

# Antiepileptic drug use and mortality among community-dwelling persons with Alzheimer disease

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## Abstract

### Objective

To evaluate the risk of death in relation to incident antiepileptic drug (AED) use compared with nonuse in people with Alzheimer disease (AD) through the assessment in terms of duration of use, specific drugs, and main causes of death.

### Methods

The MEDALZ (Medication Use and Alzheimer Disease) cohort study includes all Finnish persons who received a clinically verified AD diagnosis ( $n = 70,718$ ) in 2005–2011. Incident AED users were identified with 1-year washout period. For each incident AED user ( $n = 5,638$ ), 1 nonuser was matched according to sex, age, and time since AD diagnosis. Analyses were conducted with Cox proportional regression models and inverse probability of treatment weighting (IPTW).

### Results

Nearly 50% discontinued AEDs within 6 months. Compared with nonusers, AED users had an increased relative risk of death (IPTW hazard ratio [HR], 1.23; 95% confidence interval [CI], 1.12–1.36). This was mainly due to deaths from dementia (IPTW HR, 1.62; 95% CI, 1.42–1.86). There was no difference in cardiovascular and cerebrovascular deaths (IPTW HR, 0.98; 95% CI, 0.67–1.44). The overall mortality was highest during the first 90 days of AED use (IPTW HR, 2.40; 95% CI, 1.91–3.03). Among users of older AEDs, relative risk of death was greater compared to users of newer AEDs (IPTW HR, 1.79; 95% CI, 1.52–2.16).

### Conclusion

In older vulnerable patients with a cognitive disorder, careful consideration of AED initiation and close adverse events monitoring are needed.

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## Glossary

**AD** = Alzheimer disease; **AED** = antiepileptic drug; **ATC** = Anatomical Therapeutic Chemical; **CI** = confidence interval; **CYP** = cytochrome P450; **DSM-IV** = Diagnostic and Statistical Manual of Mental Disorders, 4th edition; **HR** = hazard ratio; **ICD-10** = *International Classification of Diseases-10*; **IPT** = inverse probability of treatment; **IPTW** = inverse probability of treatment weighting; **MEDALZ** = Medication Use and Alzheimer Disease; **NSAID** = nonsteroidal anti-inflammatory drug; **PRE2DUP** = from prescription drug purchase to drug use periods; **SII** = Social Insurance Institution of Finland; **SUDEP** = sudden unexpected death in epilepsy.

Prevalence of Alzheimer disease (AD) has rapidly increased across the globe<sup>1</sup> and it is among the leading causes of death.<sup>2</sup> We have previously shown that use of antiepileptic drugs (AEDs) was more common among people with AD in comparison to a matched cohort without AD.<sup>3</sup> Concerningly, a substantial proportion of people with AD used older AEDs, which have a less favorable safety profile,<sup>4</sup> and their use was linked to higher rate of hospitalizations<sup>5</sup> and may result in increased mortality. Such older AEDs as carbamazepine, phenobarbital, phenytoin, and primidone induce cytochrome P450 (CYP) enzymes and thus lead to altered serum concentrations of certain concomitantly used medications. For example, concentrations of anticoagulants (i.e., warfarin, apixaban, dicoumarol, and clopidogrel) would be consequently decreased, which could lead to increased risk of thromboembolic events.<sup>6</sup> Dose of cardiovascular medications (i.e., dihydropyridine calcium-channel blockers) might be reduced by 80%–90% and result in loss of antihypertensive control.<sup>7</sup> It has been suggested that formation of a toxic metabolite may occur with concomitant use of quetiapine and carbamazepine.<sup>8</sup> In contrast, due to the CYP450-inhibiting effect, valproic acid might increase the serum concentrations of concomitantly used drugs that are metabolized by the same enzyme.<sup>9</sup> In addition, AED inducers may alter bone and lipid metabolism indirectly and increase risk of hip fractures and vascular comorbidities in this population.<sup>10</sup>

The higher incidence and prevalence of AED use among people with AD was only partly explained by epilepsy, which is not surprising, as in addition to seizure control, AEDs are also used for other indications. Mostly newer AEDs (pregabalin and gabapentin) are effective in neuropathic pain treatment,<sup>11</sup> and topiramate and valproic acid might be used for migraine prophylaxis.<sup>12</sup> Carbamazepine, valproic acid, and lamotrigine are also used for treating bipolar disorder,<sup>13</sup> while occasionally, carbamazepine and valproic acid are used for controlling severe behavioral and psychological symptoms of dementia.<sup>14,15</sup>

