0.04	6.0±3.7	5.5±3.5	0.10	2.4±3.2	2.3±3.1	0.03	2.4±3.3	2.2±3.2	0.05
Comorbid conditions															
Infectious disease of genitourinary system (n, %)	16.52	37.81	0.29	12.78	36.05	0.33	19.32	37.74	0.24	5.91	20.85	0.29	6.25	21.23	0.28
Osteoporosis (n, %)	2.62	14.14	0.29	1.64	3.72	0.09	2.94	14.23	0.27	0.69	2.91	0.12	0.75	4.08	0.15
Alcoholism (n, %)	12.07	4.67	-0.28	20.88	7.99	-0.24	5.01	1.36	-0.14	10.37	4.62	-0.15	14.34	6.66	-0.17
Acquired hypothyroidism (n, %)	6.63	14.96	0.18	4.04	7.19	0.09	9.51	18.09	0.16	3.64	9.50	0.16	1.82	4.69	0.11
Psychoactive substance dependence (n, %)	12.24	4.83	-0.18	21.38	8.73	-0.23	5.03	1.43	-0.14	10.55	4.72	-0.15	14.73	7.06	-0.16
Depressive disorder (n, %)	19.68	30.07	0.15	29.23	37.64	0.10	15.00	20.88	0.10	12.54	20.22	0.13	14.71	23.70	0.14
Drug dependence (n, %)	26.91	17.48	-0.13	48.20	38.35	-0.10	10.57	6.15	-0.11	22.78	15.19	-0.12	31.01	21.50	-0.13
Migraine (n, %)	3.21	7.52	0.13	4.19	12.24	0.20	1.32	2.82	0.07	4.48	11.96	0.18	4.52	13.58	0.21
Anxiety (n, %)	17.23	25.47	0.13	24.12	34.72	0.14	9.53	14.82	0.11	14.18	22.36	0.13	18.79	31.45	0.15
Coronary atherosclerosis (n, %)	24.17	16.96	-0.13	11.62	9.07	-0.06	30.87	19.73	-0.16	6.23	3.21	-0.10	9.52	5.68	-0.10
Arthropathy (n, %)	40.87	50.60	0.11	33.16	37.88	0.06	46.61	55.34	0.09	27.86	31.23	0.04	28.29	31.29	0.04
Type of epilepsy (categorized by SNOMED concept names)															
Generalized non-convulsive epilepsy (n, %)	1.67	2.27	0.03	1.56	1.79	0.01	3.12	3.58	0.02	2.57	3.01	0.02	-	-	--
Epilepsia partialis continua (n, %)	1.68	1.32	-0.03	1.69	1.3	-0.03	1.22	1.24	-0.00	1.29	1.08	-0.014	2.38	1.76	-0.03
Localization-related (partial) idiopathic epilepsy and epileptic syndromes with seizures of localized onset (n, %)	11.43	12.22	0.02	6.90	7.39	0.01	8.29	8.03	-0.01	7.19	8.09	0.02	18.42	20.41	0.03
Generalized epilepsy (n, %)	23.66	23.41	-0.01	22.81	22.51	-0.00	26.31	25.32	-0.01	27.91	27.11	-0.01	21.94	21.12	-0.01
Generalized convulsive epilepsy (n, %)	12.26	12.38	0.00	10.51	10.84	0.01	18.98	17.95	-0.02	16.75	16.93	0.00	-	-	-
Idiopathic generalized epilepsy (n, %)	3.44	3.38	-0.00	4.53	4.0	-0.02	1.71	1.63	-0.01	3.38	3.30	-0.00	8.27	8.60	0.01
Tonic-clonic epilepsy (n, %)	15.75	15.79	0.00	15.13	14.86	-0.00	20.74	19.62	-0.02	20.17	20.26	0.00	8.76	9.06	0.01

TABLE 2 Number of men and women with epilepsy and number of men and women who developed treatment resistant epilepsy

Database	Age and gender	Subjects at risk (N)	Subjects with treatment resistant epilepsy (n)	Percentage of subjects who developed treatment resistant epilepsy
CCAIE	Male	21 006	1023	4.87
	Female	20 813	1244	5.98
	41-65 and male	12 342	574	4.65
	41-65 and female	12 039	711	5.91
	18-40 and male	8664	449	5.18
	18-40 and female	8774	533	6.07
MDCD	Male	8985	283	3.15
	Female	11 175	543	4.86
	41-65 and male	4429	125	2.82
	41-65 and female	4336	189	4.36
	18-40 and male	3501	151	4.31
	18-40 and female	5188	333	6.42
	>65 and female	1651	21	1.27
>65 and male	1055	7	0.66	
MDCR	Male	7405	213	2.88
	Female	8207	292	3.56
	41-65 and male	213	12	5.63
	41-65 and female	122	8	6.56
	>65 and female	8085	284	3.51
	>65 and male	7191	201	2.80
Optum	Male	23 158	792	3.42
	Female	23 969	996	4.16
	41-65 and male	7142	289	4.05
	41-65 and female	6347	366	5.77
	18-40 and male	4182	193	4.62
	18-40 and female	3853	216	5.61
	>65 and female	13 769	414	3.01
	>65 and male	11 834	310	2.62
IQVIA	Male	11 896	432	3.63
	Female	10 720	472	4.40
	41-65 and male	5884	208	3.54
	41-65 and female	5230	223	4.26
	18-40 and male	4971	208	4.18
	18-40 and female	4670	220	4.71
	>65 and female	820	29	3.54
	>65 and male	1041	16	1.54

