# Association of recent hospitalization with initiation of antiepileptic drugs use among persons with Alzheimer´s disease

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## DECLARATIONS

**Ethics approval and consent to participate:** The study was based on pseudonymized data. Cohort members were not contacted. Therefore, according to Finnish legislation (including Personal Data Act 23/1999, Act on the Openness of Government Activities 621/1999 and Act on the Secondary Use of Health and Social Data 552/2019 (and previous Act on the National Health Care registers, official English translation is not available 556/1989)), no ethic committee approval was needed. Permission for data use was received from the register maintainers.

**Consent for publication:** not applicable

**Availability of data and materials:** The data are nor publicly available but may be received from the authors with permission of the register maintainers.

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## ABSTRACT

**Objectives**: Antiepileptic drugs (AEDs) are frequently prescribed for persons with Alzheimer´s disease (AD), but little is known on factors associated with AED initiation in this population. We investigated whether recent hospitalization is associated with AED initiation in persons with AD.

**Design**: Nested case-control study in the nationwide register-based Medication use and Alzheimer´s disease (MEDALZ) cohort.

**Participants and Settings**: The MEDALZ cohort includes 70,718 persons diagnosed with AD during 2005-2011 in Finland. Altogether 6,814 AED initiators and 6,814 age-, sex- and time since AD diagnosis-matched non-initiators were included in this study. Matching date was the date of AED initiation.

**Methods**: AED purchases were identified from the Prescription Register and hospitalizations from the Care Register for Health Care. Recent hospitalization was defined as hospitalization ending within two weeks before the matching date. Association between recent hospitalization and AED initiation was assessed with conditional logistic regression.

**Results**: The most frequently initiated AEDs were pregabalin (42.9%) and valproic acid (32.2%). A bigger proportion of AED initiators (36.9%) than non-initiators (5.3%) were recently hospitalized (OR 10.5, 95% CI 9.22-11.9). Dementia was the most frequent discharge diagnosis among AED initiators (29.1%) and non-initiators (27.9%). Among AED initiators the next most frequent diagnosis was epilepsy (20.6%). Musculoskeletal diagnoses and use of analgesics including opioids was more common among gabapentinoid initiators compared to other AED initiators.

**Conclusions and implications**: Recent hospitalization was significantly related to AED initiation. Initiations of AED might have been related to common symptoms in persons with AD like neuropathic pain, epilepsy and neuropsychiatric symptoms.

## INTRODUCTION

Antiepileptic drugs (AEDs) have multiple indications: besides epilepsy, they are also used to treat other conditions such as neuropathic pain, migraine, bipolar disorder and sometimes also neuropsychiatric symptoms of dementia.[1–3] Before prescribing AEDs to older person, careful consideration is needed as AEDs may have negative impact on cognition[4] and increase the risk of stroke[5] and falls.[6] Use of AEDs has also been associated with increased risk of pneumonia[7] and death[8] in persons with AD. In addition, older AEDs like carbamazepine, have multiple drug-drug interactions[9,10] and so their use in this population has particular challenges.

Persons with AD use AEDs more frequently than the general older population.[11,12] This may be due to higher seizure incidence in people with AD[13–16] as well as higher incidence of epilepsy diagnosis.[12,17] On the other hand, these conditions do not entirely explain the higher incidence of AED use after AD diagnosis.[12]

Previous studies have found that recent hospitalization was associated with an increased risk of psychotropic drug initiation in people with AD.[18,19] As far as we know, there are no previous studies on AED initiation with relation to recent hospitalization.

We studied whether recent hospitalization was associated with AED initiation in people with AD and investigated which were the most common discharge diagnoses of the hospital care period preceding AED initiation.

## METHODS

The register-based Medication use and Alzheimer´s disease (MEDALZ) cohort study[20] utilizes data from several nationwide Finnish registers. MEDALZ study contains 70,718 community-dwelling Finnish residents diagnosed with AD between 2005 and 2011. Persons diagnosed with AD were identified from the Finnish Special Reimbursement register maintained by the Social Insurance Institution of Finland (SII). Diagnosis of AD is based on the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCS-ADRDA)[21] and Diagnostic and Statistical Manual Fourth Edition (DSM-IV)[22] criteria. A computed tomography or magnetic resonance imaging and confirmation of the diagnosis by a neurologist or geriatrician are required in order to receive a diagnosis of AD.

This study was conducted as a nested case-control study within the MEDALZ cohort. Persons with AD who initiated AED between 2005 and 2015 were included as cases. On the date of first AED purchase after the AD diagnosis (index date), each initiator was matched with comparison person who did not initiate AED according to sex, age (±2 years) and date of AD diagnosis (±90 days). Persons who purchased AED during one year washout period before the index date were excluded from both groups. Comparison persons were not allowed to initiate AED within one year after the index date. With these criteria the final sample size was 6,814 matched pairs (Figure 1).

