Received: 8 July 2024 | Revised: 12 August 2024 | Accepted: 14 August 2024

DOI: 10.1002/trc2.70001

Alzheimer's & Dementia
Translational Research & Clinical Interventions

SHORT REPORT

Anti-epileptic drug use and subsequent degenerative dementia occurrence

Naoki Ikegaya[1,2] | Honoka Nakamura[3] | Yutaro Takayama[1,2] | Yohei Miyake[2] | Takahiro Hayashi[1,2] | Masaki Sonoda[1,2] | Mitsuru Sato[2] | Kensuke Tateishi[2] | Jun Suenaga[2] | Masao Takaishi[1,4] | Yu Kitazawa[1,5] | Misako Kunii[1,5] | Hiroki Abe[6] | Tomoyuki Miyazaki[7] | Tetsuaki Arai[8] | Manabu Iwasaki[3,9] | Takayuki Abe[3,10] | Tetsuya Yamamoto[1,2]

[1]YCU Epilepsy Center, Yokohama City University Hospital, Yokohama, Japan

[2]Department of Neurosurgery, Yokohama City University Graduate School of Medicine, Yokohama, Japan

[3]School of Data Science, Yokohama City University, Yokohama, Japan

[4]Department of Psychiatry, Yokohama City University Graduate School of Medicine, Yokohama, Japan

[5]Department of Neurology and Stroke Medicine, Yokohama City University Graduate School of Medicine, Yokohama, Japan

[6]Department of Physiology, Yokohama City University Graduate School of Medicine, Yokohama, Japan

[7]Department of Core Project Promotion, Center for Promotion of Research and Industry-Academic Collaboration, Yokohama City University, Yokohama, Japan

[8]Department of Psychiatry, Division of Clinical Medicine, Institute of Medicine, University of Tsukuba, Tsukuba, Japan

[9]The Institute of Statistical Mathematics, Center for Training Professors in Statistics, Tachikawa, Japan

[10]Faculty of Data Science, Kyoto Women's University, Kyoto, Japan

Correspondence
Naoki Ikegaya, YCU Epilepsy Center, Department of Neurosurgery, Yokohama City University Graduate School of Medicine, 3-9 Fukuura, Kanazawa-ku, Yokohama, Kanagawa 236-0004, Japan.
Email: nikegaya@yokohama-cu.ac.jp

Funding information
Yokohama City University; Japan Society for the Promotion of Science, Grant/Award Numbers: 22K16665, 23K11011

Abstract

INTRODUCTION: The use of anti-epileptic drugs (AEDs) in degenerative dementia (DD) remains uncertain. We aimed to evaluate the association of early AED administration with subsequent DD occurrence.

METHODS: Using a large nationwide database, we enrolled patients newly diagnosed with epilepsy from 2014 to 2019 (n = 104,225), and using propensity score matching, we divided them into treatment (those prescribed AEDs in 2014) and control groups. The primary outcome was subsequent DD occurrence in 2019.

RESULTS: Overall, 4489 pairs of patients (2156 women) were matched. The odds ratio (treatment/control) for DD occurrence was 0.533 (95% confidence interval: 0.459–0.617). The DD proportions significantly differed between the treatment (340/4489 = 0.076) and control (577/4489 = 0.129) groups.

DISCUSSION: Among patients newly diagnosed with epilepsy, compared to non-use, early AED use was associated with a lower occurrence of subsequent DD. Further

investigations into and optimization of early intervention for epilepsy in DD are warranted.

KEYWORDS
Alzheimer's disease, anti-epileptic drug, degenerative dementia, epilepsy, neuronal hyperexcitability, nationwide cohort

Highlights

- Anti-epileptic drug (AED) use before epilepsy diagnosis was linked with a lower subsequent degenerative dementia (DD) occurrence.
- Identifying the epileptic phenotype was crucial for justifying early AED use in DD.
- AED use with an epilepsy diagnosis did not pose an additional risk of DD.
- The potential contribution of combination drug therapy to the strategy was noted.

1 | BACKGROUND

Degenerative dementia (DD) is a major cause of death, disability, and dependency, and is associated with a significant health-care cost. There are currently > 35 million individuals with DD worldwide.[1,2] Amyloid beta (Aβ) and tau proteins play critical pathogenic roles in Alzheimer's disease (AD), which is the major cause of DD. Treatments targeting these proteins in preclinical or prodromal AD are key strategies to slow or prevent disease progression and clinical manifestations.[3]

Over the past two decades, the reciprocal connection of Aβ and tau proteins with neuronal hyperactivity, including epilepsy characterized by seizures, subclinical epileptic activities, and interictal epileptiform discharges (IEDs), has gained increasing recognition.[4–13] Aβ and tau proteins trigger neuronal hyperexcitability long before the symptomatic onset of AD,[14–16] and this hyperexcitability is intricately linked to cognitive decline and may be involved in disease progression.[10,17–21] This suggests that neuronal hyperactivity could serve as an early surrogate indicator of AD pathogenesis and may offer a potential target for early intervention strategies. The substantial probability that preclinical and prodromal DD present with epileptic phenotypes, such as seizures, subclinical epileptic activities, and IEDs, highlights the promising impact of the intervention for this pathological epileptic condition.[21–23] Moreover, given that this strategy operates under a distinct mechanism compared to approved current treatments such as cholinesterase inhibitors, glutamate regulators, and anti-amyloid antibody therapy, it is reasonable to anticipate an enhanced additional therapeutic effect on DD.[1]

Anti-epileptic drugs (AEDs) are supposed to mitigate neuronal hyperexcitability, the underlying mechanism of epileptic phenotypes, thereby theoretically reducing the clinical manifestations or disease progression of DD.[10] Experimental studies and small case series suggest that certain AEDs may mitigate epileptic phenotypes and ameliorate cognitive decline in AD.[24–26] However, the lack of cohort studies with large sample sizes that substantiate this idea impedes the practical use of AEDs in DD.[27–30] Establishing clearer criteria for determining the optimal timing of AED use and identifying suitable candidates could help bridge this gap in the literature.

