Hospital-Treated Pneumonia Associated with Opioid Use Among Community Dwellers with Alzheimer's Disease

Hamina, A

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Hospital-treated pneumonia associated with opioid use among community dwellers with Alzheimer’s disease

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Detailed author contributions:

AH: Design of the study, analysis and interpretation of the data, preparation of manuscript
HT: Design of the study, analysis and interpretation of the data, preparation of manuscript
NK: Design of the study, interpretation of the data
AT: Design of the study, interpretation of the data
AMT: Design of the study, interpretation of the data
JT: Design of the study, interpretation of the data
SH: Design of the study, interpretation of the data
Abstract

Background: Pneumonia is a common cause for hospitalization and excess mortality among persons with Alzheimer’s disease (AD), but little research exists evaluating drug use as its risk factor.

Objective: We investigated the association between opioid use and hospital-treated pneumonia among community dwellers with AD.

Methods: This study was part of the Medication use and Alzheimer’s disease (MEDALZ) cohort. We included all community dwellers newly diagnosed with AD during 2010–2011 in Finland with incident prescription opioid use (n=5,623) and age-, sex- and time since AD diagnosis-matched nonusers (n=5,623). Opioid use data, modelled from pharmacy dispensing data, and hospital-treated pneumonia were retrieved from nationwide registers. Patients with active cancer treatment were excluded. Hazard models compared opioid users to nonusers, adjusting for comorbidities, socioeconomic position and other drug use.

Results: Incident opioid use was associated with an increased risk of hospital-treated pneumonia compared to nonuse (adjusted HR, aHR 1.34, 95% CI 1.14–1.57). Highest risk was observed during the first two months of use (aHR 2.58, 95% CI 1.87–3.55). Compared to weak opioids, buprenorphine was not associated with a higher risk of pneumonia (aHR 1.20, 95% CI 0.83–1.76), but strong opioids were (aHR 1.84, 95% CI 1.15–2.97). The risk was higher for those using ≥50 morphine milligram equivalents (MME)/day (aHR 2.03, 95% CI 1.24–3.31), compared to using <50 MME/day.

Conclusions: Opioid use was associated with a risk of hospital-treated pneumonia in a dose-dependent manner among persons with AD. Risk-minimization strategies should be considered if opioid therapy is needed.

Keywords: opioids; pneumonia; Alzheimer’s disease; dementia; aged; pharmacoepidemiology

Introduction

Due to global aging, the number of persons with a dementive disorder is expected to rise from 35 million in 2015 to 116 million in 2050 [1]. Alzheimer’s disease (AD) is the most common cause of cognitive decline and comprises 60–80% of persons with dementia. As among the older population in general, pain is a common symptom among persons with dementia [2]. Recent studies have shown that pain in dementia is frequently treated with opioids [3,4]. Even long-term use of opioids is common in dementia, yet slightly less so than among older people generally [5,6]. However, older
persons are more susceptible to opioid-related adverse drug effects and events (ADEs) [7,8]. These ADEs include sedation, cough suppression and respiratory depression, and this has led to a suspicion of an increased risk for pneumonia among opioid users. Similarly, opioids have displayed immunosuppressive properties in previous studies, further contributing to these concerns [9]. Pneumonia is a common cause for hospitalization and excess mortality among persons with AD [10,11]. Furthermore, persons with AD may be at a higher risk for opioid-induced aspirations and possibly pneumonia, due to frequent dysphagia-related problems [12].

Previous research has associated opioid use with a higher risk of pneumonia in different population groups [13–17]. However, the risk of pneumonia among opioid users with cognitive disorders has not been studied previously. Furthermore, no study has analyzed the risk comparing different opioid strength categories.

We investigated whether opioid use increases the risk of hospital-treated pneumonia among community-dwelling persons with AD. Further, we studied the risk in relation to different opioid strength categories and duration of use.