Data on purchased AEDs and other drugs were collected from the Prescription Register according to the Anatomical Therapeutic Chemical (ATC) classification system.[20,23] AEDs included all drugs with ATC code N03A: primidone (N03AA03), phenytoin (N03AB02), clonazepam (N03AE01), carbamazepine (N03AF01), oxcarbazepine (N03AF02), valproic acid (N03AG01), lamotrigine (N03AX09), topiramate (N03AX11), gabapentin (N03AX12), levetiracetam (N03AX14) and pregabalin (N03AX16). AEDs were categorized to gabapentinoids, comprising pregabalin and gabapentin, and other antiepileptics.

Furthermore, we investigated use of any anti-dementia drugs (N06D) including acetylcholinesterase inhibitors (N06DA) and memantine (N06DX01), psychotropics including benzodiazepines and related drugs (BZDR) (N05BA, N05CD, N05CF), antidepressants (N06A) and antipsychotics (N05A excluding lithium (N05AN) and prochlorperazine (N05AB04)), analgesics including paracetamol (N02BE01, N02AJ01, N02AJ06, N02AJ13, N02AJ17, N02BE51, N02BE71), NSAIDs (M01A, N02AJ08, N02AJ14) and opioids (N02A), within one year time period before the index date.

We investigated association of recent hospitalization with AED initiation. The information about hospitalizations, hospital type (central/university hospital vs. other including municipal and regional hospitals), length of hospital stay and discharge diagnosis were extracted from the Finnish National Care Register for Health Care.[20] Discharge diagnosis was grouped based on the main chapters of ICD-10 classification with dementia F00-F03 and AD G30 separated to their own group. Only hospital periods that ended within two-week time period before the index date were taken into account.

Comorbidities including cardiovascular diseases, diabetes, asthma/COPD, active cancer treatment, epilepsy, stroke, substance abuse, schizophrenia, bipolar disorder/mania and other mood disorders were identified from Care Register for Health Care, Special Reimbursement register Prescription register.[20] The data sources, codes and time periods for comorbidity definitions are listed in Supplementary Table 1. Data on the highest occupational social class was obtained from Statistics Finland.[20]

We investigated the differences between any AED initiators and non-initiators as well as differences between gabapentinoid initiators and their matched non-initiators. We also compared gabapentinoid initiators to those who initiated with other antiepileptics. Between-group differences in normally distributed variables were evaluated with T-test and median test was used for continuous variables with skewed distribution. Categorical variables were compared using chi-square test. Odds ratios for the association between recent hospitalization and AED initiation were calculated with conditional logistic regression. Categorical variables were compared using chi-square test. Statistical analyses were performed with Stata MP14.0.

## RESULTS

Majority of the study population (64.9%) were women (Table 1). There were differences in occupational social class between initiators and non-initiators but without consistent pattern.

The median time since AD diagnosis at antiepileptic initiation was 864 days (interquartile range 353-1532). All comorbidities except active cancer treatment were more common among AED initiators and they used psychotropics and analgesics more frequently than non-initiators. There was no difference in the use of antidementia drugs between groups. Similar differences were observed between gabapentinoid initiators and their matched non-initiators (Supplementary Table 2). However, there were no clinically relevant differences on the prevalence of stroke, schizophrenia, substance abuse and bipolar disorder or mania.

The most frequently initiated AED group was gabapentinoids and most frequently initiated drug substance was pregabalin (42.9%) followed by valproic acid (32.2%) (Supplementary Table 3). Almost 90% of the gabapentinoid initiators used pregabalin. Gabapentinoid initiators were older (mean age 81.8 years) than other AED initiators (79.1 years) at the time of AD diagnosis, and at the initiation (Table 2). Time from AD diagnosis to AED initiation was shorter among gabapentinoid initiators (median 683 days) than initiators of other AEDs (median 1056 days). Other comorbidities except stroke and schizophrenia were more common among initiators of gabapentinoid, but there was no clinically relevant difference in substance abuse and bipolar disorder or mania. Use of BZDR, antidepressants and analgesics was more common, and use of memantine and antipsychotics less common among gabapentinoid initiators in comparison to initiators of other AEDs.

Recent hospitalization was strongly associated with initiation of any AED (OR 10.5, 95% CI 9.22-11.9): 36.9% of them had been hospitalized within two weeks before the index date, in comparison to 5.3% of their matched non-initiators (Table 3). Longer hospitalizations were more common among AED initiators compared to their matched non-initiators. Dementia was the most common main discharge diagnosis in both initiators (29.1%) and non-initiators (27.9%). Every fifth (20.6%) of AED initiators and none of the matched comparison persons had epilepsy as discharge diagnosis. Diagnosis of circulatory and respiratory system were more common among non-initiators.