Therefore, in this study, we created cohorts comprising patients with epileptic phenotypes but without a history of long-term epilepsy, which is a known risk factor for DD.[31] Our aim was to assess the association between early AED use (defined as use before the epilepsy diagnosis) and the subsequent occurrence of DD, using data from a large nationwide cohort. We further discuss the appropriate timing of, and eligible candidates for, the use of AEDs in DD.

2 | METHODS

2.1 | Data source and selection

The study data were obtained from the National Database of Health Insurance Claims and Specific Health Checkups in Japan. As of 2014, > 90% of all medical claims have been stored in this database, making it highly comprehensive. The research was approved by an expert panel of the Ministry of Health, Labour and Welfare of Japan and the relevant institutional review board (No. B200400010). Informed consent was not required owing to the anonymous nature of the data.

The following domestic outpatient data from August 2014 and August 2019 were extracted: sex, age (55–84 years, 5-year age categories), disease (dementia, stroke, epilepsy syndromes, intellectual disability, epilepsy, hypertension, diabetes mellitus, and hyperlipidemia; Table S1 in supporting information), International Classification of Diseases 10th edition code, and AED prescription (Table S2 in supporting information).

2.2 | Exposure and outcomes

Our primary objective was to evaluate the association between AED use and DD occurrence in patients with epileptic phenotypes. To accurately include DD, we excluded patients diagnosed with intellectual

RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed the literature using PubMed. Experimental and small case studies suggested that anti-epileptic drugs (AEDs) help to reduce Alzheimer's disease symptoms and potentially slow its progression. However, no large studies support the idea. This gap may arise from the complexity of the timing of AED administration and the lack of clear criteria for selecting eligible candidates.
2. **Interpretation**: Our findings suggested that patients in the prodromal phase of epilepsy were promising candidates. AED use before an epilepsy diagnosis and continued use thereafter led to a lower subsequent degenerative dementia occurrence, compared to later or non-use of AEDs.
3. **Future directions**: AED use before an epilepsy diagnosis might mitigate dementia symptoms, slow disease progression, and postpone diagnosis. To this end, the (1) early detection of prodromal epilepsy, (2) optimal AED type and doses, and (3) required duration of AED administration to exert a preventive effect ought to be established.

disabilities that could affect this diagnosis (Table S1C,D) and defined DD as "dementia, except vascular dementia (dementia minus stroke)" plus "AD." Patients aged 55 to 79 years as of 2014 and diagnosed with DD in 2014 were excluded (n = 16,253,567; Figure 1 and supporting information).

The exposure was defined as any AED prescription in 2014. The outcome was a DD diagnosis in 2019. In the primary analysis, patients who were not diagnosed with epilepsy in 2014 and were eventually diagnosed in 2019 were included. This enabled us to isolate the effect of AED use on DD occurrence from long-term epilepsy effects[31] and evaluate AED use in patients with epileptic phenotypes, whether noticed or unnoticed (Cohort 1: n = 104,225). For the sensitivity analysis, a cohort of patients with epilepsy, either in 2014, 2019, or both, was analyzed (Cohort 2: n = 235,716).

2.3 | Statistical analyses

Propensity score matching was conducted between the treatment (AED) and control (non-AED) groups in 2014. The scores were estimated using a logistic regression model, including sex, age, hypertension, diabetes mellitus, and hyperlipidemia. The greedy algorithm (matching ratio = 1:1 without replacement) with a caliper width of 0.1 standard deviation of the propensity score's logit was used. Age categories and sex were matched exactly. The odds ratio (OR) of DD occurrence in 2019 was estimated using a conditional logistic regression model with matched pairs as a stratum. The proportions of DD occurrence were compared between the treatment and control groups using the conditional logistic model. The significance level for all tests was set at 5% (two-sided). All data were analyzed using SAS version 9.4 (SAS Institute). For the subgroup analysis, the proportions of patients with DD by AED type and prescription time points were aggregated.

3 | RESULTS

For the primary analysis, 4489 pairs from Cohort 1 (2156 women), aged 55 to 59 (21%), 60 to 64 (22%), 65 to 69 (21%), 70 to 74 (20%), and 75 to 79 (16%) years, were matched (Table 1). The estimated OR (treatment/control) for DD occurrence was 0.533 (95% confidence interval: 0.459–0.617), and the DD proportions were significantly different between the treatment (340/4489 = 0.076) and control (577/4489 = 0.129) groups. For the sensitivity analysis, 23,953 pairs from Cohort 2, aged 55 to 59 (21%), 60 to 64 (23%), 65 to 69 (22%), 70 to 74 (20%), and 75 to 79 (14%) years, were matched. The estimated OR was 0.556 (95% confidence interval: 0.514–0.601), and the DD proportions were significantly different between the treatment (1128/23,953 = 0.047) and control (1906/23,953 = 0.080) groups. Thus, both cohorts (those with newly diagnosed epilepsy in 2019 and those with an epilepsy diagnosis in 2014, 2019, or both) demonstrated a lower DD occurrence in patients taking AEDs than in those not taking AEDs. Furthermore, a stratified subgroup analysis of DD occurrence across different age groups consistently corroborated these findings for all age categories (Table 2 and Figure S1 in supporting information).