**Methods**

**Setting:**

We conducted this research as a part of the previously described MEDALZ (Medication use and Alzheimer’s disease) study [18]. The MEDALZ cohort comprises all persons newly diagnosed with AD in Finland in 2005–2011 (n = 70,718). For the current study we restricted the analyses to those diagnosed with AD in 2010 or 2011 (n = 23,100) due to inconsistent reimbursement and consequent data availability of codeine combination products before 2010. The cohort comprises data from nationwide registers spanning several decades. These registers are linkable through a personal
identification number assigned for each resident. Persons with AD were identified from the Special Reimbursement Register (data since 1972), which consists of data on entitlement to higher reimbursement of drugs for chronic illnesses and is maintained by the Social Insurance Institution (SII). Special reimbursement for AD requires diagnosis based on the NINCDS-ADRDA [19] and DSM-IV [20] criteria, including a computed tomography or magnetic resonance imaging scan, and confirmation of the diagnosis by a neurologist or geriatrician. If the criteria are met, a medical statement of fulfillment is sent for evaluation to the SII, which then grants a permanent special reimbursement for antidementia drugs.

**Exposure:**

The Prescription Register (data since 1995) includes information on all purchases of prescribed and reimbursed drugs from community pharmacies. Over-the-counter (OTC) drugs or drugs used during stays in hospitals or public nursing homes are not included. However, opioids, excluding antitussives, are only available with prescription and were consistently reimbursed in Finland during the study period. The Hospital Discharge Register (data since 1972) consists of data on all inpatient hospital days, including dates and discharge diagnoses utilizing International Classification of Diseases (ICD) codes from versions 8, 9 and 10. Data from the registers were linked by the SII and was de-identified before being submitted to the research team and participants were not contacted in any way. According to Finnish law, ethics committee approval is therefore not required.

Drugs in the Prescription Register were classified according to the WHO Anatomical Therapeutic Chemical (ATC) classification system [21]. Opioids (N02A) used in this study are presented in Table 1. For opioid users, we analyzed the first opioid initiated after AD diagnosis. Drug use periods from Prescription Register purchases were modelled using a mathematical modelling method PRE2DUP, as described previously [22,23]. The method was utilized for constructing drug use periods, i.e.,
when continuous drug use started and ended, for each person and ATC code. The method is based on calculation of sliding averages of daily dose, according to individual purchasing behavior, by taking into account regularity of purchases, hospitalizations and stockpiling. Date of the first drug purchase was considered the start of the drug use. PRE2DUP has been validated previously. It estimates actual drug use more precisely compared to other modelling methods [24].

**Outcome:**

We utilized the Hospital Discharge Register for identifying diagnoses of pneumonia. The register includes hospital-treated pneumonia and excludes community-treated cases (referred to as pneumonia here on). We used the following ICD-10 codes to define a diagnosis of pneumonia: J10.0, J11.0, J12, J13, J14, J15, J16, J18 and J69.0. Only the first recorded pneumonia for each person was considered after the diagnosis of AD, as this was considered most reliable.

**Study cohort:**

We included only new opioid users utilizing a 12-month wash-out period prior to opioid initiation to avoid prevalent user bias [25]. We further excluded persons who were hospitalized for >50% of the washout period or had >90 days hospitalization at the end of the washout period, or who were institutionalized throughout the follow-up period due to lack of data on drug use during hospital days. Similarly, persons with active cancer within a year or a pneumonia six months before opioid initiation were excluded (Figure 1). Active cancer treatment was defined as any cancer as a main or side diagnosis (ICD-10 codes C00-97) or cancer-related operations in the Hospital Discharge Register, or as anticancer drug purchases within 12 months (see Hamina et al. for details [5]). The follow-up after opioid initiation continued until treatment discontinuation, death, start of >90 days of hospitalization/institutionalization, incident pneumonia, after 1000 days (due to sparsity of data
with a longer follow-up time), or end of the study period (December 31, 2015), whichever came first.

A comparison cohort was compiled after the exclusions. At the opioid initiation date, we matched all opioid initiating persons with a nonuser according to age (±2 years), sex and time since AD diagnosis (±90 days), with same exclusion criteria as described for users using incidence density sampling. Opioid initiation, or the corresponding matching date was considered as an index date when follow-up started. Follow-up of non-users was censored if they initiated opioid use, in addition to the same reasons as for users. Users were available as comparison persons in the matching before they initiated opioid use. After matching, we included 5,623 opioid users and 5,623 nonusers into our analyses. Altogether 101 users were excluded due to not finding matching non-users. Their mean age was 84.6 years and most (n=77) were women.