Initiators of other AEDs (44.7%) were more likely to have been recently hospitalized compared to gabapentinoid initiators (28.7%), had shorter hospital stays and have been discharged from central/university hospitals (Table 4). The distribution of discharge diagnosis category was also different between the groups. Dementia (31.7%) and epilepsy (32.9%) were the most common discharge diagnosis among initiators of other AED and more common compared to gabapentinoid initiator (24.8% and 0.11% respectively). Nearly one third of gabapentinoid initiators had discharge diagnosis of musculoskeletal system (20.8%) or injuries (9.5%) compared to initiators of other AEDs (0.57% and 3.8% respectively).

## DISCUSSION

Findings of our nationwide study show that recent hospitalization was associated with initiation of any AEDs in persons with AD, and AED initiation was more common after longer hospital stays. Among all AED initiators, dementia and epilepsy were the most common discharge diagnoses, while dementia and musculoskeletal system diagnosis were the most common

diagnoses among gabapentinoid initiators. The most frequently initiated AEDs were pregabalin and valproic acid.

Although recent hospitalization was associated with AED initiation, less than 30 percent of gabapentinoid initiators and less than 50 percent of other AED initiators had been hospitalized within the two-week time period before the initiation. Median time from the index date to AED initiation was over two years. One explanation might be commonly existing neuropsychiatric symptoms in mild and moderate AD.[24] If other treatment have not been successful, carbamazepine can be occasionally used to treat agitation and aggression in dementia.[25] Dementia was the main discharge diagnosis for more than a quarter of cases, which also suggests that these persons might be hospitalized at least partly due to neuropsychiatric symptoms of dementia. Physical health problems like urinary tract infection or dehydration[26] as well as several somatic symptoms and other discomfort states, such as pain or constipation[27] are risk factors for neuropsychiatric symptoms and might have provoked these symptoms in persons with AD. Majority of persons with AD have neuropsychiatric symptoms at some state of the disease.[28] However, hospital care may also provoke these neuropsychiatric symptoms of dementia.[29]

Diseases of the musculoskeletal system and injuries were common discharge diagnosis among gabapentinoid initiators. Furthermore, there were significant differences on comorbidities and medication use among gabapentinoid initiators compared to other AED initiators implying different reasons for initiation. Our results of higher prevalence of diagnoses related to injuries and musculoskeletal problems, common use of analgesics and relatively common active cancer treatments among gabapentinoid initiators might indicate treatment of neuropathic pain. These findings are supported by a previous study,[30] in which gabapentinoids were mostly used to treat neuropathic pain, including painful diabetic peripheral neuropathy.[31,32] In our study, a quarter of gabapentinoid initiators had diabetes. In addition, hypothesis of neuropathic pain is supported by high opioid use among gabapentinoid initiators as nearly four out of five used opioids in our study. Other possible indications for gabapentinoid use in our study include anxiety, as gabapentinoid initiators used frequently antidepressants and benzodiazepines and related drugs.

Epilepsy was more common among AED initiators compared to non-initiators. This is at least partly explained by the history of stroke, which was also more common among AED initiators, particularly among those who initiated with other AEDs than gabapentinoids. Stroke is a known risk factor for secondary epilepsy.[33] Valproic acid, which was the most frequently initiated AED after pregabalin in our study, is recommended as a first-line therapy in generalized epilepsy and as a secondary option in focal epilepsy.[34] It is also the most common AED among older persons with recently diagnosed epilepsy in Finland.[35] Therefore, its use in our study was likely mainly due to epilepsy. In addition, nearly one third of recently hospitalized initiators of other AEDs had epilepsy as the main discharge diagnosis. However, valproic acid may also have been used for agitation in dementia, although this is not recommended due to lack of efficacy and safety.[36,37]

AEDs have potential adverse effects especially in old vulnerable people due to age-related pharmacodynamic and pharmacokinetic changes.[38] Decline in renal[39] and hepatic[38] functions should be taken into account when prescribing and defining doses of AEDs. Older AEDs like carbamazepine and phenytoin have several clinically important drug-drug interactions as strong inducers of cytochrome P450 and can reduce efficacy of concomitantly used drugs like oral anticoagulants and antibiotics.[9] Gabapentinoids are eliminated by renal excretion and doses need be reduced also in aged related renal impairment.