In the exploratory analysis (Table 3 and Table S3 in supporting information), the proportion of use of each AED was not substantially different but was the lowest for the combination drug (phenytoin and phenobarbital). The DD proportion based on the AED prescription timepoint was as follows (low to high): 5.5% (both in 2014 and 2019), 9.9% (only in 2014), 11.7% (only in 2019), and 13% (not in either year).

4 | DISCUSSION

We evaluated the association between early AED use and DD occurrence using data from a large nationwide cohort. To our knowledge, this study is the first to show a significantly lower subsequent DD occurrence in the treatment group (early AED use; 7.6%) than in the control group (non-AED; 12.9%) among patients with newly diagnosed epilepsy. This suggests that early AED use may help reduce or postpone the occurrence of DD in patients with epileptic phenotypes who are not yet diagnosed with epilepsy, relieving cognitive dysfunction associated with epilepsy and/or dementia or suppressing disease progression. The sub-analysis underscored the significance of continuing AED treatment for reducing DD occurrence. Additionally, the findings on AED types expanded our knowledge of the potential of combination drug therapies. The sensitivity analysis revealed that AED use in patients with a diagnosis of epilepsy in any of the years of study (2014 and 2019) did not lead to an increased occurrence of DD.

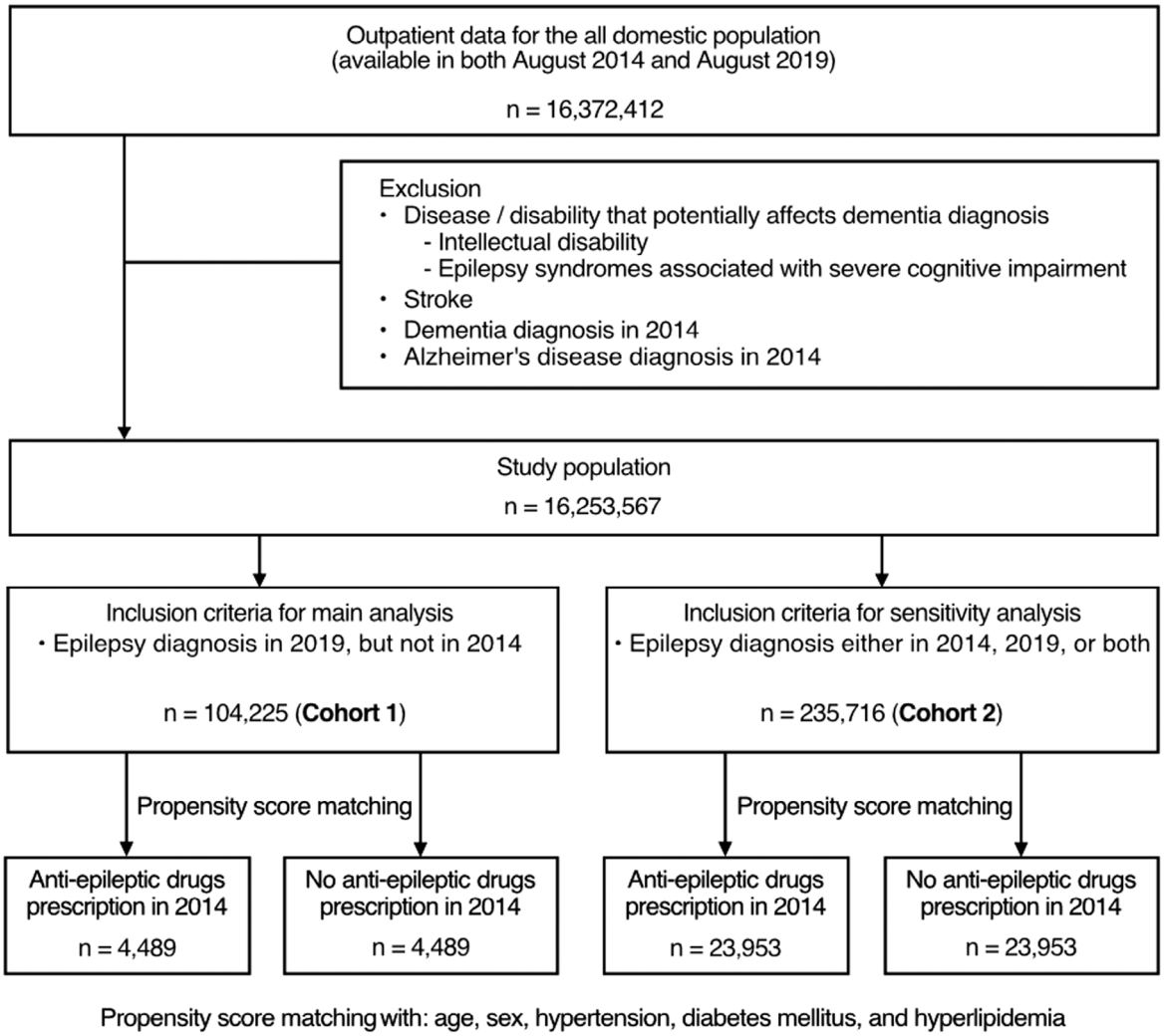

FIGURE 1 Flow diagram of study participants.