Covariates:

The Hospital Discharge Register was utilized for identifying comorbid conditions, i.e. history of hip fracture (ICD-10 codes S72.0, S72.1, S72.2 and corresponding ICD-8 and ICD-9 codes), history of stroke (ICD-10 codes I60-I64) and history of substance abuse, defined as hospitalization based on the diagnoses of alcohol or narcotic use or alcoholic pancreatitis at any time point before the index date. To account for the effects of recent hospitalization, we identified those discharged from hospital care in the last 7 days prior to opioid initiation. For identifying persons with asthma/chronic obstructive pulmonary disease (COPD), cardiovascular disease, diabetes (type 1 or 2) or rheumatoid arthritis, we utilized the Special Reimbursement Register. Cardiovascular disease was defined as chronic heart failure, chronic arterial hypertension, coronary artery disease and/or chronic arrhythmia. For covariate drug use, we collected data at the index date on non-steroidal anti-inflammatory drugs (NSAIDs, ATC code M01A, excluding glucosamine), acetaminophen (N02BE01),
antidepressants (N06A), antiepileptics (N03A), antipsychotics (N05A, excluding lithium), benzodiazepines and related drugs (BZDRs, ATC codes N05BA, N05CD and N05CF) immunosuppressants for non-malignant diseases (L04A), proton-pump inhibitors (PPIs, A02BC) and oral corticosteroids (H02AB). Socioeconomic position was defined as the highest socioeconomic position recorded in population census for study persons when they were 45–55 years old, based on a classification by Statistics Finland. Socioeconomic position was categorized into four classes; the highest class included entrepreneurs and higher clerical workers, medium class included lower clerical workers and employees, and the lowest class included unemployed, retirees and students. Data on socioeconomic class were missing (no records at Statistics Finland) for about 1% of the cohort; this was included as the class ‘unknown’. Other variables did not include missing data.

**Statistical analyses:**

In our main analyses, we evaluated the risk of pneumonia comparing opioid users to nonusers with Cox proportional hazard models. Multivariable analyses were adjusted for possible confounders of opioid use and pneumonia [26]: cardiovascular disease, diabetes, asthma/COPD, rheumatoid arthritis, baseline use of antidepressants, antipsychotics, PPIs, BZDRs, immunosuppressants for nonmalignant diseases, oral corticosteroids and antiepileptics, history of stroke, hip fracture and substance abuse, socioeconomic position and discharge from hospital care in the last 7 days. Opioid use was further categorized according to duration of use as ≤60 days, 61–180 days, 181–365 days, and 365–1000 days of exposure. The Cox regression analyses included a robust variance estimator which accounted for clustering within the matched design.

To obtain continuous duration of any opioid use in the main analyses, overlapping use periods of different opioids were combined. In analyses of different opioid strength categories, to retrieve use of, for example “weak opioids”, overlapping use periods of weak opioids were combined. Thus,
during a use period of, e.g. “weak opioids”, drug use is censored if person initiates concomitant use with or switches to a partial agonist or a strong opioid.

Estimated daily doses of opioids (in DDDs per day) were transformed into morphine equivalent doses according to equivalency ratio to morphine by Svendsen et al. and by drug form (Table 1) [27]. The role of immunosuppressive status of opioids was analyzed separately utilizing a definition from previous studies [13,16]. We classified opioids as immunosuppressive, non-immunosuppressive and of unknown status (Table 1). Censoring was executed as in analyses with opioid strength categories. Both of these analyses were restricted to the first 250 days of use due to sparsity of data with a longer follow-up time.

Further dose-response analyses were undertaken by comparing the risk of doses of ≤50 and >50 morphine milligram equivalents (MME) per day [27]. We selected the dose of 50 MME due to this being a limit for careful reassessing of individual benefits and risks of opioid treatment in Centers for Disease Control (CDC) guidelines [28]. Sensitivity analyses with 40 and 60 MME were also conducted. Persons initiating opioid use with two or more opioids of different categories were excluded from these analyses. Similarly, persons were censored if they started concomitant use or switched the drug class, as in the analyses per opioid strength categories.

In secondary analyses, we investigated death as a competing risk for pneumonia in cause-specific hazards models [29]. Here, we considered death as a competing risk, which prevents the occurrence of incident pneumonia as a censoring event. Cause-specific hazard ratios (HRs) for pneumonia were modelled by applying the main Cox model for pneumonia and competing event separately and censoring all other events.