A strength of our study is that we utilized nationwide registers that cover citizens and long-term residents of Finland. Our population was community-dwelling at the time of AD diagnosis, so the results are not representative of persons living in institutional care. In addition, we have no information on indications of AED use or whether AEDs were initiated during the hospital period or prescribed after the discharge, because medications administered in hospitals are not recorded in the Prescription register. Moreover, we utilized data on purchased drugs but lacked information whether they were actually used. On the other hand, purchased prescriptions are more accurate measure of drug utilization than written prescriptions.[40]

## CONCLUSIONS AND IMPLICATIONS

Recent hospitalization is strongly associated with AED initiation in persons with AD. Discharge diagnosis of dementia, epilepsy and musculoskeletal disorders and common use of analgesics and psychotropics among initiators indicate that main indications for AED use in addition to epilepsy may also include neuropathic pain and neuropsychiatric symptoms of dementia. AED should be prescribed after careful consideration to avoid possible adverse effects and events in vulnerable older persons with Alzheimer´s disease.

Table 1. Characteristics of antiepileptic initiators and non-initiators on the index date (date of AED initiation). Data are given as n (%) unless otherwise indicated.

| | Initiators (n=6814) | Non-initiators (n=6814) | P |
|---|---|---|---|
| Age at AD diagnosis, mean (95% CI) | 80.4 (80.3-80.6) | 80.5 (80.3-80.7) | 0.84 |
| Age at AED initiation, mean (95% CI) | 83.2 (83.0-83.4) | 83.3 (83.1-83.5) | 0.86 |
| Time since AD diagnosis, median (IQR) | 864 (353-1532) | 863 (351-1539) | 0.93 |
| **Sex** | | | 1.00 |
| Men | 2393 (35.1) | 2393 (35.1) | |
| Women | 4421 (64.9) | 4421 (64.9) | |
| **Highest occupational social class before AD** | | | 0.016 |
| Managerial/professional | 1575 (23.1) | 1520 (22.3) | |
| Office | 610 (9.0) | 607 (8.9) | |
| Farming, forestry | 1082 (15.9) | 1224 (18.0) | |
| Sales, industrial, cleaning | 2952 (43.3) | 2919 (42.8) | |
| Unknown | 595 (8.7) | 544 (8.0) | |
| **Comorbidities** | | | |
| Cardiovascular disease | 3325 (48.8) | 3181 (46.7) | 0.014 |
| Diabetes | 1487 (21.8) | 1283 (18.8) | <0.001 |
| Stroke | 1188 (17.4) | 879 (12.9) | <0.001 |
| Asthma/COPD | 838 (12.3) | 761 (11.2) | 0.040 |
| Active cancer treatment | 1132 (16.6) | 1122 (16.5) | 0.82 |
| Epilepsy | | | <0.001 |
| - Before the index date | 1115 (16.4) | 940 (13.8) | |
| - Within 3 months after the index date | 14 (0.2) | 9 (0.1) | |
| Substance abuse | 518 (7.6) | 454 (6.7) | 0.033 |
| Schizophrenia | | | 0.020 |
| - Before the index date | 263 (3.9) | 213 (3.1) | |
| Bipolar disorder or mania | | | <0.001 |
| - At least 5 years before AD diagnosis | 16 (0.2) | 14 (0.2) | |
| - From 5 years before AD until the index date | 29 (0.4) | 10 (0.2) | |
| Other mood disorder | | | <0.001 |
| - At least 5 years before AD diagnosis | 212 (3.1) | 123 (1.8) | |
| - From 5 years before AD until the index date | 243 (3.6) | 141 (2.1) | |
| **Medication use** | | | |
| Any anti-dementia drug | 6606 (97.0) | 6630 (97.3) | 0.22 |
| - Acetylcholinesterase inhibitor | 5988 (87.9) | 5990 (87.9) | 0.96 |
| - Memantine | 4567 (67.0) | 4541 (66.6) | 0.64 |
| Psychotropics | | | |

| | | | |
|---|---|---|---|
| - Benzodiazepines and related drugs | 5056 (74.2) | 4041 (59.3) | <0.001 |
| - Antidepressants | 4639 (68.1) | 3744 (55.0) | <0.001 |
| - Antipsychotics | 4223 (62.0) | 3524 (51.7) | <0.001 |
| Analgesics | | | |
| - Paracetamol | 5803 (85.2) | 5075 (74.5) | <0.001 |
| - NSAID | 5987 (87.9) | 5681 (83.4) | <0.001 |
| - Opioids | 4357 (63.9) | 3134 (46.0) | <0.001 |

Table 2. Characteristics of gabapentinoid initiators and those who initiated with other antiepileptics on the index date (date of AED initiation). Data are given as n (%) unless otherwise indicated.