The significantly lower occurrence of DD in 2019 in patients taking AEDs in 2014 (those presumably with subclinical epileptic activities or IEDs before overt seizures, that is, still without an epilepsy diagnosis) highlights the potential benefit of early AED intervention for DD. This observation aligns with the concept of AEDs mitigating neuronal hyperexcitability, leading to therapeutic significance in preclinical and prodromal DD.[10] The optimal timing of intervention is intricately tied to the presumed mechanism underlying the effectiveness of AEDs. The currently proposed mechanisms behind the positive AED effects on DD involve two pathways: (1) mitigating cognitive dysfunction linked to epilepsy, seizures, and epileptic activities and (2) slowing disease progression by modifying the hyperexcitability-dependent or -independent metabolism (release, propagation, and accumulation) of pathological proteins such as Aβ and tau.[10,32] Among these considerations, the second point (slowing disease progression) is likely to be time sensitive. As we have demonstrated, early intervention during the pathogenic period of DD—before its completion or symptomatization—and the prodromal phase of epilepsy would be preferred to enhance effectiveness. Conversely, the mechanism described in the first point (mitigating cognitive dysfunction) targets epileptic factors rather than DD itself, suggesting the potential utility of AEDs after the pathogenesis of DD has progressed to some extent. Our findings substantiate this idea, indicating that regardless of early intervention, administering AEDs in 2019, presumably after the onset of epilepsy, demonstrated greater effectiveness for DD than not administering AEDs. In this context, seizure detection is crucial to take advantage of the opportunity for DD intervention.[33]

Regarding the selection of candidates, our findings yielded promising results in patients with epileptic phenotypes but without a history of long-term epilepsy. The presence of long-term epilepsy is a factor intricately linked to both AEDs and AD, thereby complicating the interpretation of their association.[31] Using data from a large nationwide cohort, Schnier et al. demonstrated that participants with epilepsy exhibit a higher AD incidence, compared to those without epilepsy, after the age of 70 to 75 years.[31] As this cohort comprised > 80% of participants diagnosed with epilepsy before the age of 60 years, a delay of at least 10 to 15 years may exist before epilepsy becomes

TABLE 1 Demographics, characteristics, and number of patients with degenerative dementia in Cohorts 1 and 2.

	Cohort 1		Cohort 2	
Before PSM	**AED (*n* = 4489)**	**Non-AED (*n* = 99,736)**	**AED (*n* = 23,953)**	**Non-AED (*n* = 211,763)**
Sex				
Female	2156 (0.480)	46,304 (0.464)	11,580 (0.483)	97,804 (0.462)
Male	2333	53,432	12,373	113,959
Age (years)				
55–60	954 (0.213)	14,599 (0.146)	5129 (0.214)	36,961 (0.175)
60–65	981 (0.219)	17,888 (0.179)	5489 (0.229)	41,955 (0.198)
65–70	942 (0.210)	21,591 (0.216)	5214 (0.218)	46,116 (0.218)
70–75	907 (0.202)	24,520 (0.246)	4673 (0.195)	47,661 (0.225)
75–80	705 (0.157)	21,138 (0.212)	3448 (0.144)	39,070 (0.184)
Comorbidities				
Hypertension	1172 (0.261)	38,366 (0.385)	9594 (0.401)	89,826 (0.424)
Diabetes mellitus	186 (0.041)	6503 (0.065)	1540 (0.064)	15,994 (0.076)
Hyperlipidemia	1003 (0.223)	31,910 (0.320)	8268 (0.345)	78,233 (0.369)
	Cohort 1		**Cohort 2**	
After PSM	**AED (*n* = 4489)**	**Non-AED (*n* = 4489)**	**AED (*n* = 23,953)**	**Non-AED (*n* = 23,953)**
Sex				
Female	2156 (0.480)	2156 (0.480)	11,580 (0.483)	11,580 (0.483)
Male	2333	2333	12,373	12,373
Age (years)				
55–60	954 (0.213)	954 (0.213)	5129 (0.214)	5129 (0.214)
60–65	981 (0.219)	981 (0.219)	5489 (0.229)	5489 (0.229)
65–70	942 (0.210)	942 (0.210)	5214 (0.218)	5214 (0.218)
70–75	907 (0.202)	907 (0.202)	4673 (0.195)	4673 (0.195)
75–80	705 (0.157)	705 (0.157)	3448 (0.144)	3448 (0.144)
Comorbidities				
Hypertension	1172 (0.261)	1172 (0.261)	9594 (0.401)	9594 (0.401)
Female/male	556/616	556/616	4799/4795	4799/4795
Diabetes mellitus	186 (0.041)	186 (0.041)	1540 (0.064)	1540 (0.064)
Female/male	97/89	97/89	865/675	865/675
Hyperlipidemia	1003 (0.223)	1003 (0.223)	8268 (0.345)	8268 (0.345)
Female/male	382/621	382/621	3625/4643	3625/4643
Number of participants with DD				
Total	340 (0.076)	577 (0.129)	1128 (0.047)	1906 (0.080)
Female/male	138/202	255/322	455/673	868/1038
Odds ratio (AED/non-AED)	0.533 (95% CI: 0.459–0.617)		0.556 (95% CI: 0.514–0.601)	

Abbreviations: AED, anti-epileptic drug; CI, confidence interval; DD, degenerative dementia; PSM, propensity score matching.

a risk factor for AD. To eliminate this long-term epilepsy effect, we excluded patients diagnosed with epilepsy in 2014 and aimed to obtain an accurate understanding of the association of AEDs with DD. Epileptic phenotype is another factor that influences the association between AEDs and AD. In experimental studies with animal models, excessive discharges have been shown to alter the metabolism of Aβ and tau.[5,7,8,12,24] AEDs, in turn, may modify these metabolic alterations by alleviating hyperexcitability.[34] Recent human studies have

TABLE 2 Age-stratified subgroup analysis of comorbidities and degenerative dementia.