epilepsy with other anti-epileptic treatments to see if results are consistent with this study.

The type of epilepsy syndrome at baseline was similar in men and women and thus does not explain the higher risk of TRE in women. Men and women differed in the type of comorbidities, which should not be a surprise. It is

well known that women have a higher prevalence of depression, anxiety,³² and lower risks of substance use disorders.³³ Adjusting for these dissimilarities in comorbidity patterns would not be recommended as they represent innate differences between the two sexes and controlling for these characteristics would be an overadjustment

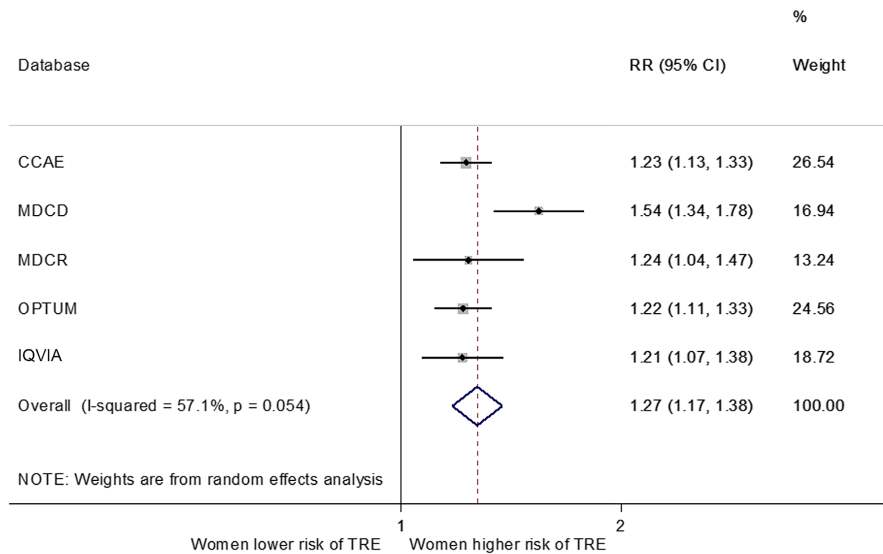


FIGURE 1 Risk of developing treatment resistant epilepsy (TRE) in women compared to men in each of the five databases. CCAE, IBM MarketScan® commercial database; CI, confidence interval; IQVIA, the IQVIA® adjudicated health plan claims data; MDCD, IBM® MarketScan® multi-state Medicaid database; MDCR, IBM® MarketScan® Medicare supplemental database; OPTUM, Optum® De-identified Clinformatics® data Mart database; RR, risk ratio; TRE, treatment resistant epilepsy.

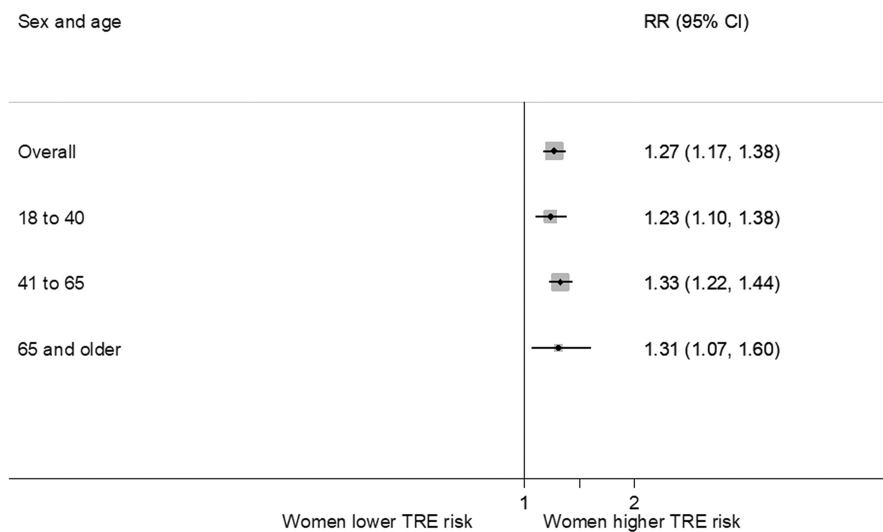


FIGURE 2 Pooled risk of developing treatment resistant epilepsy (TRE) in women compared to men by age categories. RR, risk ratio; TRE, treatment resistant epilepsy.

and would lead to an underestimation of sex differences. Therefore, we adjusted only for age via stratification.