| | Gabapentinoid initiators (n=3301) | Other AED initiators (n=3513) | P |
|---|---|---|---|
| Age at AD diagnosis, mean (95% CI) | 81.8 (81.6-82.0) | 79.1 (78.9-79.4) | <0.001 |
| Age at AED initiation, mean (95% CI) | 84.2 (84.0-84.5) | 82.3 (82.0-82.6) | <0.001 |
| Time since AD diagnosis, median (IQR) | 683 (282-1284) | 1056 (452-1734) | <0.001 |
| **Sex** | | | <0.001 |
| Men | 1002 (30.4) | 1391 (39.6) | |
| Women | 2299 (69.7) | 2122 (60.4) | |
| **Comorbidities** | | | |
| Cardiovascular disease | 1737 (52.6) | 1588 (45.2) | <0.001 |
| Diabetes | 835 (25.3) | 652 (18.6) | <0.001 |
| Stroke | 485 (14.7) | 703 (20.0) | <0.001 |
| Asthma/COPD | 493 (14.9) | 345 (9.8) | <0.001 |
| Active cancer treatment | 650 (19.7) | 482 (13.7) | <0.001 |
| Epilepsy | | | <0.001 |
| - Before the index date | 650 (19.7) | 465 (13.2) | |
| - Within 3 months after the index date | 7 (0.2) | 7 (0.2) | |
| Substance abuse | 250 (7.6) | 268 (7.6) | 0.93 |
| Schizophrenia | | | <0.001 |
| - Before the index date | 97 (2.9) | 166 (4.7) | |
| Bipolar disorder or mania | | | 0.066 |
| - At least 5 years before AD diagnosis | 5 (0.15) | 11 (0.3) | |
| - From 5 years before AD until the index date | 9 (0.3) | 20 (0.6) | |
| Other mood disorder | | | 0.033 |
| - At least 5 years before AD diagnosis | 119 (3.6) | 93 (2.7) | |
| - From 5 years before AD until the index date | 127 (3.9) | 116 (3.3) | |
| **Medication use** | | | |
| Any anti-dementia drug | 3211 (97.3) | 3395 (96.6) | 0.13 |
| - Acetylcholinesterase inhibitor | 2908 (88.1) | 3080 (87.7) | 0.60 |
| - Memantine | 2130 (64.5) | 2437 (69.4) | <0.001 |
| Psychotropics | | | |
| - Benzodiazepines and related drugs | 2501 (75.8) | 2555 (72.7) | 0.004 |
| - Antidepressants | 2384 (72.2) | 2255 (64.2) | <0.001 |
| - Antipsychotics | 1773 (53.7) | 2450 (69.7) | <0.001 |
| Analgesics | | | |

| | | | |
|---|---|---|---|
| - Paracetamol | 3021 (91.5) | 2782 (79.2) | <0.001 |
| - NSAID | 3065 (92.9) | 2922 (83.2) | <0.001 |
| - Opioids | 2551 (77.3) | 1806 (51.4) | <0.001 |

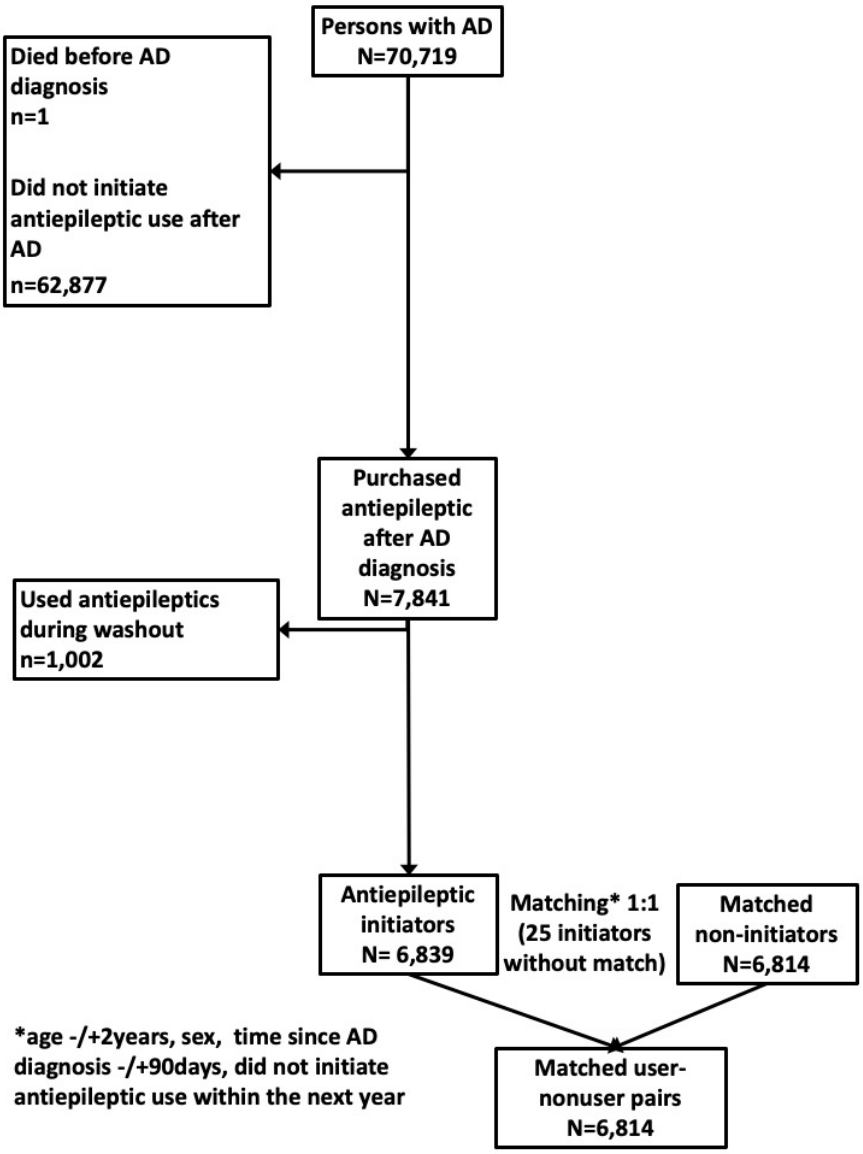
Table 3. Prevalence and characteristics of recent hospitalization among antiepileptic initiators and their matched non-initiators. Data are given as n (%).