We assessed the impact of informative censoring, i.e. if drug use was discontinued due to adverse effects that would lead to the studied outcome, in separate intention-to-treat (ITT) analyses. In
these analyses, opioid initiators were considered as users for 180 days regardless of possible discontinuation of use or hospitalizations due to other causes than pneumonia. The follow-up ended on pneumonia, death, or the end of study. We further constructed as-treated analyses for comparisons sake, in which the comparison of users with nonusers was restricted similarly to the first 180 days of follow-up.

Descriptive analyses in this study were reported as means or as medians with interquartile ranges (IQRs). Results of the Cox regression were reported as HRs and adjusted HRs (aHRs) with 95% confidence intervals (CI). All analyses were performed using SAS software (version 9.4, SAS Institute Inc., Cary, North Carolina, USA).

To account for unmeasured confounding, e.g. smoking status, we conducted sensitivity analyses with a self-controlled case-crossover design. A case-crossover design utilizes within-person comparisons of transient exposure and non-exposure, i.e. opioid use and nonuse, thus eliminating unmeasured inter-individual confounders [30,31]. Persons with pneumonia and opioid use during the follow-up were included, without any wash-out period for opioid use. We excluded persons with pneumonia ≤120 days prior to the AD diagnoses to ensure actual new cases of pneumonia. Persons with a >90 days long-term care period during the follow-up and/or active cancer were excluded. The case period was defined as 1–14 days before the date of first pneumonia, and two control periods were applied: 31–45 and 60–74 days before the event. We required a minimum outpatient follow-up of 2/3 of both windows for persons to be included in these analyses. The prevalence of opioid use between the case and control periods was compared with conditional logistic regression adjusted for time-dependent use of antipsychotics, BZDRs, immunosuppressants for nonmalignant diseases and oral corticosteroids.

Results
We included 5,623 opioid users and 5,623 opioid nonusers in this study; 71.8% in both groups were women and the mean matched age was 83.3 and 83.2 years, respectively (Table 2). Studied comorbidities were more common among opioid users compared to nonusers. The median follow-up for opioid users was 45 days (IQR 21–133 days) and 497 days (IQR 218–920) for opioid nonusers. Kaplan-Meier curves are shown in Supplementary Figure 1.

Most frequently opioid use was started with buprenorphine (34.4% of all opioids) and codeine (30.8%) (Figure 2). The follow-up time for opioid users was 2,195 person-years, during which there were 242 cases of pneumonia (Table 3). Nonusers were followed for 9,448 person-years, with 600 cases of pneumonia. The pneumonia rate per 100 person-years was 11.03 (95% CI 10.89–11.16) among opioid users and 6.35 (95% CI 6.30–6.40) among nonusers; a difference of 4.68 pneumonias per 100 person-years. Opioid use was associated with a higher risk of pneumonia (aHR 1.34 95% CI 1.14–1.57).

The risk of pneumonia was highest in the beginning of opioid use: aHR for the first 60 days of use was 2.58 (95% CI 1.87–3.55) (Table 3). The risk attenuated in longer term use. Compared to weak opioid use, strong opioid use was associated with a higher risk of pneumonia (HR 2.20, 95% CI 1.38–3.51, aHR 1.84, 95% CI 1.15–2.97), as was buprenorphine use in the non-adjusted hazard models 1.47 1.01–2.15, but not in the adjusted models (aHR 1.20, 95% 0.83–1.76). Compared to buprenorphine, strong opioids were associated with an increased risk of pneumonia (HR 1.50, 95% CI 1.00–2.24 and aHR 1.53, 95% CI 1.02–2.29). In analyses of dose comparing to nonusers, risk of pneumonia was greater for those using ≥50 MME of opioids (aHR 2.86, 95% CI 1.73–4.72) than to those using doses of <50 MME (aHR 1.36, 95% CI 1.13–1.62). Compared to those with a lower dose, risk of pneumonia was higher for those using a higher dose of opioids (HR 2.08, 95% CI 1.28–3.38 and aHR 2.03, 95% CI 1.24–3.31). Immunosuppressive opioids were associated with lower
pneumonia risk when compared to non-immunosuppressive (HR 0.57, 95% CI 0.35–0.90 and aHR 0.58, 95% CI 0.36–0.93), while both immunosuppressive (aHR 1.68, 95% CI 1.20–2.36) and non-immunosuppressive (1.87, 95% CI 1.41–2.36) were associated with higher risk of pneumonia in comparison to nonuse.