Several previous studies have investigated the role of AEDs in risk of sudden unexpected death in epilepsy (SUDEP). A Swedish study<sup>16</sup> suggested that AED polytherapy as well as high frequency in dose changes explained the increased risk of SUDEP, while other studies have attributed the increased death risk to potential adverse effects of AEDs.<sup>17,18</sup> Possible mechanisms behind this association have been proposed, with

proarrhythmic properties of certain AEDs being the most common culprit.<sup>19</sup> The higher risk of death among AED users may also be a reflection of such severe AED adverse events as stroke,<sup>20</sup> myocardial infarction,<sup>21</sup> and hip fractures.<sup>22</sup>

AED treatment of older people and particularly people with AD is challenging due to aging-related changes in pharmacokinetics, frequent comorbid conditions, and comedications.<sup>4</sup> Although people with AD used AEDs more frequently than did people without AD<sup>3</sup> and might be more susceptible to AED adverse effects, to our knowledge, previous studies have not evaluated the risk of death associated with AED use in this population. Therefore, we investigated the association between AED use and risk of death, also in terms of duration of use, specific drugs, and main causes of death in a nationwide cohort of people with AD.

## Methods

### Study design and participants

This study was conducted on the nationwide register-based MEDALZ (Medication Use and Alzheimer Disease) cohort. The MEDALZ cohort includes all community-dwelling people who received diagnoses of AD in Finland in 2005–2011 ( $n = 70,718$ ).<sup>23</sup>

People with AD diagnosis were identified from the Special Reimbursement Register, which contains records of people who are entitled to higher medication reimbursement due to chronic diseases, including AD. All citizens and long-term residents of Finland are covered under the Finnish National Health Insurance scheme and are thus eligible for reimbursement of medical expenses under the Health Insurance Act.

To be entitled to special reimbursement due to a chronic disease, a patient must meet predefined criteria and a diagnosis statement must be submitted to the Social Insurance Institution of Finland (SII) for approval. For AD, the SII requires that the medical statement verifies that the patient has (1) symptoms consistent with AD; (2) experienced a decrease in social capacity over a period of at least 3 months; (3) received a CT or MRI scan; (4) had possible alternative diagnoses excluded; and (5) received confirmation of the diagnosis by a registered geriatrician or neurologist. The diagnosis of AD is based on the National Institute of Neurologic

and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association and DSM-IV criteria for AD. The accuracy of AD diagnosis in the register has been validated previously.<sup>24</sup> For a diagnosis of epilepsy to be verified and recorded in the Special Reimbursement Register, a neurologist provides a medical statement to the SII indicating that the person has (1) been examined by a neurologist or at a neurology clinic; (2) received relevant examinations including EEG, a CT or MRI scan, and relevant laboratory tests for diagnosis according to the ICD-10; and (3) has a care plan in accordance with good clinical practice.

People who initiated AED use after AD diagnosis were considered for this study. Incident users were identified with 1-year washout period to avoid prevalent user bias.<sup>25</sup> People hospitalized or institutionalized for more than 182 days during the washout period, or >90 days at the end of the washout period, were excluded. Dates of long-term institutionalization were obtained from the SII and durations of hospital stays from the Care Register for Health Care. People with a history of any cancer (ICD-10, C00-C97) as a main or auxiliary diagnosis in the Care Register for Health Care or purchases of antineoplastic or immunomodulating agents during the 12 months preceding the AED initiation were also excluded (table e-1, doi.org/10.5061/dryad.q3b38p9).

For each AED user, a matched nonuser was identified based on the same inclusion and exclusion criteria (figure 1) applying incidence density sampling without replacement. The matching criteria were age ( $\pm 730$  days), sex, and time since AD diagnosis ( $\pm 90$  days). People without a match ( $n = 360$ ) were excluded from further analyses.

The follow-up started on the index date, which was the date of AED initiation or the corresponding matching date for nonusers. People were followed until death, AED use discontinuation (for users) or AED initiation (for nonusers), continuous hospitalization or institutionalization more than 90 days, after 3 years of follow-up, or the end of the study (December 31, 2015). In drug–drug comparisons, the follow-up also ended if there were switches between AEDs or pol-therapy was initiated.

The maximum follow-up was restricted to 3 years based on our previous data<sup>20</sup> showing that a high proportion of users discontinued AED use within this period.

### Standard protocol approvals, registrations, and patient consents

According to Finnish legislation, no ethics committee approval was required for this study because only deidentified register-based data were used and the study participants were not contacted.

### AED use exposure

Data on purchased drugs since 1995 were extracted from the prescription register maintained by the SII. This register

contains all reimbursed prescription drug purchases made by Finnish community-dwellers and includes dispensing date of each prescription, the WHO Anatomical Therapeutic Chemical (ATC) code, and such information as the quantity, strength, and formulation of dispensed drugs. In this study, antiepileptics were defined as ATC code N03A and categorized to older and newer according to previous classifications.<sup>26</sup> Older AEDs included valproic acid, carbamazepine, clonazepam, and phenytoin; newer AEDs included pregabalin, gabapentin, lamotrigine, oxcarbazepine, topiramate, and levetiracetam.