| | Initiators (n=6814) | Non-initiators (n=6814) | P |
|---|---|---|---|
| Hospitalization within the previous 2 weeks | 2516 (36.9) | 363 (5.3) | <0.001 |
| **Duration of hospitalization in days** | | | 0.002 |
| 1-7 | 918 (36.5) | 151 (41.6) | |
| 8-14 | 379 (15.1) | 72 (19.8) | |
| 15-60 | 784 (31.1) | 98 (27.0) | |
| 61-2113 | 435 (17.3) | 42 (11.6) | |
| **Hospital** | | | 0.164 |
| Central or university hospital | 574 (22.8) | 71 (19.6) | |
| Municipal or regional hospital | 1942 (77.2) | 292 (80.4) | |
| **Diagnosis category** (ICD-10 main groups) | | | <0.001 |
| Dementia | 733 (29.1) | 101 (27.9) | 0.607 |
| Other nervous system (G) | 612 (24.3) | 6 (1.7) | <0.001 |
| - Epilepsy (G40) | 517 (20.6) | 0 (0.0) | |
| Circulatory system (I) | 185 (7.4) | 43 (11.9) | 0.003 |
| Musculoskeletal system (M) | 206 (8.2) | 16 (4.4) | 0.012 |
| - Dorsalgia (M54) | 67 (2.7) | 2 (0.6) | |
| Symptoms and signs not elsewhere classified (R) | 200 (8.0) | 15 (4.1) | 0.010 |
| Injury, poisoning (ST) | 149 (5.9) | 32 (8.8) | 0.034 |
| Infectious and parasitic diseases (AB) | 75 (3.0) | 15 (4.1) | 0.239 |
| Genitourinary system (N) | 62 (2.5) | 16 (4.4) | 0.033 |
| Respiratory system (J) | 60 (2.4) | 34 (9.4) | <0.001 |

Table 4. Prevalence and characteristics of recent hospitalization among gabapentinoid initiators and those who initiated with other antiepileptics. Data are given as n (%).

| | Gabapentinoid initiators (n=3301) | Other AED initiators (n=3513) | P |
|---|---|---|---|
| Hospitalization within the previous 2 weeks | 946 (28.7) | 1570 (44.7) | <0.001 |
| **Duration of hospitalization in days** | | | <0.001 |
| 1-7 | 232 (24.5) | 686 (43.7) | |
| 8-14 | 162 (17.1) | 217 (13.8) | |
| 15-60 | 351 (37.1) | 433 (27.6) | |
| 61-2113 | 201 (21.2) | 234 (14.9) | |
| **Hospital** | | | <0.001 |
| Central or university hospital | 110 (11.6) | 464 (29.6) | |
| Municipal or regional hospital | 836 (88.4) | 1106 (70.5) | |
| **Diagnosis category** (ICD-10 main groups) | | | <0.001 |
| Dementia | 235 (24.8) | 498 (31.7) | <0.001 |
| Other nervous system (G) | 32 (3.4) | 580 (36.9) | <0.001 |
| - Epilepsy (G40) | 1 (0.11) | 516 (32.9) | |
| Musculoskeletal system (M) | 197 (20.8) | 9 (0.57) | <0.001 |
| Symptoms and signs not elsewhere classified (R) | 51 (5.4) | 149 (9.5) | <0.001 |
| Circulatory system (I) | 93 (9.8) | 92 (5.9) | <0.001 |
| Injury, poisoning (ST) | 90 (9.5) | 59 (3.8) | <0.001 |

Figure 1. Formation of the study sample. Antiepileptic initiators and their matched comparison persons.