The follow-up was censored at death for 14.1% of opioid users and 14.7% for nonusers. In secondary analyses, opioid use was associated with a higher risk of pneumonia compared to nonuse, when competing risk of death was considered. A higher risk was found in both unadjusted (HR 1.55, 95% CI 1.33–1.80) and adjusted hazard models (aHR 1.34, 95% CI 1.14–1.57).

Similarly to the main analyses, opioid use was associated with a higher risk of pneumonia compared to nonuse in the secondary analyses of ITT for the first 180 days of use (aHR 1.63, 95% CI 1.33–2.01) (Table 3). In the as-treated analyses for the first 180 days of use, the aHR was 1.89 (95% CI 1.49–2.40).

Altogether 3,736 opioid users were included in case-crossover analyses. The odds of opioid use were significantly higher in case windows than in control windows regardless of observed time points (with the control window of 31–45 days before pneumonia OR 2.91, 95% CI 1.94–4.34 and control window 61–74 days before 2.74, 95% CI 1.95–3.84). Adjusting for the use of antipsychotics, BZDRs, immunosuppressants and oral corticosteroids decreased the ORs (2.87, 95% 1.92–4.32 and 2.65, 95% 1.89–3.72).

**Discussion**

In this nationwide cohort study among community dwellers with AD, we found a 34% increased risk of hospital-treated pneumonia among opioid users compared to nonusers. This risk was most profound in the first 60 days of opioid use. Further, we observed a dose-dependent increase in the
risk. To our knowledge, this is the first study to describe the risk of pneumonia associated with opioid use among persons with a cognitive disorder.

Our main result, that opioid use is associated with an increased risk of pneumonia, is supported by previous studies [13–17]. Opioid use has been associated with a higher risk of pneumonia among older community-dwelling people [13], people with rheumatoid arthritis [15], COPD [14], Medicaid beneficiaries [16] and, more recently, among veterans with and without HIV [17]. Similarly, a higher risk of pneumonia-related mortality has been previously described among opium users [32]. Among opioid users with COPD the risk estimates for pneumonia have been similar, although somewhat lower than in our study [14]. These differences may be due to methodological differences, but also as a consequence of the high inherent risk of pneumonia in AD [33]. Moreover, we found an association between a higher dose of opioids and a higher risk of pneumonia, which has been similarly described previously [13–16]. Our results on the associated risk according to opioid strength categories need to be confirmed in future studies.

The exact mechanisms by which opioid use could promote pneumonia are yet unclear. Central nervous system (CNS) and respiratory system depression are known adverse effect of opioid use and risk factors for aspiration [34,35]. Opioid-induced cough reflex suppression and esophageal dysfunction [36,37], paired with swallowing difficulties, could lead to a greater risk of aspiration of foodstuff. Persons with dementia are at an increased risk for aspiration and consequent pneumonia [33]. Moreover, risk for pneumonia among persons with AD is increased with the use of other sedative drugs, e.g. benzodiazepines and related drugs [38] and antipsychotics [39]. Another possible mechanism may be immunosuppression. Animal and human models have demonstrated opioid-induced immunosuppression through macrophage, lymphocyte and natural killer cell activity reduction, among other possible mechanisms [9]. The clinical relevance of these findings
has previously been disputed, however [40]. In our sub-analyses, previous categorization as immunosuppressive opioid agents was associated with a lower risk of pneumonia compared to non-immunosuppressive opioids. It should be noted, however, that the doses of opioids used in our study were relatively low and the used opioids somewhat different compared to previous studies [13–17]. These factors, as well as different study populations, may explain some of the dissimilarities in the results. Future studies should investigate the mechanisms of possible immunosuppression among humans.

In this study, we found an increased risk of pneumonia in the first two months of opioid use. The number of opioid users in longer term use periods was somewhat low and thus, it is possible that associations are not strong enough to be seen with our data. In addition, persons who terminate opioid use due to adverse effects are more likely to do so in the beginning of use. One possible explanation for this finding may also be that those who continued opioid use past two months had acquired tolerance to opioid-induced sedation [41] and thus, possibly had a reduced risk of aspirations and subsequent pneumonia.