AED purchases were modeled to use periods for each person and for each ATC code during the follow-up with a validated PRE2DUP (from prescription drug purchase to drug use periods) method.<sup>27</sup> In brief, based on each person's purchase history for each ATC code, this method constructs continuous drug use periods, calculates sliding average of daily dose in defined daily doses, and combines purchases of the same drug by taking into account stockpiling, purchases regularity, dose changes, and periods of hospitalization or institutionalization.<sup>28</sup> After modeling for each drug substance, overlapping periods of AEDs were combined to retrieve time when any AED was used for use vs nonuse comparisons and similarly time on old vs new AED use.

### Outcome

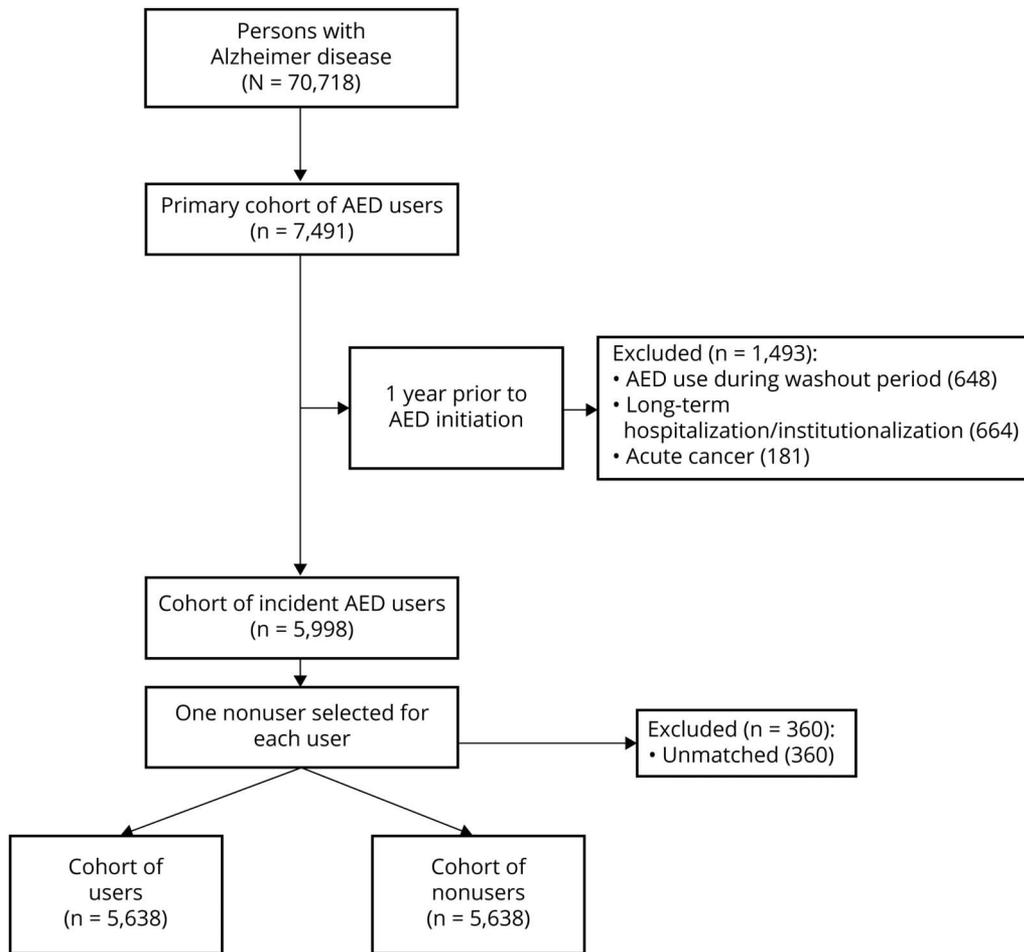
The primary outcome was all-cause mortality. Dates and causes of death were obtained from the causes of death register maintained by Statistics Finland. The register is compiled on the basis of death certificates, which are issued by physicians and if an autopsy is required, the death certificate is issued by a medicolegal officer after autopsy completion. Death certificates are delivered to the regional unit of the National Institute for Health and Welfare of the region where the decedent resided. A provincial medical officer confirms the correctness of the certificates before they are sent to Statistics Finland for registration. Causes of death are reported according to ICD-10 codes. In this study, cause-specific mortality was based on underlying causes of death, which are determined according to the selection and application rules of ICD-10 maintained by the WHO.

### Confounders

Data on hospitalization-based confounders since 1996 until the index date were retrieved from the Care Register for Health Care on the basis of ICD-10 codes, whereas those based on entitlements to higher special reimbursements were defined as occurring ever after establishment of the Special Reimbursement register in 1972 until the index date.