Supplementary Table 1. Data sources and definitions of antiepileptic use, hospitalizations and covariates. Index date refers to matching date (AED initiation).

| Characteristic | Data sources & coding | Years |
|---|---|---|
| Antiepileptic use | Prescription register ATC-code: N03A (Gabapentinoid use: N03AX12, N03AX16) | 1995-2015 |
| Recent hospitalization | Hospital discharge within two weeks time period before the index date (initiation of antiepileptic or matching date) | 2004-2015 |
| Acute cancer | Cancer as main or side diagnosis Care Register for Health Care ICD-10 code: C<br>Prescription register ATC-codes: L01 (antineoplastic agents), L02 (endocrine therapy), L03AA (colony stimulating factors), L03AB01 (interferon alpha natural), L03AB04 (interferon alpha-2a), L03AB05 (interferon alpha-2b), L03AC (interleukins), L03AX (other immunostimulants, excluding L03AX13, glatiramer acetate), L04AA10 (sirolimus), L04AA18 (everolimus), L04AA34 (alemtuzumab), L04AX02 (thalidomide). For users of L04AX03 or L01BA01 (methotrexate, persons with a Special Reimbursement for rheumatoid arthritis were excluded).[41] | Within one year before the index date |
| Schizophrenia | Care Register for Health Care<br>ICD 9: 295, 297, 298<br>ICD-10: F20-F29 | From 1987 until the index date |
| Bipolar disorder or mania | Care Register for Health Care<br>ICD 9: 2962, 2963, 2964, 2967<br>ICD-10: F30, F31 | From 1987 until the index date (1=five years before AD diagnosis, 2=after that) |
| Other mood disorder | Care Register for Health Care<br>ICD-9: 2961, 2968A, 3004A, 3011D<br>ICD-10: F32-F39 | From 1987 until the index date (1=five years before AD diagnosis, 2=after that) |
| Asthma/COPD | Special Reimbursement register code 203<br>Care Register for Health Care<br>ICD-10: J44-J46 | From 1972 until the index date<br><br>From 1995 until the index date |
| Substance abuse | Prescription register: ATC codes N07BB, N07BC<br>Care Register for Health Care | 1995 until AD diagnosis |

| | | |
|---|---|---|
| | Reason for admission:<br>(33,71,72,73,74,75)<br>ICD-10 F1*, K860, K70, G621, G312, G721, I426, K292, R78<br>ICD-9 291,292,303,304,305,3575, 3594A, 4255A,5353A,5770D-F,5771C,5710A,5711A, 5712A,5713X<br>ICD-8: 291,303,304,57100, 57101,57700-57708 | From 1995 until AD diagnosis<br>From 1995 until AD diagnosis<br><br>1987-1994 until AD diagnosis<br><br>1972-1986 until AD diagnosis |
| Cardiovascular disease | Special Reimbursement register codes 205, 206, 213, 280, 201 | From 1972 until the index date |
| Diabetes | Prescription register: ATC code A10 excluding A10BX01(guar gum)<br><br>Special Reimbursement register code 103 | From 1995 until the index date<br><br>From 1972 until the index date |
| Epilepsy | Special Reimbursement register code 111 | From 1972 until three months after the index date (1=before the index date, 2=after that) |
| Stroke | Care Register for Health Care<br>ICD-10 I60-I64, I69 | From 1995 until the index date |
| Occupational social class | Highest occupational social class (Statistics Finland classification)[42] | 1972 until the index date |
| Acetylcholinesterase inhibitor and memantine use | Prescription register: ATC code N06DA (acetylcholinesterase inhibitor) N06DX (memantine) | One year before the index date |
| Antidepressant use | Prescription register: ATC code N06A | One year before the index date |
| Antipsychotic use | Prescription register: ATC code N05A excluding N05AN and N05AB04 | One year before the index date |
| Benzodiazepines & related drugs | Prescription register: ATC code N05BA, N05CD, N05CF | One year before the index date |
| Opioid use | Prescription register: ATC code N02A | One year before the index date |
| Paracetamol use | Prescription register: ATC code N02BE01, N02AJ01, N02AJ06, N02AJ17, N02AJ13, N02BE51, N02BE71 | One year before the index date |
| NSAID use | M01A N02AJ08 and N02AJ14 | One year before the index date |