	Cohort 1		Cohort 2	
After PSM	AED ($n = 4489$)	Non-AED ($n = 4489$)	AED ($n = 23,953$)	Non-AED ($n = 23,953$)
Age (years)				
55–60	954 (0.213)	954 (0.213)	5129 (0.262)	5129 (0.214)
60–65	981 (0.219)	981 (0.219)	5489 (0.337)	5489 (0.229)
65–70	942 (0.210)	942 (0.210)	5214 (0.414)	5214 (0.218)
70–75	907 (0.202)	907 (0.202)	4673 (0.491)	4673 (0.195)
75–80	705 (0.157)	705 (0.157)	3448 (0.566)	3448 (0.144)
Comorbidities				
Hypertension	1172 (0.261)	1172 (0.261)	9594 (0.401)	9594 (0.401)
55–60	156 (0.164)	156 (0.164)	1346 (0.262)	1346 (0.262)
60–65	198 (0.202)	198 (0.202)	1849 (0.337)	1849 (0.337)
65–70	251 (0.266)	251 (0.266)	2156 (0.414)	2156 (0.414)
70–75	290 (0.320)	290 (0.320)	2293 (0.491)	2293 (0.491)
75–80	277 (0.393)	277 (0.393)	1950 (0.566)	1950 (0.566)
Diabetes mellitus	186 (0.041)	186 (0.041)	1540 (0.064)	1540 (0.064)
55–60	27 (0.028)	27 (0.028)	262 (0.051)	262 (0.051)
60–65	42 (0.043)	42 (0.043)	325 (0.059)	325 (0.059)
65–70	38 (0.040)	38 (0.040)	340 (0.065)	340 (0.065)
70–75	43 (0.047)	43 (0.047)	336 (0.072)	336 (0.072)
75–80	36 (0.051)	36 (0.051)	277 (0.080)	277 (0.080)
Hyperlipidemia	1003 (0.223)	1003 (0.223)	8268 (0.345)	8268 (0.345)
55–60	147 (0.154)	147 (0.154)	1499 (0.292)	1499 (0.292)
60–65	211 (0.215)	211 (0.215)	1785 (0.325)	1785 (0.325)
65–70	205 (0.218)	205 (0.218)	1822 (0.349)	1822 (0.349)
70–75	213 (0.235)	213 (0.235)	1745 (0.373)	1745 (0.373)
75–80	227 (0.322)	227 (0.322)	1417 (0.411)	1417 (0.411)
Number of participants with DD				
Total	340 (0.076)	577 (0.129)	1128 (0.047)	1906 (0.080)
55–60	14 (0.014)	30 (0.031)	49 (0.010)	92 (0.018)
60–65	40 (0.041)	74 (0.075)	146 (0.027)	189 (0.034)
65–70	70 (0.074)	111 (0.118)	211 (0.040)	358 (0.069)
70–75	91 (0.100)	162 (0.179)	324 (0.069)	580 (0.124)
75–80	125 (0.177)	200 (0.284)	398 (0.115)	687 (0.199)

Abbreviations: AED, anti-epileptic drug; DD, degenerative dementia; PSM, propensity score matching.

identified Aβ and tau proteins in surgical specimens from patients with drug-resistant epilepsy,[35,36] implying a relationship between abnormal neural discharges and the presence of these pathogenic proteins. Although direct comparisons are challenging due to the rarity of resective surgery in non–drug-resistant epilepsy cases, these findings suggest that abnormal discharges, which are not sufficiently controlled by AEDs, may be associated with the exhibition of Aβ and tau. As demonstrated in our cohort, epileptic phenotypes could serve as a potential predictor of a favorable DD response to AEDs. This AED responsiveness based on epileptic phenotypes was indicated in a subanalysis of a small prospective trial of AD.[37] Conversely, Taipale et al. reported on the potential risk of AEDs for AD in a large cohort.[30] Their cohort comprised a small proportion of patients with epilepsy, implying that AEDs may have adverse effects in patients without epileptic phenotypes. In this context, methods for early and highly sensitive detection of epileptic phenotypes or ideally the prodromal phase of epilepsy (hyperexcitability without overt seizure) are crucial.[20–23] Our findings contribute to further evidence supporting the concept of the use of AEDs in DD, underscoring the importance of intervening during the early pathological stage, ideally in the prodromal phase

TABLE 3 Subgroup analysis of the proportion of participants with degenerative dementia in 2019.

By AED type	Cohort 1			Cohort 2		
AED	*n*	# of DD	Proportion	*n*	# of DD	Proportion
VPA	1373	99	0.072	9943	405	0.041
CZP	1311	103	0.079	6767	342	0.051
CBZ	900	53	0.059	4664	199	0.043
PHT	555	32	0.058	3265	117	0.036
ZNS	402	36	0.090	2043	125	0.061
LEV	160	13	0.081	920	56	0.061
LTG	156	11	0.071	631	35	0.055
GBP	NA[a]	NA[b]	0.048	569	15	0.026
PB	NA[a]	NA[b]	0.038	502	13	0.026
CLB	NA[a]	NA[b]	0.071	343	22	0.064
PHT+PB	NA[a]	NA[b]	0.017	1151	29	0.025
Control	4489	577	0.129	23,953	1906	0.080

By AED prescription	Cohort 1		
AED	*N*	# of DD	Proportion
2014+/2019+	2376	130	0.055
2014+/2019−	2113	210	0.099
2014−/2019+	359	42	0.117
2014−/2019−	4130	535	0.130

Abbreviations: AED, anti-epileptic drug; CBZ, carbamazepine; CLB, clonazepam; CZP, clonazepam; DD, degenerative dementia; GBP, gabapentin; LEV, levetiracetam; LTG, lamotrigine; PB, phenobarbital; PHT, phenytoin; VPA, valproic acid; ZNS, zonisamide.
[a]Not available (< 200).
[b]Not available (< 10), notation according to relevant guidelines.

of epilepsy, and identifying promising candidates as patients without long-term epilepsy but with epileptic phenotypes. Stratification by epilepsy type may also facilitate the optimization of candidates. Additionally, it is noteworthy that these effects can be independent of age stratification.