From these registers, we identified the following comorbidities: stroke, ischemic heart disease, cardiac arrhythmias, hypertension, chronic heart failure, and peripheral arterial disease; and diabetes, chronic renal failure, asthma or chronic obstructive pulmonary disease, rheumatoid arthritis, epilepsy, head injuries, and hip fracture.

**Figure 1** Flowchart of exclusion criteria of the study cohort with Alzheimer disease diagnoses



AED = antiepileptic drug.

In addition, we considered mental comorbidities, such as schizophrenia, depression, or bipolar disorders, and substance abuse as confounders. Schizophrenia diagnoses were restricted to those that were diagnosed at least 5 years before AD. Substance abuse was defined as alcohol-induced chronic pancreatitis, mental and behavioral disorders due to psychoactive substance abuse, or substance abuse as a reason for admission.

Use of acetylcholinesterase inhibitors, memantine, anti-psychotics, benzodiazepines and related drugs, antidepressants, nonsteroidal anti-inflammatory drugs (NSAIDs), statins, proton pump inhibitors, and antithrombotic agents within a 1-year period prior to the index date were identified from the PRE2DUP modeled drug use data.

Detailed definitions and classifications of confounders are provided in table e-2 ([doi.org/10.5061/dryad.q3b38p9](https://doi.org/10.5061/dryad.q3b38p9)).

### Statistical analyses

All analyses were performed with Stata (version 14; Stata-Corp, College Station, TX). Descriptive statistics are presented as means with SDs or frequencies with proportions.

The risk of death between AED users and nonusers was compared by Cox proportional hazards regression models. We used robust variance estimator in the models for AED user and nonuser comparisons to account for the matching. Proportional hazards assumptions were confirmed by exploring parallelism of log negative and log estimated survival curves for each covariate (figures e-1 through e-4, [doi.org/10.5061/dryad.q3b38p9](https://doi.org/10.5061/dryad.q3b38p9)). Hazard ratios (HRs) with their corresponding 95% confidence intervals (CIs) were estimated by crude and confounder-adjusted models.

For control of confounding by indication and balance potential confounders between the comparison groups, the Cox models were weighted with inverse probability of treatment (IPT) weights based on propensity score. Selection of variables (table e-2, [doi.org/10.5061/dryad.q3b38p9](https://doi.org/10.5061/dryad.q3b38p9)) for the IPT weights was based on their potential association with the outcome and the exposure. We estimated propensity score with logistic regression model as the conditional probability of AED use conditioned on the covariates measured at the baseline. Balancing properties of the IPT weighting (IPTW)

between the AED users and matched nonusers were ascertained by comparing covariate distributions before and after IPTW using the standardized difference. Standardized difference >10% was considered as an indication of a meaningful difference.<sup>29</sup>

In addition to all-cause mortality, we investigated cause-specific mortality. These analyses were restricted to diseases of the circulatory system (ICD10 codes I\*), dementia and Alzheimer disease (ICD10 codes F01–F03 and G30–G31), and other diseases due to small proportion of causes of deaths due to other diseases.

All-cause mortality, according to the duration of AED use, was studied by dividing the duration of AED use into 4 periods: 1–90 days, 91–180 days, 181–365 days, and 366–1,095 days.

In drug–drug comparison (user only design), risk of death was compared between most frequently used AEDs, where users of multiple AEDs were excluded ( $n = 38$ ). Valproic acid was chosen as a reference AED.

The main analyses included people with and without epilepsy. In order to exclude potential influence of epilepsy on mortality risk, we conducted sensitivity analyses after excluding people with epilepsy.

### Data availability

The data used to conduct the research are available from the corresponding author but restrictions by the register maintainers and Finnish legislation apply to the availability of these data. Therefore the data are not publicly available. However, data are available from the authors upon reasonable request and with permission of the register maintainers.

## Results

Altogether 7,491 individuals initiated AED use during the follow-up, of whom 5,638 met the inclusion criteria and 360 people were excluded without a match (figure 1). AED users without a matched pair were younger, had a longer time since AD diagnosis, used antipsychotics more often, and more often had epilepsy; however, other comorbid diagnoses were less common in this group (table e-3, doi.org/10.5061/dryad.q3b38p9).

Compared to nonusers, AED users had more chronic cardiovascular diseases and mental and behavioral disorders such as depression and bipolar disorders, and almost all diagnosis of epilepsy were observed among them (table e-4, doi.org/10.5061/dryad.q3b38p9). AED users were also more likely to use antidepressants, antipsychotics, benzodiazepines and related drugs, proton pump inhibitors, and NSAIDs. A substantial proportion of AED users (19.8%) were hospitalized or institutionalized during the observation period compared to nonusers (0.5%). These differences were balanced after IPTW.