Our results have implications for clinicians engaged in the pain treatment of persons with AD. Opioid treatment for non-malignant pain should be carefully weighed against the possible adverse events, including the risk of pneumonia. This is especially important when initiating opioid therapy. Careful dose titration and low initial doses are emphasized by pain treatment guidelines for older persons [8,42]. Similarly, high sedative load and especially co-treatment with other sedative drugs, e.g. benzodiazepines and antipsychotics, should be avoided when possible.

The main strengths of this study arise from the utilized inclusive, nationwide registers comprising all community-dwelling Finns with a newly diagnosed AD from 2010–2011. Due to the strict criteria of the SII, which are based on international definitions [19,20], the diagnosis for AD can be
considered reliable. As an additional strength, we utilized the Prescription Register, including reimbursed prescribed drugs purchased from pharmacies in this study, which reflects actual drug use more accurately compared to drug prescriptions [43,44]. As opposed to questionnaire-based measures of drug use, register-based data do not have recall bias, which would be of particular concern when studying persons with cognitive disorders. Further, estimates of actual drug use are more precise with PRE2DUP modelling compared to fixed assumptions of dose [22,24].

Some limitations for this study need to be considered. Our risk estimates are likely to include at least some residual confounding, especially by indication of opioid therapy and by lifestyle factors, such as smoking. However, within-individual sensitivity analyses eliminate fixed confounding across individuals, and yielded comparable results to our main analyses. The registers utilized in this study did not include data on pain severity or the severity of AD. We matched opioid users and nonusers according to time since diagnosis as attempt to control for AD severity. Furthermore, the Prescription register does not include data on drug use during hospital stays and thus, our results are only applicable to community dwellers. Similarly, we defined our study endpoint as hospital-treated pneumonia, limiting our results to more severe cases of the disease. The etiology of the pneumonias was not specified in the majority of cases and thus was not possible to analyze. Subsequent research needs to determine whether pneumococcal vaccinations could lower the risk of pneumonias among opioid using persons with AD.

In conclusion, opioid use was associated with risk of hospital-treated pneumonia in a dose-dependent manner among persons with AD. This risk appears to be highest in the initiation of opioid treatment. Our results underline the importance of careful consideration of possible opioid-related adverse events, including pneumonia, when treating persons with AD. Risk minimization strategies, including avoidance of co-prescribing of other sedative drugs, should be considered.
Conflicts of interest:

AT, HT and JT have participated in research projects funded by grants from Janssen-Cilag and Eli Lilly to their employing institution. JT reports personal fees from the Finnish Medicines Agency (Fimea), European Medicines Agency (EMA), Eli Lilly, Janssen-Cilag, Lundbeck, and Otsuka; and has received grants from the Stanley Foundation and Sigrid Jusélius Foundation.

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References


[21] The Anatomical Therapeutic Chemical Classification System. Available http://www.whocc.no/atc_ddd_index/


Figure 1. Formation of the study sample. AD = Alzheimer’s disease.

Figure 2. Proportions of opioid agents used by persons with Alzheimer’s disease in this study.

Supplementary Figure 1. Kaplan-Meier survival curves.
Table 1. Opioid classifications utilized in this study.

<table>
<thead>
<tr>
<th>Opioid agent</th>
<th>Administration route(s)</th>
<th>ATC code</th>
<th>Strength category</th>
<th>Immunosuppressive status [13,16]</th>
<th>Equianalgesic ratio [27]</th>
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<tr>
<td>Codeine</td>
<td>Oral</td>
<td>N02AA59</td>
<td>Weak</td>
<td>Immunosuppressive</td>
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<td>Tramadol</td>
<td>Oral, parenteral, rectal</td>
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<td>Weak</td>
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<td>Buprenorphine</td>
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<td>Partial agonist</td>
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<td>Pentazocine</td>
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ATC = Anatomical Therapeutic Chemical
Table 2. Characteristics of opioid users and nonusers with Alzheimer’s disease.