Supplementary Table 2. Characteristics of gabapentinoid initiators and their matched non-initiators on the index date (date of AED initiation). Data are given as n (%) unless otherwise indicated.

| | Initiators (n=3301) | Non-initiators (n=3301) | P |
|---|---|---|---|
| Age at AD diagnosis, mean (95% CI) | 81.8 (81.6-82.0) | 81.8 (81.6-82.0) | 0.93 |
| Age at AED initiation, mean (95% CI) | 84.2 (84.0-84.5) | 84.2 (83.9-84.4) | 0.92 |
| Time since AD diagnosis, median (IQR) | 683 (282-1284) | 690 (271-1302) | 0.81 |
| **Sex** | | | 1.00 |
| Men | 1002 (30.4) | 1002 (30.4) | |
| Women | 2299 (69.7) | 2299 (69.7) | |
| **Highest occupational social class before AD** | | | 0.052 |
| Managerial/professional | 682 (20.7) | 666 (20.2) | |
| Office | 294 (8.9) | 298 (9.0) | |
| Farming, forestry | 517 (15.7) | 604 (18.3) | |
| Sales, industrial, cleaning | 1521 (46.1) | 1438 (43.6) | |
| Unknown | 287 (8.7) | 295 (8.9) | |
| **Comorbidities** | | | |
| Cardiovascular disease | 1737 (52.6) | 1602 (48.5) | 0.0010 |
| Diabetes | 835 (25.3) | 628 (19.0) | <0.001 |
| Stroke | 485 (14.7) | 434 (13.2) | 0.070 |
| Asthma/COPD | 493 (14.9) | 368 (11.2) | <0.001 |
| Active cancer treatment | 650 (19.7) | 592 (17.9) | 0.068 |
| Epilepsy | | | <0.001 |
| - Before the index date | 650 (19.7) | 463 (14.0) | |
| - Within 3 months after the index date | 7 (0.2) | 6 (0.2) | |
| Substance abuse | 250 (7.6) | 216 (6.5) | 0.10 |
| Schizophrenia | | | 0.62 |
| - Before the index date | 97 (2.9) | 104 (3.2) | |
| Bipolar disorder | | | 0.21 |
| - At least 5 years before AD diagnosis | 5 (0.2) | 6 (0.2) | |
| - From 5 years before AD until the index date | 9 (0.3) | 3 (0.09) | |
| Other mood disorder | | | <0.001 |
| - At least 5 years before AD diagnosis | 119 (3.6) | 58 (1.8) | |
| - From 5 years before AD until the index date | 127 (3.9) | 72 (2.2) | |
| **Medication use** | | | |
| Any anti-dementia drug | 3211 (97.3) | 3190 (96.6) | 0.13 |
| - Acetylcholinesterase inhibitor | 2908 (88.1) | 2856 (86.5) | 0.055 |
| - Memantine | 2130 (64.5) | 2125 (64.4) | 0.90 |

| | | | |
|---|---|---|---|
| Psychotropics | | | |
| - Benzodiazepines and related drugs | 2501 (75.8) | 1993 (60.4) | <0.001 |
| - Antidepressants | 2384 (72.2) | 1806 (54.7) | <0.001 |
| - Antipsychotics | 1773 (53.7) | 1691 (51.2) | 0.043 |
| Analgesics | | | |
| - Paracetamol | 3021 (91.5) | 2502 (75.8) | <0.001 |
| - NSAID | 3065 (92.9) | 2765 (83.8) | <0.001 |
| - Opioids | 2551 (77.3) | 1556 (47.1) | <0.001 |

Supplementary Table 3. Initiated antiepileptics.

| ATC | Drug name | N | % |
|---|---|---|---|
| N03AX16 | Pregabalin | 2926 | 42.9 |
| N03AG01 | Valproic acid | 2191 | 32.2 |
| N03AF01 | Carbamazepine | 421 | 6.2 |
| N03AX12 | Gabapentin | 375 | 5.5 |
| N03AE01 | Clonazepam | 322 | 4.7 |
| N03AF02 | Oxcarbazepine | 306 | 4.5 |
| N03AB02 | Phenytoin | 153 | 2.3 |
| N03AX14 | Levetiracetam | 118 | 1.7 |
| N03AX09 | Lamotrigine | 38 | 0.6 |
| N03AX11 | Topiramate | 10 | 0.2 |
| N03AA03 | Primidone | 5 | 0.07 |
| N03AX18 | Lacosamide | 2 | 0.03 |

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