In the comparison between most frequently used individual AED substances, users who initiated with valproic acid, carbamazepine, clonazepam, or phenytoin were more likely to have a history of epilepsy, head injuries, or substance abuse, as well as to use antipsychotics more frequently (table e-5, doi.org/10.5061/dryad.q3b38p9). In contrast, users of pregabalin, oxcarbazepine, and gabapentin were more likely to have a history of cardiovascular and metabolic diseases including ischemic heart disease, chronic heart failure, and cardiac arrhythmia, as well as diabetes (table e-5, doi.org/10.5061/dryad.q3b38p9). They also used NSAIDs and antithrombotic agents more frequently.

Mean follow-up time was shorter among users compared to nonusers (356.2 vs 795.6 days, respectively). Overall, 48.7% discontinued AED use within 6 months. AEDs discontinuation (58.4%) was the most common reason for censoring among AED users, whereas nonusers were censored most often at the end of follow-up (50.3%).

In total, 2,182 people died during the 3 years of follow-up (mortality rate, 95% CI; 14.5, 13.5–15.5 among users and 11.2, 10.7–11.8 per 100 person-years among nonusers; table 1). In unadjusted Cox proportional hazards regression models, AED use was associated with a 27% increased relative risk of death (crude HR, 1.27; 95% CI, 1.17–1.39) compared with nonuse. When the model was adjusted for baseline confounders, HR decreased to 1.16 (95% CI, 1.05–1.28). After applying IPTW, AED use was associated with a 23% increased relative risk of death compared to nonuse (IPTW HR, 1.23; 95% CI, 1.12–1.36). When the analyses were stratified by causes of death (table e-6, doi.org/10.5061/dryad.q3b38p9), AED use was related to an increased risk of death from dementia and AD causes (table 1; IPTW HR, 1.62; 95% CI, 1.42–1.86), but not to death due to cardiovascular and cerebrovascular or other causes.

The association between AED use and all-cause mortality was strongest during the first 90 days after AED initiation (table 2; IPTW HR, 2.40; 95% CI, 1.91–3.03), diminished during the next 90-day interval (IPTW HR for 3–6 months use, 1.58; 95% CI, 1.22–2.06) and disappeared after that.

In drug–drug comparisons (table 3), pregabalin (IPTW HR, 0.56; 95% CI, 0.40–0.78), gabapentin (IPTW HR, 0.31; 95% CI, 0.13–0.72), and clonazepam (IPTW HR, 0.48; 95% CI, 0.26–0.89) users had lower risk of death in comparison to valproic acid users. The risk of death among users of other frequently used AEDs was similar to that of valproic acid users, although there were some suggestions of lower risk of death among phenytoin users in comparison to valproic acid users. Use of older AEDs was associated with 79% higher relative risk of death (IPTW HR, 1.79; 95% CI, 1.52–2.16) compared to use of newer AEDs (table 3), and this association was even stronger in the relation to dementia deaths (IPTW HR, 3.54; 95% CI, 2.77–4.51) in cause-specific drug–drug comparison analyses (table e-7, doi.org/10.5061/dryad.q3b38p9).

**Table 1** Association between antiepileptic drug (AED) use and mortality overall and stratified by causes of death (follow-up is restricted to 3 years)

	No. of persons	No. of deaths	Person-years of follow-up	Deaths per 100 person-years (95% CI)	Unadjusted HR (95% CI)	Adjusted HR <sup>b</sup> (95% CI)	IPT-weighted HR <sup>c</sup> (95% CI)
<b>All-cause mortality</b>							
<b>Nonusers</b>	5,638	1,380	12,281	11.2 (10.7–11.8)	1.00	1.00	1.00
<b>AED users</b>	5,638	800	5,499	14.5 (13.5–15.5)	1.27 (1.17–1.39)	1.16 (1.05–1.28)	1.23 (1.12–1.36)
<b>Causes of death</b>							
<b>Cardiovascular and cerebrovascular diseases<sup>a</sup></b>							
<b>Nonusers</b>	5,638	515	12,281	4.19 (3.85–4.57)	1.00	1.00	1.00
<b>AED users</b>	5,638	252	5,499	4.58 (4.12–5.28)	1.07 (0.92–1.24)	0.96 (0.81–1.14)	1.01 (0.86–1.19)
<b>Dementia, Alzheimer disease<sup>a</sup></b>							
<b>Nonusers</b>	5,638	562	12,281	4.58 (4.21–4.97)	1.00	1.00	1.00
<b>AED users</b>	5,638	424	5,499	7.71 (6.88–8.36)	1.67 (1.47–1.89)	1.50 (1.30–1.72)	1.62 (1.42–1.86)
<b>Other causes</b>							
<b>Nonusers</b>	5,638	303	12,281	2.47 (2.20–2.76)	1.00	1.00	1.00
<b>AED users</b>	5,638	124	5,499	2.26 (1.81–2.61)	0.92 (0.74–1.13)	0.85 (0.68–1.07)	0.89 (0.71–1.12)

Abbreviations: CI = confidence interval; HR = hazard ratio; IPT = inverse probability of treatment.