Despite the use of various AEDs, including potential AD-promoting drugs,[29,30,38,39] our overall result highlights their benefits in DD, suggesting further optimization through AED selection.[10] In recent years, levetiracetam and lamotrigine have garnered broad recognition for their efficacy in managing epilepsy and in addressing cognitive decline linked to AD.[25,26,40] Contrastingly, our exploratory analysis inferred a potential benefit of combination drug therapy on DD occurrence. This viewpoint is intriguing as the existing evidence predominantly centers around the efficacy of a single type of AED.[34,41] The potential pharmacological strategy of combination drug therapy merits further investigation. In an approach to optimize AED selection, the localization of hyperexcitability may provide some clues. However, while prodromal AD is presumably associated with abnormal focal (temporal) discharges,[23] the present study did not clarify the difference in the effect of narrow-spectrum AEDs (which mainly focus on specific epilepsy types, including focal epilepsy) versus wide-spectrum AEDs on DD. Therefore, this remains a topic for further debate. In addition, establishing the appropriate dosage and duration of AED use is essential.

4.1 | Limitations

As is the nature of health-care claims database studies, there is an inherent limitation in the exact concordance between diagnostic codes and clinical diagnoses. In the UK Biobank's primary care database, the accuracy for all-cause dementia was 86.8%, and that for AD was 74.1%, but these have not been validated in the database used in this study.[42,43] In addition, our definition of DD may not have identified non-AD DD completely, although it captured most cases of AD, the vast majority of cause of DD in the database. Diseases besides epilepsy, for which AEDs are prescribed, may affect DD occurrence; however, its major reasons—bipolar disorder or migraine—appear to either increase or be unrelated to AD occurrence.[44,45] Therefore, even if patients with these conditions were included in the AED group, it would not lead to a lower DD occurrence after AED use, thus not compromising our results. As epilepsy among older individuals can be caused by neoplasms, degenerative diseases, and metabolic diseases, epilepsy in our cohort may not have been the DD-related pathological condition.[46] Nevertheless, our results suggest that suppressing the unexplained hyperexcitability using AEDs reduces DD occurrence. A non-AED prescription, despite an epilepsy diagnosis, may be attributed to less severe epilepsy (for example, less frequent seizures),[47] suggesting a different background; however, both groups in the primary analysis included these cases, negating their effects. Major

comorbidities were accounted for and balanced through propensity score matching, but there are other factors not addressed in this study. For example, ketogenic diets for epilepsy have been implicated in the suppression of AD,[48] but no relevant data were collected in this study. Traumatic brain injury has also been implicated in the relation to both epilepsy and dementia,[49,50] but data were not collected. Finally, the time difference from epilepsy diagnosis to DD diagnosis varied by up to 5 years in the primary analysis. However, epilepsy takes longer to become a risk factor for dementia;[31] thus, the effect did not compromise the outcome. Collectively, the observed benefit of AED use is not diminished. Further investigations into early intervention and diagnosis for neuronal hyperexcitability and epilepsy in DD and prospective studies with clinically well-described cohorts are required to validate our findings.

4.2 | Conclusions

A lower occurrence of subsequent DD was observed in patients with newly diagnosed epilepsy taking AEDs before epilepsy diagnosis than in those not taking AEDs. Further investigations into and optimization of earlier interventions for epilepsy in DD are required.

ACKNOWLEDGMENTS

The authors thank the staff members at the Yokohama City University Epilepsy Center. This work was supported by an intramural basic grant from Yokohama City University and the Japan Society for the Promotion of Science (JSPS) KAKENHI (Grant Number: 22K16665 to N.I., 23K11011 to T.Abe). The funders did not have any role in the design of the study, acquisition and analysis of the data, or writing of the manuscript.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest. Author disclosures are available in the supporting information.

CONSENT STATEMENT

This study was approved by an expert panel of the Ministry of Health, Labour and Welfare of Japan and the relevant institutional review board (No. B200400010). Informed consent was not required owing to the anonymous nature of the data.