<table>
<thead>
<tr>
<th></th>
<th>Opioid user, % (N)</th>
<th>Opioid nonuser, % (N)</th>
<th>p-value</th>
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<tbody>
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<td><strong>Matching criteria</strong></td>
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<tr>
<td>Women</td>
<td>71.8 (4,036)</td>
<td>71.8 (4,036)</td>
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<td>Age, years (mean)</td>
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<td>Time since AD diagnosis at the start of follow-up (mean, days)</td>
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<td>837</td>
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<tr>
<td>High</td>
<td>32.8 (1,843)</td>
<td>34.8 (1,954)</td>
<td></td>
</tr>
<tr>
<td>Medium</td>
<td>59.1 (3,322)</td>
<td>58.5 (3,290)</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>6.9 (385)</td>
<td>5.6 (314)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>1.3 (73)</td>
<td>1.2 (65)</td>
<td></td>
</tr>
<tr>
<td><strong>Comorbidities</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Asthma/COPD</td>
<td>9.5 (535)</td>
<td>7.3 (412)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>53.1 (2,986)</td>
<td>48.7 (2,737)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>17.1 (960)</td>
<td>14.5 (815)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>4.6 (261)</td>
<td>3.5 (198)</td>
<td>0.0027</td>
</tr>
<tr>
<td>History of hip fracture</td>
<td>12.3 (689)</td>
<td>7.1 (397)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>History of stroke</td>
<td>13.3 (750)</td>
<td>10.7 (599)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>History of substance abuse</td>
<td>3.1 (174)</td>
<td>2.4 (133)</td>
<td>0.0177</td>
</tr>
<tr>
<td><strong>Prescription drug use</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antidepressant use</td>
<td>29.6 (1,661)</td>
<td>23.1 (1,298)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Antipsychotic use</td>
<td>25.5 (1,380)</td>
<td>18.3 (1,028)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Benzodiazepine and related drug use</td>
<td>22.2 (1,248)</td>
<td>15.6 (876)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Use of immunosuppressants for non-malignant diseases</td>
<td>0.9 (48)</td>
<td>1.3 (73)</td>
<td>0.0223</td>
</tr>
<tr>
<td>Non-opioid analgesic use</td>
<td>64.0 (3,599)</td>
<td>24.2 (3,599)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Antiepileptic drug use</td>
<td>8.9 (501)</td>
<td>4.3 (240)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Oral corticosteroid use</td>
<td>6.5 (368)</td>
<td>3.0 (171)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Proton-pump inhibitor use</td>
<td>28.1 (1,582)</td>
<td>16.0 (902)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

AD = Alzheimer’s disease; COPD = Chronic obstructive pulmonary disease
Table 3. Opioid use and associated risk of hospital-treated pneumonia among persons with Alzheimer’s disease.