<sup>a</sup> According to ICD-10, cardiovascular and cerebrovascular deaths include I\*, and dementia and Alzheimer disease deaths include F01–F03 and G30–G31.

<sup>b</sup> Adjusted for age; sex; use of acetylcholinesterase inhibitors, memantine, antidepressants, antipsychotics, benzodiazepines and related drugs, antithrombotic agents, statins, proton pump inhibitors, and nonsteroidal anti-inflammatory drugs; and history of hypertension, ischemic heart disease, stroke, chronic heart failure, atrial fibrillation, cancer, diabetes, fractures, pneumonia, asthma or chronic obstructive pulmonary disease, epilepsy, head injuries, depression, schizophrenia, or substance abuse.

<sup>c</sup> Inverse probability of treatment weighting on propensity score derived from characteristics listed in table e-2 (doi.org/10.5061/dryad.q3b38p9).

Similar results were observed after excluding people with epilepsy (tables e-8 through e-11, doi.org/10.5061/dryad.q3b38p9).

## Discussion

In this study among people with AD, AED users had a 23% higher relative risk of death, or 3 more deaths per 100 person-years, than nonusers. The difference was strongest during the first 6 months of treatment, and mainly explained by death from dementia or AD as underlying causes of death. Use of newer AEDs was associated with lower risk of death than use of older AEDs. A similar trend was also observed in drug–drug comparisons, in which pregabalin and gabapentin users had lower risk of death in comparison with valproic acid users.

There is a paucity of studies on risk of death associated with AED use. The majority of them have been restricted to people with epilepsy.<sup>16–19</sup> In these studies, AED use management and features of the mechanism of action of some AEDs were

related to higher mortality. In our study, people with epilepsy were included in the main analyses, but the increase in risk of death was similar after excluding them from sensitivity analyses. This might be explained by the fact that only a minority of AED users had an epilepsy diagnosis in our cohort, and the incidence of epilepsy diagnosis only partially explained increase in the incidence of AED use in people with AD in our previous study.<sup>3</sup> It is possible that some cases of epilepsy remained undetected as seizure diagnosis in people with AD can be particularly challenging.<sup>30</sup>

In our study, the greatest increase in risk of death was observed during the first 6 months of AED use, with more than 2-fold increased risk during the first 90 days compared to nonusers. The decline in risk with longer periods may be explained by selective discontinuation: nearly 50% of AED users discontinued treatment within 6 months of follow-up. It is possible that AEDs were discontinued after clinical improvement or stabilization of symptoms and conditions for which they had been used or due to treatment-related adverse effects, and in this case, people remaining on AED treatment

**Table 2** Association of antiepileptic drug (AED) use and all-cause mortality stratified by follow-up time

Duration of follow-up, days	No. of persons	No. of deaths	Person-years of follow-up	Deaths per 100 person-years (95% CI)	Unadjusted HR (95% CI)	Adjusted HR <sup>a</sup> (95% CI)	IPT-weighted HR <sup>b</sup> (95% CI)
<b>1-90</b>							
<b>Nonusers</b>	5,638	119	1,355	8.78 (7.34-10.51)	1.00	1.00	1.00
<b>AED users</b>	5,638	211	1,049	20.1 (17.58-23.02)	2.27 (1.82-2.85)	2.14 (1.68-2.72)	2.40 (1.91-3.03)
<b>91-180</b>							
<b>Nonusers</b>	5,340	131	1,268	10.3 (8.70-12.26)	1.00	1.00	1.00
<b>AED users</b>	3,417	121	733	16.5 (13.82-19.74)	1.60 (1.25-2.05)	1.42 (1.09-1.85)	1.58 (1.22-2.06)
<b>181-365</b>							
<b>Nonusers</b>	5,075	284	2,418	11.7 (10.46-13.20)	1.00	1.00	1.00
<b>AED users</b>	2,744	140	1,144	12.2 (10.37-14.44)	1.04 (0.85-1.28)	1.01 (0.81-1.27)	1.08 (0.87-1.33)
<b>366-1,095</b>							
<b>Nonusers</b>	4,514	113	7,199	11.7 (10.92-12.50)	1.00	1.00	1.00
<b>AED users</b>	2,064	48	2,393	12.4 (11.03-13.86)	1.06 (0.93-1.21)	0.91 (0.78-1.05)	1.01 (0.88-1.17)

Abbreviations: CI = confidence interval; HR = hazard ratio; IPT = inverse probability of treatment.