As stated above, the higher risk of developing TRE in women is likely multifactorial and measuring the impact of individual factors in the real world is extremely difficult. For example, women were more likely to have depression, but treatments for this or other co-occurring conditions could lead to drug interactions that would affect the pharmacokinetic of antiseizure medications. On the other hand, using the Charlson score as an indicator of burden of disease, there was no difference between men and women and the observed increased risk in women may not be related to the overall comorbidity profile.

The use of five different US healthcare databases that cover all ages, geographic regions, and different socioeconomic statuses, and the consistency of the results across strata are evidence of the robustness of the results. Beyond differences in sex, this work highlights the importance of health care that is more tailored to the individual, that is,

“personalized medicine.” There is no one-size-fits-all answer for the treatment of epilepsy, and there is much we can learn from existing data to understand the nuances of what treatments are most effective for which patients and for which patients are the most common treatments failing.

4.1 | Limitations

Evidence of TRE was used as a proxy for response to antiseizure medications. It was assumed that the need for exposure to multiple distinctive antiseizure medications in 1 year is likely due to lack of response. However, it could also be the result of adverse events or the need to treat concomitant conditions, like migraine or mood swings in bipolar disorder, which are also more prevalent in women. We addressed this issue by requiring third distinct antiseizure medication in 1 year in order to classify

an individual as having TRE. Using the number of unique antiseizure medications filled by a patient to define TRE is consistent with prior research utilizing claims data.³⁴ While the true prevalence of TRE identified in this study cannot be measured due to the limitations noted above, we do not believe this misclassification would differ between men and women. The incidence of TRE in this study (5%-6%) is lower than what has been found in previous research which averaged 15% in a meta-analysis of adult and mixed-age populations.³⁵ This discrepancy is likely due to the relatively short follow-up time of 1 year in this study compared with 75% of studies having at least 2 years of follow-up in the meta-analysis. It may take more than 1 year for an antiseizure regimen to be considered as ineffective and lead to a treatment change, and our study would fail to identify patients whose second antiseizure medication regimen was unsuccessful after the 1-year follow-up period.

In this study, we focused on one antiseizure medication to avoid confounding the results and the results may not be generalizable to all antiseizure medications; however, levetiracetam is currently the most commonly used antiseizure medication.¹³

The relative 27% increase in the risk of developing TRE in women could be considered modest in magnitude and the absolute difference in risk between men and women as small, as the risk of developing TRE in 1 year is around 4%. An exploration of the potential explanations for why this difference exists was out of the scope for this study. However, knowledge that this difference exists introduces new hypotheses that could be the focus of future research. Potential differences between men and women could be due to dissimilarities in compliance, experiences with adverse events, the influence of comorbid conditions, or other characteristics. The findings highlighted in this study warrant further scrutiny. Additionally, more work is needed to understand if there are specific types of antiseizure medications that are more effective in women that should be prioritized earlier in their treatment.

5 | CONCLUSIONS

In summary, we found that sex differences in response to antiseizure medications exist. Women newly exposed to levetiracetam are more likely to develop TRE than men, independent of age.

CONFLICT OF INTEREST

DMK, RET, and GN are employees of Janssen and have stock interests in Johnson & Johnson. MSC was an employee of Janssen R&D when the study was conducted

and the manuscript was drafted. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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APPENDIX 1

TABLE A1 SNOMED concepts and anticonvulsant ingredients used in the study

SNOMED concept for epilepsy

Epileptic seizure
Seizure disorder
Refractory epilepsy
Status epilepticus due to refractory epilepsy

Anticonvulsants considered

Levetiracetam
Barbexaclone
Beclamide
Brivaracetam
Carbamazepine
Clonazepam
Dipropylacetamide
Eslicarbazepine
Ethosuximide
Ethotoin
Ezogabine
Felbamate
Fosphenytoin
Gabapentin
Lacosamide
Lamotrigine
Mephenytoin
Mephobarbital
Metharbital
Methsuximide
Oxcarbazepine
Paramethadione
Perampanel
Phenacemide
Phenobarbital
Phensuximide
Phenytoin
Pregabalin
Primidone
Progabide
Rufinamide
Sulthiame
Tiagabine
Topiramate
Trimethadione
Valproate
Vigabatrin
Zonisamide