<table>
<thead>
<tr>
<th>Opioid use and associated risk of hospital-treated pneumonia among persons with Alzheimer’s disease.</th>
<th>Number of events</th>
<th>Person years</th>
<th>Rate per 100-person years</th>
<th>Unadjusted HR</th>
<th>Adjusted HR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Opioid user vs. nonuser</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonuser</td>
<td>600</td>
<td>9448</td>
<td>6.35 (6.30–6.40)</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>User</td>
<td>242</td>
<td>2195</td>
<td>11.03 (10.89–11.16)</td>
<td>1.55 (1.33–1.80)</td>
<td>1.34 (1.14–1.57)</td>
</tr>
<tr>
<td><strong>Opioid use according to duration of use</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–60 days</td>
<td>116</td>
<td>611</td>
<td>18.99 (18.64–19.33)</td>
<td>2.94 (2.15–4.03)</td>
<td>2.58 (1.87–3.55)</td>
</tr>
<tr>
<td>61–180 days</td>
<td>50</td>
<td>521</td>
<td>9.60 (9.33–9.86)</td>
<td>1.65 (1.17–2.32)</td>
<td>1.42 (1.00–2.02)</td>
</tr>
<tr>
<td>181–365 days</td>
<td>32</td>
<td>440</td>
<td>7.27 (7.01–7.52)</td>
<td>1.06 (0.73–1.56)</td>
<td>0.91 (0.62–1.33)</td>
</tr>
<tr>
<td>&gt;365 days</td>
<td>44</td>
<td>638</td>
<td>6.90 (6.69–7.10)</td>
<td>1.07 (0.78–1.47)</td>
<td>0.90 (0.65–1.25)</td>
</tr>
<tr>
<td><strong>Analyses according to opioid strength</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weak opioids</td>
<td>39</td>
<td>314</td>
<td>12.41 (12.02–12.80)</td>
<td>1.64 (1.14–2.31)</td>
<td>1.54 (1.09–2.17)</td>
</tr>
<tr>
<td>Partial-agonist</td>
<td>100</td>
<td>724</td>
<td>13.80 (13.53–14.07)</td>
<td>2.27 (1.60–2.97)</td>
<td>1.75 (1.23–2.50)</td>
</tr>
<tr>
<td>Strong opioids</td>
<td>32</td>
<td>131</td>
<td>24.51 (23.66–25.36)</td>
<td>3.45 (2.37–5.04)</td>
<td>2.83 (1.89–4.24)</td>
</tr>
<tr>
<td>&lt;50 MME</td>
<td>190</td>
<td>1686</td>
<td>11.27 (11.11–11.43)</td>
<td>1.57 (1.33–1.83)</td>
<td>1.36 (1.13–1.62)</td>
</tr>
<tr>
<td>≥50 MME</td>
<td>18</td>
<td>73</td>
<td>24.72 (23.58–25.86)</td>
<td>3.35 (2.03–5.52)</td>
<td>2.86 (1.73–4.72)</td>
</tr>
<tr>
<td><strong>Analyses according to immunosuppressive status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-immunosuppressive</td>
<td>30</td>
<td>121</td>
<td>24.76 (23.87–25.64)</td>
<td>3.35 (2.26–4.96)</td>
<td>2.91 (1.94–4.34)</td>
</tr>
<tr>
<td>Immunosuppressive</td>
<td>42</td>
<td>309</td>
<td>13.61 (13.20–14.02)</td>
<td>1.87 (1.34–2.61)</td>
<td>1.68 (1.20–2.36)</td>
</tr>
<tr>
<td>Unknown</td>
<td>100</td>
<td>725</td>
<td>13.80 (13.53–14.07)</td>
<td>2.15 (1.69–2.73)</td>
<td>1.87 (1.41–2.36)</td>
</tr>
<tr>
<td><strong>Intention-to-treat analyses, first 180 days</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonuser</td>
<td>160</td>
<td>2576</td>
<td>6.21 (6.11–6.31)</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Opioid user</td>
<td>275</td>
<td>2333</td>
<td>11.79 (11.65–11.93)</td>
<td>1.88 (1.55–2.89)</td>
<td>1.63 (1.33–2.01)</td>
</tr>
<tr>
<td><strong>As-treated analyses, first 180 days</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonuser</td>
<td>147</td>
<td>2481</td>
<td>5.92 (5.83–6.02)</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Opioid user</td>
<td>166</td>
<td>1123</td>
<td>14.78 (14.56–15.01)</td>
<td>2.24 (1.80–2.78)</td>
<td>1.89 (1.49–2.40)</td>
</tr>
</tbody>
</table>

HR = Hazard ratio; MME = Morphine milligram equivalents. Analyses adjusted for cardiovascular disease, diabetes, asthma/COPD, rheumatoid arthritis, baseline use of antidepressants, antipsychotics, PPIs, BZDRs, immunosuppressants for nonmalignant diseases, oral corticosteroids and antiepileptics, history of stroke, hip fracture and substance abuse, socioeconomic position and discharge from hospital care in the last 7 days.
Figure 1

Opioid initiation after AD diagnosis
N = 7,730

No opioid use during one year before AD diagnosis (wash-out)
N = 863

No hospitalization periods during wash-out
N = 348

No active cancer year before opioid initiation
N = 491

No pneumonia six months before opioid initiation
N = 277

Community follow-up found (not in long-term care throughout the study period)
N = 27

New opioid users
N = 5,724

No match found
N = 101

Matched according to age, sex and time since diagnosis

Persons with opioid initiation included in the analyses
N = 5,623

Persons without opioid initiation included in the analyses
N = 5,623
Figure 2

- Codeine: 30.8%
- Tramadol: 7.1%
- Buprenorphine: 34.4%
- Oxycodone: 8.9%
- Fentanyl: 3.5%
- Other: 0.3%
- Two or more opioids: 15.0%
Supplementary Figure 1