<sup>a</sup> Adjusted for age; sex; use of acetylcholinesterase inhibitors, memantine, antidepressants, antipsychotics, benzodiazepines and related drugs, antithrombotic agents, statins, proton pump inhibitors, or nonsteroidal anti-inflammatory drugs; and history of hypertension, ischemic heart disease, stroke, chronic heart failure, atrial fibrillation, cancer, diabetes, fractures, pneumonia, asthma or chronic obstructive pulmonary disease, epilepsy, head injuries, depression, schizophrenia, or substance abuse.

<sup>b</sup> Inverse probability of treatment weighting on propensity score derived from characteristics listed in table e-2 (doi.org/10.5061/dryad.q3b38p9).

were a more tolerant and thus more selected population. Frequent discontinuation of AEDs was also observed in the previous study, where approximately 50% of AED users discontinued AED treatment within a year.<sup>31</sup> In addition, poor short-term tolerability of certain AEDs was shown in another study,<sup>32</sup> where the time frame for development of intolerable adverse effects ranged from 3.1 months to 11.6 months.

In drug-drug comparisons, overall use of older AEDs was associated with greater risk of death in comparison to use of newer AEDs. In these analyses, pregabalin and gabapentin were associated with lower risk of death compared to valproic acid. One possible explanation is that newer AEDs may have lower risk of adverse events.<sup>33</sup> Alternatively, different indications for use may explain these findings. For example, valproic acid can be used in the late stage of AD for treatment of seizures or other seizure-like nonspecific symptoms.<sup>14</sup> In addition, gabapentinoids are approved for the treatment of neuropathic pain.<sup>11</sup> They must be used in reduced doses in elderly patients with age-related renal changes and should be avoided in persons with renal impairment. Thus, it is possible that gabapentinoids were used by healthier people, and this selection may partially explain the lower risk of death from dementia causes and all-cause mortality among users of pregabalin and gabapentin. These results should be interpreted

with caution, as the number of users for specific drug substances was restricted.

In our study, use of AEDs was associated with higher risk of death from dementia causes. One possible explanation is that AEDs were initiated for indications that are reflecting more severe AD. We did not observe an association between AED use and risk of death from cardiovascular or cerebrovascular causes, despite their previously observed proarrhythmic mechanisms and effects on the cardiac conduction system.<sup>17-19</sup> For example, carbamazepine, phenytoin, and phenobarbital have sodium channel-blocking properties,<sup>18,19</sup> and some AEDs such as lamotrigine, gabapentin, and topiramate have an effect on hERG potassium currents.<sup>17</sup> Our results might be explained by use of the underlying causes of death in cause-specific mortality analyses, where cause ascertainment can be affected by AD diagnosis. It is possible that in some cases the immediate cause of death was, for example, cardiovascular disease, while the underlying cause was recorded as dementia.

Our study covers all community-dwelling people with AD in Finland and the accuracy of AD diagnosis has been validated previously.<sup>24</sup> Thus the study cohort is in general representative, although the results are not generalizable to institutionalized

**Table 3** Association between type of antiepileptic drug (AED) and all-cause mortality by type of AED (follow-up is restricted to 3 years)

Type of AED	No. of persons	No. of deaths	Person-years of follow-up	Deaths per 100 person-years (95% CI)	Unadjusted HR (95% CI)	Adjusted HR <sup>b</sup> (95% CI)	IPT-weighted HR <sup>c</sup> (95% CI)
Valproic acid	1,694	335	1,522	22.01 (19.78–24.50)	1.00	1.00	1.00
Pregabalin	2,522	219	2,303	9.51 (2.06–3.50)	0.44 (0.37–0.52)	0.51 (0.42–0.63)	0.56 (0.40–0.78)
Carbamazepine	319	51	284	17.9 (13.64–23.61)	0.83 (0.62–1.11)	0.91 (0.67–1.25)	0.93 (0.65–1.33)
Clonazepam	271	15	193	7.76 (4.68–12.88)	0.35 (0.21–0.59)	0.44 (0.26–0.76)	0.48 (0.26–0.89)
Oxcarbazepine	236	44	246	22.01 (13.32–24.06)	0.86 (0.62–1.19)	0.93 (0.65–1.32)	1.18 (0.80–1.74)
Gabapentin	328	23	256	8.88 (5.90–13.37)	0.41 (0.27–0.63)	0.40 (0.26–0.62)	0.31 (0.13–0.72)
Phenytoin	110	15	124	12.14 (7.32–20.14)	0.57 (0.34–0.97)	0.63 (0.37–1.07)	0.59 (0.35–1.00)
Other AEDs <sup>a</sup>	120	26	125	20.76 (14.14–30.50)	0.97 (0.65–1.45)	1.01 (0.65–1.56)	1.13 (0.66–1.92)
Newer AEDs	3,095	320	2,904	11.02 (9.88–12.29)	1.00	1.00	1.00
Older AEDs	2,277	428	2,116	20.23 (18.40–22.24)	1.80 (1.56–2.08)	1.64 (1.39–1.93)	1.79 (1.52–2.16)
Concomitant use of newer and older AEDs	228	43	419	10.25 (7.60–13.83)	0.96 (0.71–1.31)	1.15 (0.83–1.59)	0.92 (0.63–1.34)

Abbreviations: CI = confidence interval; HR = hazard ratio; IPT = inverse probability of treatment.