ORCID

Naoki Ikegaya https://orcid.org/0000-0003-4439-3785

REFERENCES

1. Alzheimer's Association. 2023 Alzheimer's disease facts and figures. *Alzheimers Dement*. 2023;19(4):1598-1695. doi:10.1002/alz.13016
2. World Health Organization. Dementia. Fact sheets. 2023. Data accessed February 25, 2024. https://www.who.int/news-room/fact-sheets/detail/dementia
3. Rafii MS, Aisen PS. Detection and treatment of Alzheimer's disease in its preclinical stage. *Nat Aging*. 2023;3(5):520-531. doi:10.1038/s43587-023-00410-4
4. Ahmed Z, Cooper J, Murray TK, et al. A novel in vivo model of tau propagation with rapid and progressive neurofibrillary tangle pathology: the pattern of spread is determined by connectivity, not proximity. *Acta Neuropathol*. 2014;127(5):667-683. doi:10.1007/s00401-014-1254-6
5. Bero AW, Yan P, Roh JH, et al. Neuronal activity regulates the regional vulnerability to amyloid-β deposition. *Nat Neurosci*. 2011;14(6):750-756. doi:10.1038/nn.2801
6. Brown J, Camporesi E, Lantero-Rodriguez J, et al. Tau in cerebrospinal fluid induces neuronal hyperexcitability and alters hippocampal theta oscillations. *Acta Neuropathol Commun*. 2023;11(1):67. doi:10.1186/s40478-023-01562-5
7. Cirrito JR, Kang JE, Lee J, et al. Endocytosis is required for synaptic activity-dependent release of amyloid-beta in vivo. *Neuron*. 2008;58(1):42-51. doi:10.1016/j.neuron.2008.02.003
8. Cirrito JR, Yamada KA, Finn MB, et al. Synaptic activity regulates interstitial fluid amyloid-beta levels in vivo. *Neuron*. 2005;48(6):913-922. doi:10.1016/j.neuron.2005.10.028
9. Huijbers W, Mormino EC, Schultz AP, et al. Amyloid-β deposition in mild cognitive impairment is associated with increased hippocampal activity, atrophy and clinical progression. *Brain: Journal Neurol*. 2015;138(Pt 4):1023-1035. doi:10.1093/brain/awv007
10. Vossel KA, Tartaglia MC, Nygaard HB, Zeman AZ, Miller BL. Epileptic activity in Alzheimer's disease: causes and clinical relevance. *Lancet Neurol*. 2017;16(4):311-322. doi:10.1016/s1474-4422(17)30044-3
11. Wu JW, Hussaini SA, Bastille IM, et al. Neuronal activity enhances tau propagation and tau pathology in vivo. *Nat Neurosci*. 2016;19(8):1085-1092. doi:10.1038/nn.4328
12. Yamada K, Holth JK, Liao F, et al. Neuronal activity regulates extracellular tau in vivo. *J Exp Med*. 2014;211(3):387-393. doi:10.1084/jem.20131685
13. Yamamoto K, Tanei ZI, Hashimoto T, et al. Chronic optogenetic activation augments aβ pathology in a mouse model of Alzheimer disease. *Cell Rep*. 2015;11(6):859-865. doi:10.1016/j.celrep.2015.04.017
14. Palop JJ, Mucke L. Amyloid-beta-induced neuronal dysfunction in Alzheimer's disease: from synapses toward neural networks. *Nat Neurosci*. 2010;13(7):812-818. doi:10.1038/nn.2583
15. Romoli M, Sen A, Parnetti L, Calabresi P, Costa C. Amyloid-β: a potential link between epilepsy and cognitive decline. *Nat Rev Neurol*. 2021;17(8):469-485. doi:10.1038/s41582-021-00505-9
16. Zawar I, Kapur J. Does Alzheimer's disease with mesial temporal lobe epilepsy represent a distinct disease subtype? *Alzheimers Dement*. 2023;19(6):2697-2706. doi:10.1002/alz.12943
17. Lam AD, Deck G, Goldman A, Eskandar EN, Noebels J, Cole AJ. Silent hippocampal seizures and spikes identified by foramen ovale electrodes in Alzheimer's disease. *Nat Med*. 2017;23(6):678-680. doi:10.1038/nm.4330
18. Nous A, Seynaeve L, Feys O, et al. Subclinical epileptiform activity in the Alzheimer continuum: association with disease, cognition and detection method. *Alzheimer's Res Ther*. 2024;16(1):19. doi:10.1186/s13195-023-01373-9
19. Soula M, Maslarova A, Harvey RE, et al. Interictal epileptiform discharges affect memory in an Alzheimer's disease mouse model. *Proc Nat Acad Sci USA*. 2023;120(34):e2302676120. doi:10.1073/pnas.2302676120
20. Targa Dias Anastacio H, Matosin N, Ooi L. Neuronal hyperexcitability in Alzheimer's disease: what are the drivers behind this aberrant phenotype? *Transl Psychiatry*. 2022;12(1):257. doi:10.1038/s41398-022-02024-7
21. Vossel KA, Ranasinghe KG, Beagle AJ, et al. Incidence and impact of subclinical epileptiform activity in Alzheimer's disease. *Ann Neurol*. 2016;80(6):858-870. doi:10.1002/ana.24794
22. Horváth A, Szűcs A, Hidasi Z, Csukly G, Barcs G, Kamondi A. Prevalence, semiology, and risk factors of epilepsy in Alzheimer's Disease:

an ambulatory EEG Study. *J Alzheimers Dis*. 2018;63(3):1045-1054. doi:10.3233/jad-170925
23. Lam AD, Sarkis RA, Pellerin KR, et al. Association of epileptiform abnormalities and seizures in Alzheimer disease. *Neurology*. 2020;95(16):e2259-e2270. doi:10.1212/wnl.0000000000010612
24. Bakker A, Krauss GL, Albert MS, et al. Reduction of hippocampal hyperactivity improves cognition in amnestic mild cognitive impairment. *Neuron*. 2012;74(3):467-474. doi:10.1016/j.neuron.2012.03.023
25. Rizzello E, Pimpinella D, Pignataro A, et al. Lamotrigine rescues neuronal alterations and prevents seizure-induced memory decline in an Alzheimer's disease mouse model. *Neurobiol Dis*. 2023;181:106106. doi:10.1016/j.nbd.2023.106106
26. Sanchez PE, Zhu L, Verret L, et al. Levetiracetam suppresses neuronal network dysfunction and reverses synaptic and cognitive deficits in an Alzheimer's disease model. *Proc Nat Acad Sci USA*. 2012;109(42):E2895-E2903. doi:10.1073/pnas.1121081109
27. Carter MD, Weaver DF, Joudrey HR, Carter AO, Rockwood K. Epilepsy and antiepileptic drug use in elderly people as risk factors for dementia. *J Neurol Sci*. 2007;252(2):169-172. doi:10.1016/j.jns.2006.11.004
28. Coupland CAC, Hill T, Dening T, Morriss R, Moore M, Hippisley-Cox J. Anticholinergic drug exposure and the risk of dementia: a nested case-control study. *JAMA Intern Med*. 2019;179(8):1084-1093. doi:10.1001/jamainternmed.2019.0677
29. Jacob L, Bohlken J, Kostev K. Is there an association between antiepileptic drug use and dementia risk? A case-control study. *J Alzheimers Dis*. 2019;68(1):97-103. doi:10.3233/jad-181194
30. Taipale H, Gomm W, Broich K, et al. Use of antiepileptic drugs and dementia risk-an analysis of Finnish health register and German health insurance data. *J Am Geriatr Soc*. 2018;66(6):1123-1129. doi:10.1111/jgs.15358
31. Schnier C, Duncan S, Wilkinson T, Mbizvo GK, Chin RFM. A nationwide, retrospective, data-linkage, cohort study of epilepsy and incident dementia. *Neurology*. 2020;95(12):e1686-e1693. doi:10.1212/wnl.0000000000010358
32. Ito Y, Takeda S, Moroi S, et al. Antiepileptic drugs modulate Alzheimer-related tau aggregation in a neuronal activity-independent manner. *Dement Geriatr Cogn Disord*. 2023;52(2):108-116. doi:10.1159/000529915
33. Cretin B, Philippi N, Bousiges O, et al. Do we know how to diagnose epilepsy early in Alzheimer's disease? *Rev Neurol (Paris)*. 2017;173(6):374-380. doi:10.1016/j.neurol.2017.03.028
34. Bosco F, Guarnieri L, Rania V, et al. Antiseizure medications in Alzheimer's disease from preclinical to clinical evidence. *Int J Mol Sci*. 2023;24(16):12639. doi:10.3390/ijms241612639
35. Aroor A, Nguyen P, Li Y, Das R, Lugo JN, Brewster AL. Assessment of tau phosphorylation and β-amyloid pathology in human drug-resistant epilepsy. *Epilepsia Open*. 2023;8(2):609-622. doi:10.1002/epi4.12744
36. Gourmaud S, Shou H, Irwin DJ, et al. Alzheimer-like amyloid and tau alterations associated with cognitive deficit in temporal lobe epilepsy. *Brain: Journal Neurol*. 2020;143(1):191-209. doi:10.1093/brain/awz381
37. Vossel K, Ranasinghe KG, Beagle AJ, et al. Effect of levetiracetam on cognition in patients with Alzheimer disease with and without epileptiform activity: a randomized clinical trial. *JAMA Neurol*. 2021;78(11):1345-1354. doi:10.1001/jamaneurol.2021.3310
38. Billioti de Gage S, Moride Y, Ducruet T, et al. Benzodiazepine use and risk of Alzheimer's disease: case-control study. *BMJ*. 2014;349:g5205. doi:10.1136/bmj.g5205
39. Fleisher AS, Truran D, Mai JT, et al. Chronic divalproex sodium use and brain atrophy in Alzheimer disease. *Neurology*. 2011;77(13):1263-1271. doi:10.1212/WNL.0b013e318230a16c
40. Frederiksen KS, Cooper C, Frisoni GB, et al. A European Academy of Neurology guideline on medical management issues in dementia. *Eur J Neurol*. 2020;27(10):1805-1820. doi:10.1111/ene.14412
41. Kern DM, Cepeda MS, Lovestone S, Seabrook GR. Aiding the discovery of new treatments for dementia by uncovering unknown benefits of existing medications. *Alzheimers Dement (N Y)*. 2019;5:862-870. doi:10.1016/j.trci.2019.07.012
42. Suto M, Iba A, Sugiyama T, et al. Literature review of studies using the National Database of the Health Insurance Claims of Japan (NDB): limitations and strategies in using the NDB for research. *JMA J*. 2024;7(1):10-20. doi:10.31662/jmaj.2023-0078
43. Wilkinson T, Schnier C, Bush K, et al. Identifying dementia outcomes in UK Biobank: a validation study of primary care, hospital admissions and mortality data. *Eur J Epidemiol*. 2019;34(6):557-565. doi:10.1007/s10654-019-00499-1
44. Katon W, Pedersen HS, Ribe AR, et al. Effect of depression and diabetes mellitus on the risk for dementia: a national population-based cohort study. *JAMA Psychiatry*. 2015;72(6):612-619. doi:10.1001/jamapsychiatry.2015.0082
45. Kim J, Ha WS, Park SH, Han K, Baek MS. Association between migraine and Alzheimer's disease: a nationwide cohort study. *Front Aging Neurosci*. 2023;15:1196185. doi:10.3389/fnagi.2023.1196185
46. Sen A, Jette N, Husain M, Sander JW. Epilepsy in older people. *Lancet*. 2020;395(10225):735-748. doi:10.1016/s0140-6736(19)33064-8
47. Sharma S, Chen Z, Rychkova M, et al. Treatment initiation decisions in newly diagnosed epilepsy-A longitudinal cohort study. *Epilepsia*. 2020;61(3):445-454. doi:10.1111/epi.16439
48. Xu Y, Zheng F, Zhong Q, Zhu Y. Ketogenic diet as a promising non-drug intervention for Alzheimer's disease: mechanisms and clinical implications. *J Alzheimers Dis*. 2023;92(4):1173-1198. doi:10.3233/jad-230002
49. Barnes DE, Kaup A, Kirby KA, Byers AL, Diaz-Arrastia R, Yaffe K. Traumatic brain injury and risk of dementia in older veterans. *Neurology*. 2014;83(4):312-319. doi:10.1212/wnl.0000000000000616
50. Pease M, Gonzalez-Martinez J, Puccio A, et al. Risk factors and incidence of epilepsy after severe traumatic brain injury. *Ann Neurol*. 2022;92(4):663-669. doi:10.1002/ana.26443

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Ikegaya N, Nakamura H, Takayama Y, et al. Anti-epileptic drug use and subsequent degenerative dementia occurrence. *Alzheimer's Dement*. 2024;10:e70001. https://doi.org/10.1002/trc2.70001