<sup>a</sup> The group includes users of primidone (ATC code N03AA03, n = 5), lamotrigine (N03AX09, n = 27), topiramate (N03AX11, n = 8), and levetiracetam (N03AX14, n = 80). Users initiating with polypharmacy were excluded (n = 38).

<sup>b</sup> Adjusted for age; sex; use of acetylcholinesterase inhibitors, memantine, antidepressants, antipsychotics, benzodiazepines and related drugs, antithrombotic agents, statins, proton pump inhibitors, or nonsteroidal anti-inflammatory drugs; and history of hypertension, ischemic heart disease, stroke, chronic heart failure, atrial fibrillation, cancer, diabetes, fractures, pneumonia, asthma or chronic obstructive pulmonary disease, epilepsy, head injuries, depression, schizophrenia, or substance abuse.

<sup>c</sup> Inverse probability of treatment weighting on propensity score derived from characteristics listed in table e-2 (doi.org/10.5061/dryad.q3b38p9).

persons. Institutionalized people as well as people with long-term hospitalization (>90 days) were excluded in order to avoid misclassification of AED exposure as drug use during hospitalization or institutionalization is not recorded in the prescription register. AED use was modeled with the PRE2DUP method, which has been shown to have good validity for regularly used medications.<sup>28</sup> Our data lack indications for drug use as well as symptoms and severity of AD. AED users might be in a more severe stage of AD and, therefore, have a higher risk of death. Although time since AD diagnosis was a matching criterion for identifying the comparison cohort, it is possible that this did not fully control for the severity of AD.

Coding of causes of death for mortality statistics has been validated previously and was appropriate.<sup>34</sup> However, it might be that some causes of death from cardiovascular or cerebrovascular diseases were limited to underlying causes from AD and, therefore, the association with deaths from vascular causes could be diluted. The study was restricted to underlying causes of death, as their classification is based on international standards established by WHO. Another limitation of the register-based data is a lack of information on

lifestyle factors such as smoking, body mass index, and nutrition. Extensive covariate adjustment and IPTW of models in our design were used to minimize these limitations and residual confounding.

This study investigating AED use in people with AD showed that AED users had higher risk of death. The risk was highest in the first 6 months of AED use and might be associated with AED use for indications reflecting the severity of AD. Discontinuation of treatment was frequent, possibly owing to alleviation of symptoms or tolerability issues. The risk of death was greater among users of older AEDs compared to newer ones and presumably due to different indications. These findings advocate for careful consideration of AED initiation, choice of AED, and especially strict adverse events monitoring in this vulnerable group. With increasing evidence on higher frequency of nonconvulsive seizures<sup>35</sup> and epileptiform activity<sup>30,36</sup> in AD and the association of untreated seizures with worsening of cognitive performance in persons with AD, our study has clinical relevance. The use of AEDs in people with AD will likely increase in the future, and thus studies on the safety and effectiveness of AEDs in this specific population are urgently needed.

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Name	Location	Contribution
<b>Tatyana Sarycheva, MD, MSc</b>	School of Pharmacy, University of Eastern Finland, Kuopio	Designed and conceptualized study, analyzed the data, drafted and revised the manuscript for intellectual content
<b>Piia Lavikainen, PhD</b>	School of Pharmacy, University of Eastern Finland, Kuopio	Designed and conceptualized study, analyzed and preprocessed the data, interpreted data, manuscript revision
<b>Heidi Taipale, PhD (Pharm)</b>	School of Pharmacy, University of Eastern Finland, Kuopio	Designed and conceptualized study, preprocessed and interpreted the data, manuscript revision, supervision

## Appendix (continued)

Name	Location	Contribution
<b>Jari Tiihonen, MD, PhD</b>	Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden	Designed and conceptualized study, manuscript revision
<b>Antti Tanskanen, PhD</b>	Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden	Preprocessed and interpreted the data, manuscript revision
<b>Sirpa Hartikainen, MD, PhD</b>	School of Pharmacy, University of Eastern Finland, Kuopio	Designed and conceptualized study, interpreted data, manuscript revision, supervision
<b>Anna-Maija Tolppanen, PhD</b>	School of Pharmacy, University of Eastern Finland, Kuopio	Designed and conceptualized study, preprocessed and interpreted the data, manuscript revision, supervision

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